Global Initiative for Chronic Obstructive Lung Disease

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

2006

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GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (2006)

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2006)

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PREFACE

Chronic Obstructive Pulmonary Disease (COPD) remains a major public health problem. It is the fourth leading cause of chronic morbidity and mortality in the United States, and is projected to rank fifth in 2020 in burden of disease caused worldwide, according to a study published by the World Bank/World Health Organization. Furthermore, although COPD has received increasing attention from the medical community in recent years, it is still relatively unknown or ignored by the public as well as public health and government officials.

In 1998, in an effort to bring more attention to COPD, its management, and its prevention, 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 the important objectives of GOLD are to increase awareness of COPD and to help the millions of people who suffer from this disease and die prematurely from it or its complications.

The first step in the GOLD program was to prepare a consensus report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*, which was published in 2001. The report was written by an Expert Panel, which was chaired by Professor Romain Pauwels of Belgium and included a distinguished group of health professionals from the fields of respiratory medicine, epidemiology, socioeconomics, public health, and health education. The Expert Panel reviewed existing COPD guidelines and new information on pathogenic mechanisms of COPD, bringing all of this material together in the consensus document. The present, newly revised document follows the same format as the original consensus report, but has been updated to reflect the many publications on COPD that have appeared since 2001.

Since the original consensus report was published in 2001, a network of international experts known as GOLD National Leaders has been formed to implement the report's recommendations. Many of these experts have initiated investigations of the causes and prevalence of COPD in their countries, and developed innovative approaches for the dissemination and implementation of COPD management guidelines. We appreciate the enormous amount of work the GOLD National Leaders have done on behalf of their patients with COPD.

In spite of the achievements in the five years since the GOLD report was originally published, considerable additional work is ahead of all of us if we are to control this major public health problem. The GOLD initiative will continue to 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.

I would like to acknowledge the work of the members of the GOLD Science Committee who prepared this revised report. We look forward to our continued work with interested organizations and the GOLD National Leaders to meet the goals of this initiative.

We are most appreciative of the unrestricted educational grants from Altana, AstraZeneca, Boehringer Ingelheim, Chiesi, GlasoSmithKline, Mitsubishi Pharma Corporation, Nikken Chemicals, Co,. Ltd., Novartis, and Pfizer that enabled development of this report.

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GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years and die prematurely from it or its complications. COPD is the fourth leading cause of death in the world[1], and further increases in its prevalence and mortality can be predicted in the coming decades[2].

The goals of the **G**lobal Initiative for Chronic **O**bstructive **L**ung **D**isease (**GOLD**) are to increase awareness of COPD and decrease morbidity and mortality from the 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 an expanded level of research interest in this highly prevalent disease. A nihilistic attitude toward COPD continues among some health care providers, due to the relatively limited success of primary and secondary prevention (i.e., avoidance of factors that cause COPD or its progression), the prevailing notion that COPD is largely a self-inflicted disease, and disappointment with available treatment options. Another important goal of the GOLD initiative is to work toward combating this nihilistic attitude by disseminating information about available treatments (both pharmacologic and nonpharmacologic), and by working with a network of experts—the GOLD National Leaders—to implement effective COPD management programs developed in accordance with local health care practices.

Tobacco smoking continues to be a major cause of COPD, as well as of many other diseases. A worldwide decline in tobacco smoking would result in substantial health benefits and a decrease in the prevalence of COPD and other smoking-related diseases. There is an urgent need for improved strategies to decrease tobacco consumption. However, tobacco smoking is not the only cause of COPD, and it may not even be the major cause in some parts of the world. Furthermore, not all smokers develop clinically significant COPD, which suggests that additional factors are involved in determining each individual's susceptibility. Thus, investigations of COPD risk factors, ways to reduce exposure to these factors, and the molecular and cellular mechanisms involved in COPD pathogenesis continue to be important areas of research to develop more effective treatments that slow or halt the course of the disease.

One strategy to help achieve the objectives of GOLD is to provide health care workers, health care authorities, and the general public with state-of-the-art information about COPD and specific recommendations on the most appropriate management and prevention strategies. The GOLD report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*, is based on the best-validated current concepts of COPD pathogenesis and the available evidence on the most appropriate management and prevention strategies. The report, developed by individuals with expertise in COPD research and patient care and reviewed by many additional experts, provides state-of-the-art information about COPD for pulmonary specialists and other interested physicians. The document serves as a source for the production of various communications for other audiences, including an Executive Summary, a Pocket Guide for Health Care Professionals, and a Patient Guide[2].

The GOLD report is not intended to be a comprehensive textbook on COPD, but rather to summarize the current state of the field. Each chapter starts with *Key Points* that crystallize current knowledge. The chapters on the *Burden of COPD* and *Risk Factors* demonstrate the global importance of COPD and the various causal factors involved. The chapter on *Pathology, Pathogenesis, and Pathophysiology* documents the current understanding of, and remaining questions about, the mechanism(s) that lead to COPD, as well as the structural and functional abnormalities of the lung that are characteristic of the disease.

A major part of the GOLD report is devoted to the clinical Management of COPD and presents a management plan with four components: (1) *Assess and Monitor Disease*; (2) *Reduce Risk Factors*; (3) *Manage Stable COPD*; (4) *Manage Exacerbations*.

Management recommendations are presented according to the severity of the disease, using a simple classification of severity to facilitate the practical implementation of the available management options. Where appropriate, information about health education for patients is included. A new chapter at the end of the document will assist readers in *Translating Guideline Recommendations to the Context of (Primary) Care*.

A large segment of the world's population lives in areas with inadequate medical facilities and meager financial resources, and fixed international guidelines and rigid scientific protocols will not work in many locations. Thus, the recommendations found in this report must be adapted to fit local practices and the availability of health care resources. As the individuals who participate in the GOLD program expand their work, every effort will be made to interact with patient and physician groups at national, district, and local levels, and in multiple health care settings, to continuously examine new and innovative approaches that will ensure the delivery of the best care possible to COPD patients, and the initiation of programs for early detection and prevention of this disease. GOLD is a partner organization in a program launched in March 2006 by the World Health Organization, the Global Alliance Against Chronic Respiratory Diseases (GARD). Through the work of the GOLD committees, and in cooperation with GARD initiatives, progress toward better care for all patients with COPD should be substantial in the next decade.

METHODOLOGY

A. Preparation of yearly updates: Immediately following the release of the first GOLD report in 2001, the GOLD Executive Committee appointed a Science Committee, charged with keeping the GOLD documents up-to-date by reviewing published research, evaluating the impact of this research on the management recommendations in the GOLD documents, and posting yearly updates of these documents on the GOLD Website. The first update to the GOLD report was posted in July 2003, based on publications from January 2001 through December 2002. A second update appeared in July 2004, and a third in July 2005, each including the impact of publications from January through December of the previous year.

Producing the yearly updates began with a PubMed (http://www.nlm.nih.gov) search using search fields established by the Science Committee: 1) *COPD OR chronic bronchitis OR emphysema, All Fields, All Adult, 19+ years, only items with abstracts, Clinical Trial, Human, sorted by Author*; 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-reviewed journals not captured by PubMed could be submitted to individual members of the Science Committee, provided that 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 two committee members (members were not assigned papers they had authored), although any member was offered the opportunity to provide an opinion on any abstract. Each member evaluated the assigned abstracts or, where s/he judged necessary, the full publication, by answering specific written questions from a short questionnaire, and indicating whether the scientific data presented affected 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 one member of the committee to have an impact on COPD management, and to reach a consensus on the changes needed in the report. Disagreements were decided by vote.

The publications that met the search criteria for each yearly update (between 100 and 200 articles per year) mainly affected Chapter 5, Management of COPD. Lists of the publications considered by the Science Committee each year, along with the yearly updated reports, are posted on the GOLD Website, www.goldcopd.org.

B. Preparation of the New 2006 Report: In January 2005, the GOLD Science Committee initiated its work on a comprehensively updated version of the GOLD report. During a two-day meeting, the committee established that the report structure should remain the same as in the 2001 document, but that each chapter would be carefully reviewed and modified in accordance with new published literature. The committee met in May and September 2005 to evaluate progress and to reach consensus on the messages to be provided in each chapter. Throughout its work, the committee made a commitment to develop a document that would reach a global audience, be based on the most current scientific literature, and be as concise as possible, while at the same time recognizing that one of the values of the GOLD report has been to provide background information on COPD management and the scientific principles on which management recommendations are based.

In January 2006, the Science Committee met with the Executive Committee for a two-day session during which another in-depth evaluation of each chapter was conducted. At this meeting, members reviewed the literature that appeared in 2005—using the same criteria developed for the update process. The list of 2005 publications that were considered is posted on the GOLD website. At the January meeting, it was clear that work remaining would

permit the report to be finished during the summer of 2006, and the Science Committee requested that, as publications appeared throughout early 2006, they be reviewed carefully for their impact on the recommendations. At the committee's next meeting, in May 2006, publications meeting the search criteria were considered and incorporated into the current drafts of the chapters where appropriate. A final meeting of the committee was held in September 2006, at which time publications that appeared prior to July 31, 2006 were considered for their impact on the document.

Periodically throughout the preparation of this report (May and September 2005, May and September 2006), representatives from the GOLD Science Committee met with the GOLD National Leaders to discuss COPD management and issues specific to each of the chapters. The GOLD National Leaders include representatives from over 50 countries and many participated in these interim discussions. In addition, GOLD National Leaders were invited to submit comments on a DRAFT document and their comments were considered by the committee. When the committee completed its work, several other individuals were invited to submit comments on the document as reviewers. The names of reviewers and GOLD National Leaders who submitted comments are in the front material.

NEW ISSUES PRESENTED IN THIS REPORT

1. Throughout the document, emphasis has been made that COPD is characterized by chronic airflow limitation and a range of pathological changes in the lung, some significant extrapulmonary effects, and important comorbidities that may contribute to the severity of the disease in individual patients.

2. In the definition of COPD, the phrase "preventable and treatable" has been incorporated following the ATS/ERS recommendations to recognize the need to present a positive outlook for patients, to encourage the health care community to take a more active role in developing programs for COPD prevention, and to stimulate effective management programs to treat those with the disease.

3. The spirometric classification of severity of COPD now includes four stages—*Stage I: Mild; Stage II: Moderate; Stage III: Severe; Stage IV: Very Severe*. A fifth category - "*Stage 0: At Risk*," - that appeared in the 2001 report is no longer included as a stage of COPD, as there is incomplete evidence that the individuals who meet the definition of "At Risk" (chronic cough and sputum production, normal spirometry) necessarily progress on to *Stage I*. Nevertheless, the importance of the public health message that chronic cough and sputum are not normal is unchanged.

4. The spirometric classification of severity continues to recommend use of the fixed ratio, postbronchodilator $FEV_1/FVC < 0.7$, to define airflow limitation. Using the fixed ratio (FEV_1/FVC) is particularly problematic in milder patients who are elderly as the normal process of aging affects lung volumes. Postbronchodilator reference values in this population are urgently needed to avoid potential overdiagnosis.

5. Chapter 2, Burden of COPD, provides references to published data from prevalence surveys carried out in a number of countries, using standardized methods and including spirometry, to estimate that about one-quarter of adults aged 40 years and older may have airflow limitation classified as *Stage I: Mild COPD* or higher. Evidence is also provided that the prevalence of COPD (*Stage I: Mild COPD* and higher) is appreciably higher in smokers and ex-smokers than in nonsmokers, in those over 40 years than those under 40, and higher in men than in women. The chapter also provides new data on COPD morbidity and mortality.

6. Throughout it is emphasized that cigarette smoke is the most commonly encountered risk factor for COPD and elimination of this risk factor is an important step toward prevention and control of COPD. However, other risk factors for COPD should be taken into account where possible. These include occupational dusts and chemicals, and indoor air pollution from biomass cooking and heating in poorly ventilated dwellings—the latter especially among women in developing countries.

7. Chapter 4, Pathology, Pathogenesis, and Pathophysiology, continues with the theme that inhaled cigarette smoke and other noxious particles cause lung inflammation, a normal response which appears to be amplified in patients who develop COPD. The chapter has been considerably updated and revised.

8. Management of COPD continues to be presented in four components: (1) Assess and Monitor Disease; (2) Reduce Risk Factors; (3) Manage Stable COPD; (4) Manage Exacerbations. All components have been updated based on recently published literature. Throughout the document, it is emphasized that the overall approach to managing stable COPD should be individualized to address symptoms and improve quality of life.

9. In Component 4, Manage Exacerbations, a COPD exacerbation is defined as: *an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD*.

10. It is widely recognized that a wide spectrum of health care providers are required to assure that COPD is diagnosed accurately, and that individuals who have COPD are treated effectively. The identification of effective health care teams will depend on the local health care system, and much work remains to identify how best to build these health care teams. A chapter on COPD implementation programs and issues for clinical practice has been included but it remains a field that requires considerable attention.

LEVELS OF EVIDENCE

Levels of evidence are assigned to management recommendations where appropriate in Chapter 5, Management of COPD. Evidence levels are indicated in boldface type enclosed in parentheses after the relevant statement–e.g., (**Evidence A**). The methodological issues concerning the use of evidence from meta-analyses were carefully considered[3].

This evidence level scheme (**Table A**) has been used in previous GOLD reports, and was in use throughout the preparation of this document. The GOLD Science Committee was recently introduced to a new approach to evidence levels[4] and plans to review and consider the possible introduction of this approach in future reports.

Figure A. Description of Levels of Evidence

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

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CHAPTER

1

DEFINITION

CHAPTER 1: DEFINITION

KEY POINTS:

- Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

- The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person.

- COPD has a variable natural history and not all individuals follow the same course. However, COPD is generally a progressive disease, especially if a patient's exposure to noxious agents continues.

- The impact of COPD on an individual patient depends on the severity of symptoms (especially breathlessness and decreased exercise capacity), systemic effects, and any comorbidities the patient may have—not just on the degree of airflow limitation.

DEFINITION

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation and a range of pathological changes in the lung, some significant extra-pulmonary effects, and important comorbidities which may contribute to the severity of the disease in individual patients. Thus, COPD should be regarded as a pulmonary disease, but these significant comorbidities must be taken into account in a comprehensive diagnostic assessment of severity and in determining appropriate treatment.

Based on current knowledge, a working definition is:

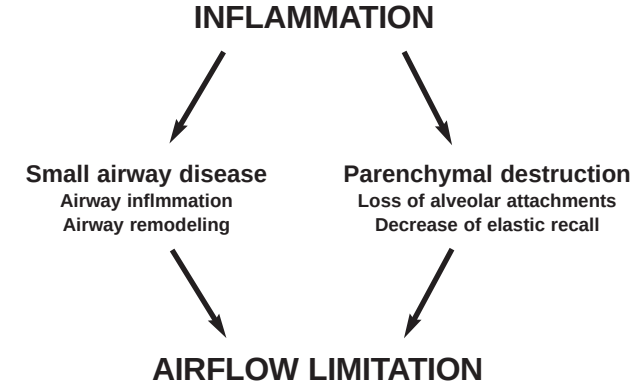
Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

Worldwide, cigarette smoking is the most commonly encountered risk factor for COPD, although in many countries, air pollution resulting from the burning of wood and other biomass fuels has also been identified as a COPD risk factor.

Airflow Limitation in COPD

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person (**Figure 1-1**). Chronic inflammation causes structural changes and narrowing of the small airways. Destruction of the lung parenchyma, also by inflammatory processes, leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil; in turn, these changes diminish the ability of the airways to remain open during expiration. Airflow limitation is best measured by spirometry, as this is the most widely available, reproducible test of lung function.

Figure 1-1. Mechanisms Underlying Airflow Limitation in COPD



Many previous definitions of COPD have emphasized the terms “emphysema” and “chronic bronchitis,” which are not included in the definition used in this and earlier GOLD reports. Emphysema, or destruction of the gas-exchanging surfaces of the lung (alveoli), is a pathological term that is often (but incorrectly) used clinically and describes only one of several structural abnormalities present in patients with COPD. Chronic bronchitis, or the presence of cough and sputum production for at least 3 months in each of two consecutive years, remains a clinically and epidemiologically useful term. However, it does not reflect the major impact of airflow limitation on morbidity and mortality in COPD patients. It is also important to recognize that cough and sputum production may precede the development of airflow limitation; conversely, some patients develop significant airflow limitation without chronic cough and sputum production.

COPD and Comorbidities

Because COPD often develops in long-time smokers in middle age, patients often have a variety of other diseases related to either smoking or aging[1]. COPD itself also has significant extrapulmonary (systemic) effects that lead to comorbid conditions[2]. Data from the Netherlands show that up to 25% of the population 65 years and older suffer from two comorbid conditions and up to 17% have three[3]. Weight loss, nutritional abnormalities and skeletal muscle dysfunction are well-recognized extrapulmonary effects of COPD and patients are at increased risk for myocardial infarction, angina, osteoporosis, respiratory infection, bone fractures, depression, diabetes, sleep-disorders, anemia, and glaucoma[4]. The existence of COPD may actually increase the risk for other diseases; this is particularly striking for COPD and lung cancer[5-8]. Whether this association is due to common risk factors (e.g., smoking), involvement of susceptibility genes, or impaired clearance of carcinogens is not clear.

Thus, COPD should be managed with careful attention also paid to comorbidities and their effect on the patient’s quality of life. A careful differential diagnosis and comprehensive assessment of severity of comorbid conditions should be performed in every patient with chronic airflow limitation.

NATURAL HISTORY

COPD has a variable natural history and not all individuals follow the same course. However, COPD is generally a progressive disease, especially if a patient's exposure to noxious agents continues. Stopping exposure to these agents, even when significant airflow limitation is present, may result in some improvement in lung function and slow or even halt progression of the disease. However, once developed, COPD and its comorbidities cannot be cured and thus must be treated continuously. COPD treatment can reduce symptoms, improve quality of life, reduce exacerbations, and possibly reduce mortality.

Spirometric Classification of Severity

For educational reasons, a simple spirometric classification of disease severity into four stages is recommended (**Figure 1-2**). Spirometry is essential for diagnosis and provides a useful description of the severity of pathological changes in COPD. Specific spirometric cut-points (e.g., post-bronchodilator FEV_1/FVC ratio < 0.70 or FEV_1 < 80, 50, or 30% predicted) are used for purposes of simplicity: these cut-points have not been clinically validated. A study in a random population sample found that the post-bronchodilator FEV_1/FVC exceeded 0.70 in all age groups, supporting the use of this fixed ratio[9].

Figure 1-2. Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV_1

Stage I: Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted
Stage II: Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted
Stage III: Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted
Stage IV: Very Severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.

However, because the process of aging does affect lung volumes, the use of this fixed ratio may result in over diagnosis of COPD in the elderly, especially of mild disease. Using the lower limit of normal (LLN) values for FEV_1/FVC, that are based on the normal distribution and classify the bottom 5% of the healthy population as abnormal, is one way to minimize the potential misclassification. In principle, all programmable spirometers could do this calculation if reference equations for the LLN of the ratio were available. However, reference equations using post-bronchodilator FEV_1 and longitudinal studies to validate the use of the LLN are urgently needed.

Spirometry should be performed after the administration of an adequate dose of an inhaled bronchodilator (e.g., 400 μg salbutamol)[10] in order to minimize variability. In a random population study to determine spirometry reference values, post-bronchodilator values differed markedly from pre-bronchodilator values[9]. Furthermore, post-bronchodilator lung function testing in a community setting has been demonstrated to be an effective method to identify individuals with COPD[11].

While post-bronchodilator FEV_1/FVC and FEV_1 measurements are recommended for the diagnosis and assessment of severity of COPD, the degree of reversibility of airflow limitation (e.g., ΔFEV_1 after bronchodilator or glucocorticosteroids) is no longer recommended for diagnosis, differential diagnosis with asthma, or predicting the response to long-term treatment with bronchodilators or glucocorticosteroids.

Stages of COPD

The impact of COPD on an individual patient depends not just on the degree of airflow limitation, but also on the severity of symptoms (especially breathlessness and decreased exercise capacity). There is only an imperfect relationship between the degree of airflow limitation and the presence of symptoms. Spirometric staging, therefore, is a pragmatic approach aimed at practical implementation and should only be regarded as an educational tool and a general indication to the initial approach to management.

The characteristic symptoms of COPD are chronic and progressive dyspnea, cough, and sputum production. Chronic cough and sputum production may precede the development of airflow limitation by many years. This pattern offers a unique opportunity to identify smokers and others at risk for COPD (**Figure 1-3**), and intervene when the disease is not yet a major health problem.

Figure 1-3. "At Risk for COPD"

A major objective of GOLD is to increase awareness among health care providers and the general public of the significance of COPD symptoms. The classification of severity of COPD now includes four stages classified by spirometry—*Stage I: Mild COPD; Stage II: Moderate COPD; Stage III: Severe COPD; Stage IV: Very Severe COPD*. A fifth category - "*Stage 0: At Risk*," – that appeared in the 2001 report is no longer included as a stage of COPD, as there is incomplete evidence that the individuals who meet the definition of "At Risk" (chronic cough and sputum production, normal spirometry) necessarily progress on to *Stage I. Mild COPD*. Nevertheless, the importance of the public health message that chronic cough and sputum are not normal is unchanged and their presence should trigger a search for underlying cause(s).

Conversely, significant airflow limitation may develop without chronic cough and sputum production. Although COPD is defined on the basis of airflow limitation, in practice the decision to seek medical help (and so permit the diagnosis to be made) is normally determined by the impact of a particular symptom on a patient's lifestyle. Thus, COPD may be diagnosed at any stage of the illness.

Stage I: Mild COPD - Characterized by mild airflow limitation ($FEV_1/FVC < 0.70$; $FEV_1 \geq 80\%$ predicted). Symptoms of chronic cough and sputum production may be present, but not always. At this stage, the individual is usually unaware that his or her lung function is abnormal.

Stage II: Moderate COPD - Characterized by worsening airflow limitation ($FEV_1/FVC < 0.70$; $50\% \leq FEV_1 < 80\%$ predicted), with shortness of breath typically developing on exertion and cough and sputum production sometimes also present. This is the stage at which patients typically seek medical attention because of chronic respiratory symptoms or an exacerbation of their disease.

Stage III: Severe COPD - Characterized by further worsening of airflow limitation ($FEV_1/FVC < 0.70$; $30\% \leq FEV_1 < 50\%$ predicted), greater shortness of breath, reduced exercise capacity, fatigue, and repeated exacerbations that almost always have an impact on patients' quality of life.

Stage IV: Very Severe COPD - Characterized by severe airflow limitation ($FEV_1/FVC < 0.70$; $FEV_1 < 30\%$ predicted *or* $FEV_1 < 50\%$ predicted plus the presence of chronic respiratory failure). Respiratory failure is defined as an arterial partial pressure of O_2 (PaO_2) less than 8.0 kPa (60 mm Hg), with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level. Respiratory failure may also lead to effects on the heart such as cor pulmonale (right heart failure). Clinical signs of cor pulmonale include elevation of the jugular venous pressure and pitting ankle edema. Patients may have *Stage IV: Very Severe COPD* even if the FEV_1 is > 30% predicted, whenever these complications are present. At this stage, quality of life is very appreciably impaired and exacerba-tions may be life threatening.

The common statement that only 15-20% of smokers develop clinically significant COPD is misleading[12]. A much higher proportion may develop abnormal lung function at some point if they continue to smoke[13]. Not all individuals with COPD follow the classical linear course as outlined in the Fletcher and Peto diagram, which is actually the mean of many individual courses[14]. Causes of death in patients with COPD are mainly cardiovascular diseases, lung cancer, and, in those with advanced COPD, respiratory failure[15].

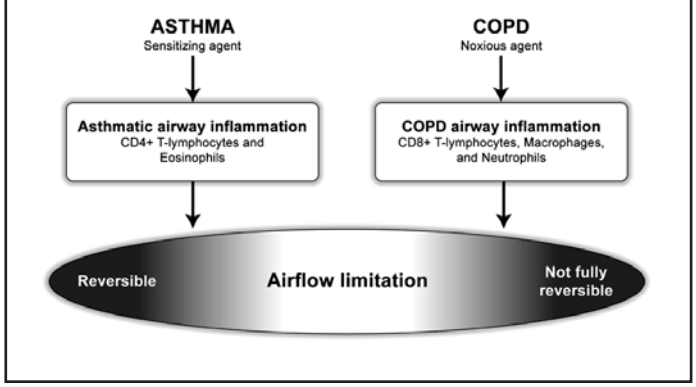
SCOPE OF THE REPORT

It is not the scope of this report to provide a comprehensive discussion of the natural history of comorbidities associated with COPD but to focus primarily on chronic airflow limitation caused by inhaled particles and gases, the most common of which worldwide is cigarette smoke. However, chronic airflow limitation may develop also in nonsmokers who present with similar symptoms and may be associated with other diseases, e.g., asthma, congestive heart failure, lung carcinoma, bronchiectasis, pulmonary tuberculosis, bronchiolitis obliterans, and interstitial lung diseases. Poorly reversible airflow limitation associated with these conditions is not addressed except insofar as these conditions overlap with COPD.

Asthma and COPD

COPD can coexist with asthma, the other major chronic obstructive airway disease characterized by an underlying airway inflammation. The underlying chronic airway inflammation is very different in these two diseases (**Figure 1-4**). However, individuals with asthma who are exposed to noxious agents, particularly cigarette smoke[16], may also develop fixed airflow limitation and a mixture of "asthma-like" and "COPD-like" inflammation. Furthermore, there is epidemiologic evidence that longstanding asthma on its own can lead to fixed airflow limitation[17]. Other patients with COPD may have features of asthma such as a mixed inflammatory pattern with increased eosinophils[18]. Thus, while asthma can usually be distinguished from COPD, in some individuals with chronic respiratory symptoms and fixed airflow limitation it remains difficult to differentiate the two diseases. Population-based surveys[19,20] have documented that chronic airflow limitation may occur in up to 10% of lifetime nonsmokers 40 years and older; the causes of airflow limitation in nonsmokers needs further investigation.

Figure 1-4. Asthma and COPD



Pulmonary Tuberculosis and COPD

In many developing countries both pulmonary tuberculosis and COPD are common[21]. In countries where tuberculosis is very common, respiratory abnormalities may be too readily attributed to this disease[22]. Conversely, where the rate of tuberculosis is greatly diminished, the possible diagnosis of this disease is sometimes overlooked. 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[23].

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CHAPTER

2

BURDEN OF COPD

CHAPTER 2: BURDEN OF COPD

KEY POINTS:

- COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing.
- COPD prevalence, morbidity, and mortality vary across countries and across different groups within countries but, in general, are directly related to the prevalence of tobacco smoking, although in many countries, air pollution resulting from the burning of wood and other biomass fuels has also been identified as a COPD risk factor.
- The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the changing age structure of the world's population.
- COPD is a costly disease with both direct costs (value of health care resources devoted to diagnosis and medical management) and indirect costs (monetary consequences of disability, missed work, premature mortality, and caregiver or family costs resulting from the illness).

INTRODUCTION

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing. COPD prevalence, morbidity, and mortality vary across countries and across different groups within countries but, in general, are directly related to the prevalence of tobacco smoking although in many countries, air pollution resulting from the burning of wood and other biomass fuels has also been identified as a COPD risk factor. The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the changing age structure of the world's population (with more people living longer, and thus reaching the age at which COPD normally develops).

EPIDEMIOLOGY

In the past, imprecise and variable definitions of COPD have made it difficult to quantify prevalence, morbidity and mortality. Furthermore, the underrecognition and underdiagnosis of COPD lead to significant underreporting. The extent of the underreporting varies across countries and depends on the level of awareness and understanding of COPD among health professionals, the organization of health care services to cope with chronic diseases, and the availability of medications for the treatment of COPD[1].

There are several sources of information on the burden of COPD: publications such as the 2003 European Lung White Book[2], international Websites such as the World Health Organization (http://www.who.int) and the World Bank/WHO Global Burden of Disease Study (http://www.who.int/topics/global_burden_of_disease), and country-specific Websites such as the US Centers for Disease Control and Prevention (http://www.cdc.gov) and the UK Health Survey for England (http://www.doh.gov.uk).

Prevalence

Existing COPD prevalence data show remarkable variation due to differences in survey methods, diagnostic criteria, and analytic approaches[3,4]. Survey methods can include:

- Self-report of a doctor diagnosis of COPD or equivalent condition
- Spirometry with or without a bronchodilator
- Questionnaires that ask about the presence of respiratory symptoms

The *lowest* estimates of prevalence are usually those based on self-reporting of a doctor diagnosis of COPD or equivalent condition. For example, most national data show that less than 6% of the population has been told that they have COPD[3]. This likely reflects the widespread underrecognition and underdiagnosis of COPD[5] as well as the fact that those with *Stage I: Mild COPD* may have no symptoms, or else symptoms (such as chronic cough and sputum) that are not perceived by individuals or their health care providers as abnormal and possibly indicative of early COPD[5]. These estimates may have value, however, since they may most accurately reflect the burden of *clinically significant* disease that is of sufficient severity to require health services, and therefore is likely to generate significant direct and indirect costs.

By contrast, data from prevalence surveys carried out in a number of countries, using standardized methods and including spirometry, estimate that up to about one-quarter of adults aged 40 years and older may have airflow limitation classified as *Stage I: Mild COPD* or higher[6-9].

Because of the large gap between the prevalence of COPD as defined by the presence of airflow limitation and the prevalence of COPD as defined by clinically significant disease, the debate continues as to which of these it is better to use in estimating the burden of COPD. Early diagnosis and intervention may help to identify the number of individuals who progress to a clinically significant stage of disease, but there is insufficient evidence at this time to recommend community-based spirometric screening for COPD[10].

Different diagnostic criteria also give widely different estimates and there is little consensus regarding the most appropriate criteria for different settings (e.g., epidemiologic surveys, clinical diagnosis), or the strengths and weaknesses of the different criteria. It is recognized that defining irreversible airflow obstruction as a post-bronchodilator FEV_1/FVC ratio less than 0.70 leads to the potential for significant misclassification, with ***under***diagnosis (false negatives) in younger adults and ***over-***diagnosis (false positives) over age 50 years[11-13]. This has led to the recommendation that the use of the lower limit of normal (LLN) of the post-bronchodilator FEV_1/FVC ratio rather than the fixed ratio be used to define irreversible airflow obstruction[14,15]. However, more information is needed from population-based longitudinal studies to determine the outcome of individuals classified using either definition.

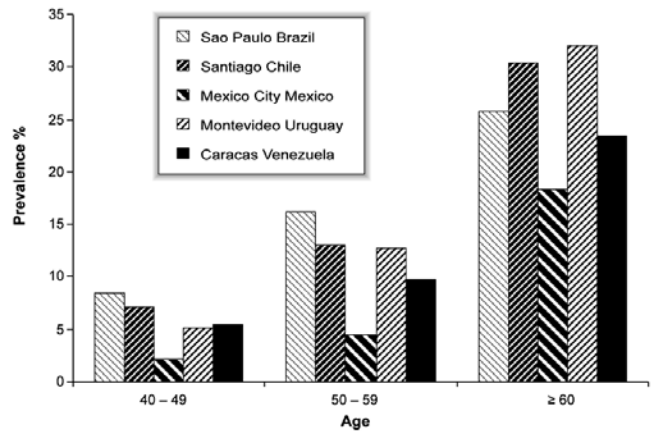
Many additional sources of variation can affect estimates of COPD prevalence, including sampling methods, response rates, quality control of spirometry, and whether spirometry is performed pre- or post-bronchodilator. Samples that are not population-based and poor response rates may give biased estimates of prevalence, with the direction of bias sometimes hard to determine. Inadequate emptying of the lungs during the spirometric maneuver is common and leads to an artificially high ratio of FEV_1/FVC and therefore to an underestimate of the prevalence of COPD. Failure to use post-bronchodilator value instead of pre-bronchodilator values leads to an overdiagnosis of irreversible airflow limitation In future prevalence surveys, *post-bronchodilator* spirometry should be used to confirm the diagnosis of COPD[16].

Despite these complexities, data are emerging that enable some conclusions to be drawn regarding COPD prevalence. A systematic review and meta-analysis of studies carried out in 28 countries between 1990 and 2004[3], and an additional study from Japan[17], provide evidence that the prevalence of COPD (*Stage I: Mild COPD* and higher) is appreciably higher in smokers and ex-smokers than in nonsmokers, in those over 40 years than those under 40, and in men than in women.

The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) examined the prevalence of post-bronchodilator airflow limitation (*Stage I: Mild COPD* and higher) among persons over age 40 in five major Latin American cities each in a different country – Brazil, Chile, Mexico, Uruguay, and Venezuela. In each country, the prevalence of *Stage I: Mild COPD* and higher increased steeply with age (**Figure 2-1**), with the highest prevalence among those over 60 years, ranging from a low of 18.4% in Mexico City, Mexico to a high of 32.1% in Mentevideo, Uruguay. In all cities/countries the prevalence was appreciably higher in men than in women. The reasons for the differences in prevalence across the five Latin American cities are still under investigation[6].

In 12 Asia-Pacific countries and regions a study based on a prevalence estimation model indicated a mean prevalence rate for moderate to severe COPD among individuals 30 years and older of 6.3% for the region. The rates varied twofold across the 12 Asian countries and ranged from a minimum of 3.5% (Hong Kong and Singapore) to a maximum of 6.7% (Vietnam)[18].

Figure 2-1. COPD Prevalence by Age in Five Latin American Cities[6]



Prevalence = postbronchodilator FEV_1/FVC < 0.70 (Stage I: Mild COPD and higher)

Morbidity

Morbidity measures traditionally include physician visits, emergency department visits, and hospitalizations. Although COPD databases for these outcome parameters are less readily available and usually less reliable than mortality databases, the limited data available indicate that morbidity due to COPD increases with age and is greater in men than in women[19-21]. In these data sets, however, COPD in its early stages (*Stage I: Mild COPD*

and *Stage 2: Moderate COPD*) is usually not recognized, diagnosed, or treated, and therefore may not be included as a diagnosis in a patient's medical record.

Morbidity from COPD may be affected by other comorbid chronic conditions[22] (e.g., musculoskeletal disease, diabetes mellitus) that are not directly related to COPD but nevertheless may have an impact on the patient's health status, or may negatively interfere with COPD management. In patients with more advanced disease (*Stage III: Severe COPD* and *Stage IV: Very Severe COPD*), morbidity from COPD may be misattributed to another comorbid condition.

Morbidity data are greatly affected by the availability of resources (e.g,, hospitalization rates are highly dependent on the availability of hospital beds) and thus have to be interpreted cautiously and with a clear understanding of the possible biases inherent in the dataset. Despite the limitations in the data for COPD, the European White Book provides good data on the mean number of consultations for major respiratory diseases across 19 countries of the European Economic Community[2]. In most countries, consultations for COPD greatly outnumbered consultations for asthma, pneumonia, lung and tracheal cancer, and tuberculosis. In the United States in 2000, there were 8 million physician office/hospital outpatient visits for COPD, 1.5 million emergency department visits, and 673,000 hospitalizations[23].

Another way of estimating the morbidity burden of disease is to calculate years of living with disability (YLD). The Global Burden of Disease Study estimates that COPD results in 1.68 YLD per 1,000 population, representing 1.8% of all YLDs, with a greater burden in men than in women (1.93% vs. 1.42%)[8,24,25].

Mortality

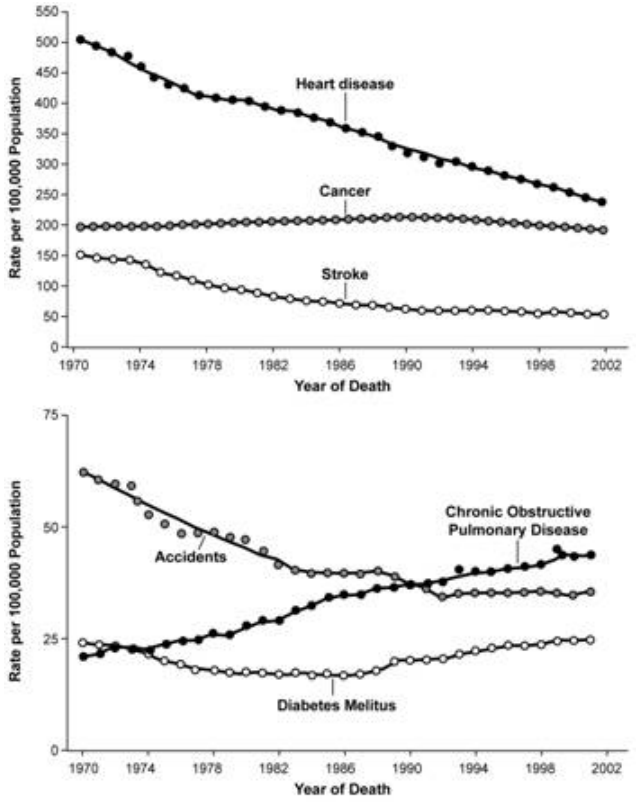
The World Health Organization publishes mortality statistics for selected causes of death annually for all WHO regions; additional information is available from the WHO Evidence for Health Policy Department (http://www.who.int/evidence). Data must be interpreted cautiously, however, because of inconsistent use of terminology for COPD. Prior to about 1968 and the Eighth Revision of the International Classification of Diseases (ICD), the terms "chronic bronchitis" and "emphysema" were used extensively. During the 1970s, the term "COPD" increasingly replaced those terms in some but not all countries, making COPD mortality comparisons in different countries very difficult. However, the situation has improved with the Ninth and Tenth Revisions of the ICD, in which deaths from COPD or chronic airways obstruction are included in the broad category of "COPD and allied conditions" (ICD-9 codes 490-496 and ICD-10 codes J42-46).

Thus, the problem of labeling has been partly solved, but underrecognition and underdiagnosis of COPD still affect the accuracy of mortality data. Although COPD is often a *primary* cause of death, it is more likely to be listed as a *contributory* cause of death or omitted from the death certificate entirely, and the death attributed to another condition such as cardiovascular disease.

Despite the problems with the accuracy of the COPD mortality data, it is clear that COPD is one of the most important causes of death in most countries. The Global Burden of Disease Study[8,24,25] has projected that COPD, which ranked sixth as the cause of death in 1990, will become the third leading cause of death worldwide by 2020. This increased mortality is driven by the expanding epidemic of smoking and the changing demographics in most countries, with more of the population living longer. Of these two forces, demographics is the stronger driver of the trend.

Trends in mortality rates over time provide further important information but, again, these statistics are greatly affected by terminology, awareness of the disease, and potential gender bias in its diagnosis. COPD mortality trends generally track several decades behind smoking trends. Trends in age-standardized death rates for the six leading causes of death in the United States from 1970 through 2002[26] indicates that while mortality from several of these chronic conditions declined over that period, COPD mortality increased (**Figure 2-2**). Death rates for COPD in Canada, in both men and women, have also been increasing since 1997. In Europe, however, the trends are different, with decreasing mortality from COPD already being seen in many countries[7]. There is no obvious reason for the difference between trends in North America and Europe, although presumably factors such as awareness, changing terminology, and diagnostic bias contribute to these differences.

Figure 2-2. Trends in Age-standardized Death Rates for the 6 Leading Causes of Death in the United States, 1970-2002[26]



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The mortality trends for COPD have been particularly striking for women. In Canada, the death rate from COPD among women accelerated in the 1990s and is expected to soon overtake the rate among men[21]. In the United States, COPD deaths among women have been rising steeply since the 1970s. In 2000, the *number* of deaths from COPD in the United States was greater among women than men (59,936 vs. 59,118), although the mortality rates among women remain somewhat lower than among men[27].

Worldwide, recent increases in COPD deaths are likely to continue. The Global Burden of Disease Study[8,24,25] projected baseline, optimistic, and pessimistic models for COPD mortality from 1990 to 2020 that take into account the expected aging of the world's population, projected increases in smoking rates, and projected declines in other causes of death such as diarrheal and HIV-related diseases.

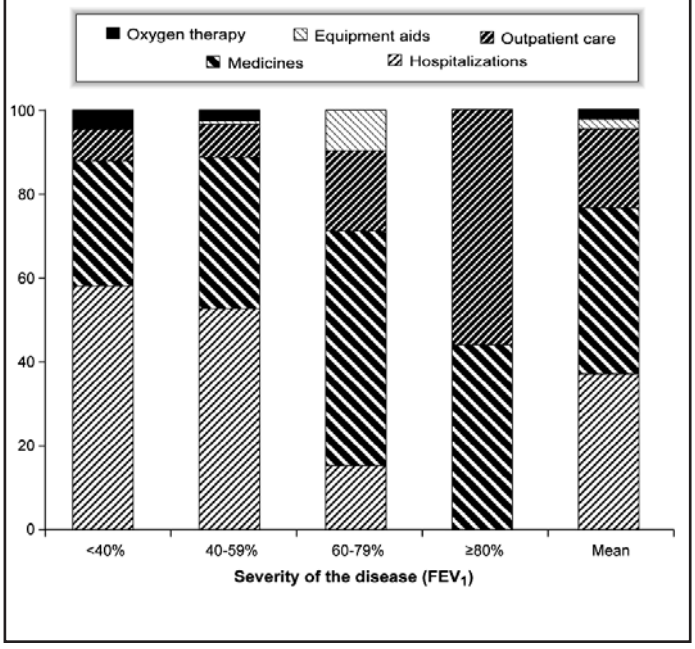
ECONOMIC AND SOCIAL BURDEN OF COPD

Economic Burden

COPD is a costly disease with both direct costs (value of health care resources devoted to diagnosis and medical management) and indirect costs (monetary consequences of disability, missed work, premature mortality, and caregiver or family costs resulting from the illness)[2]. In developed countries, exacerbations of COPD account for the greatest burden on the health care system. In the European Union, the total *direct* costs of respiratory disease are estimated to be about 6% of the total health care budget, with COPD accounting for 56% (38.6 billion Euros) of this[2]. In the United States in 2002, the direct costs of COPD were $18 billion and the indirect costs totaled $14.1 billion[28]. Costs per patient will vary across countries since these costs depend on how health care is provided and paid[7].

Not surprisingly, there is a striking direct relationship between the severity of COPD and the cost of care[29], and the distribution of costs changes as the disease progresses. For example, hospitalization and ambulatory oxygen costs soar as COPD severity increases, as illustrated by data from Sweden shown in **Figure 2-3**.

Figure 2-3. Distribution of Direct Costs of COPD by Severity[29]



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The presence of COPD greatly increases the total cost of care for patients, especially when inpatient costs are considered. In a study of COPD-related illness costs in the United States based on the 1987 National Medical Expenditure Survey, *per capita* expenditures for hospitalizations of COPD patients were 2.7 times the expenditures for patients without COPD ($5,409 vs. $2,001)[30]. In a 1992 study of Medicare, the US government health insurance program for individuals over 65, annual *per capita* expenditures for people with COPD ($8,482) were nearly 2.5 times the expenditures for people without COPD ($3,511)[31].

Individuals with COPD frequently receive professional medical care in their homes. In some countries, national health insurance plans provide coverage for oxygen therapy, visiting nursing services, rehabilitation, and even mechanical ventilation in the home, although coverage for specific services varies from country to country[32]. Any estimate of direct medical expenditures for home care underrepresents the true cost of home care to society, because it ignores the economic value of the care provided to those with COPD by family members. In developing countries, direct medical costs may be less important than the impact of COPD on workplace and home productivity. Because the health care sector might not provide long-term supportive care services for severely disabled individuals, COPD may force two individuals to leave the workplace—the affected individual and a family member who must now stay home to care for the disabled relative. Since human capital is often the most important national asset for developing countries, the indirect costs of COPD may represent a serious threat to their economies.

Social Burden

Since mortality offers a limited perspective on the human burden of a disease, it is desirable to find other measures of disease burden that are consistent and measurable across nations. The authors of the Global Burden of Disease Study designed a method to estimate 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)[8,24,25]. The DALYs for a specific condition are the sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disability. In 1990, COPD was the twelfth leading cause of DALYs lost in the world, responsible for 2.1% of the total. According to the projections, COPD will be the fifth leading cause of DALYs lost worldwide in 2020, behind ischemic heart disease, major depression, traffic accidents, and cerebrovascular disease. This substantial increase in the global burden of COPD projected over the next twenty years reflects, in large part, the continued high use of tobacco in many countries and the changing age structure of populations in developing countries.

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CHAPTER

3

RISK FACTORS

CHAPTER 3: RISK FACTORS

KEY POINTS:

- Worldwide, cigarette smoking is the most commonly encountered risk factor for COPD.
- The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin. It provides a model for how other genetic risk factors are thought to contribute to COPD.
- Of the many inhalational exposures that may be encountered over a lifetime, only tobacco smoke and occupational dusts and chemicals (vapors, irritants, and fumes) are known to cause COPD on their own. More data are needed to explore the causative role of other risk factors.
- Indoor air pollution, especially from burning biomass fuels in confined spaces, is associated with increased risk for COPD in developing countries, especially among women.

INTRODUCTION

The identification of risk factors is an important step toward developing strategies for prevention and treatment of any disease. Identification of cigarette smoking as the most commonly encountered risk factor for COPD has led to the incorporation of smoking cessation programs as a key element of COPD prevention, as well as an important intervention for patients who already have the disease. However, although smoking is the best-studied COPD risk factor, it is not the only one and there is consistent evidence from epidemiologic studies that nonsmokers may develop chronic airflow obstruction[1,2].

Much of the evidence concerning risk factors for COPD comes from cross-sectional epidemiological studies that identify associations rather than cause-and-effect relationships. Although several longitudinal studies (which are capable of revealing causal relationships) of COPD have followed groups and populations for up to 20 years[3], none has monitored the progression of the disease through its entire course, or has included the pre-and perinatal periods which may be important in shaping an individual's future COPD risk. Thus, current understanding of risk factors for COPD is in many respects incomplete.

RISK FACTORS

As the understanding of the importance of risk factors (**Figure 3-1**) for COPD has grown, so has the recognition that essentially all risk for COPD results from a gene-environment interaction. Thus, of two people with the same smoking history, only one may develop COPD due to differences in genetic predisposition to the disease, or in how long they live. Risk factors for COPD may also be related in more complex ways. For example, gender may influence whether a person takes up smoking or experiences certain occupational or environmental exposures; socioeconomic status may be linked to a child's birth weight (as it impacts on lung growth and development); and longer life expectancy will allow greater lifetime exposure to risk factors. Understanding the relationships and interactions among risk factors requires further investigation.

Figure 3-1. Risk Factors for COPD.

Genes
Exposure to particles
- Tobacco smoke
- Occupational dusts, organic and inorganic
- Indoor air pollution from heating and cooking with biomass in poorly vented dwellings
- Outdoor air pollution

Lung Growth and Development
Oxidative stress
Gender
Age
Respiratory infections
Socioeconomic status
Nutrition
Comorbidities

Genes

COPD is a polygenic disease and a classic example of gene-environment interaction. The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin[4], a major circulating inhibitor of serine proteases. This rare recessive trait is most commonly seen in individuals of Northern European origin[5]. Premature and accelerated development of panlobular emphysema and decline in lung function occur in both smokers and nonsmokers with the severe deficiency, although smoking increases the risk appreciably. There is considerable variation between individuals in the extent and severity of the emphysema and the rate of

lung function decline. Although alpha-1 antitrypsin deficiency is relevant to only a small part of the world's population, it illustrates the interaction between genes and environmental exposures leading to COPD. In this way, it provides a model for how other genetic risk factors are thought to contribute to COPD.

A significant familial risk of airflow obstruction has been observed in smoking siblings of patients with severe COPD[6], suggesting that genetic factors could influence this susceptibility. Through genetic linkage analysis, several regions of the genome have been identified that likely contain COPD susceptibility genes, including chromosome 2q[7]. Genetic association studies have implicated a variety of genes in COPD pathogenesis, including transforming growth factor beta 1 (TGF-β1)[8] microsomal epoxide hydrolase 1 (mEPHX1)[9], and tumor necrosis factor alpha (TNFα)[10]. However, the results of these genetic association studies have been largely inconsistent, and functional genetic variants influencing the development of COPD (other than alpha-1 antitrypsin deficiency) have not been definitively identified[7].

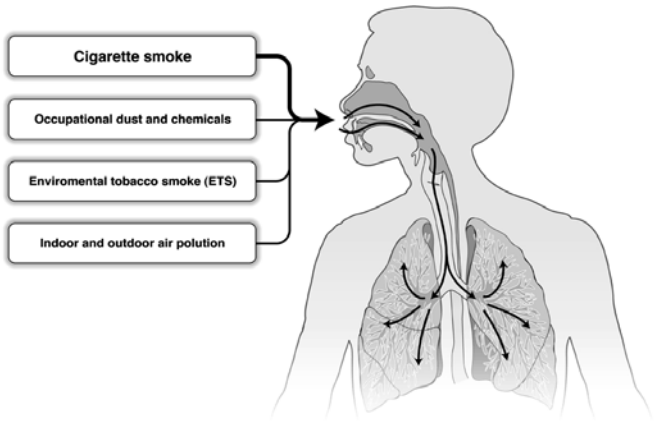
Inhalational Exposures

Because individuals may be exposed to a variety of different types of inhaled particles over their lifetime, it is helpful to think in terms of the total burden of inhaled particles. Each type of particle, depending on its size and composition, may contribute a different weight to the risk, and the total risk will depend on the integral of the inhaled exposures (**Figure 3-2**). Of the many inhalational exposures that may be encountered over a lifetime, only tobacco smoke[11,12] and occupational dusts and chemicals (vapors, irritants, and fumes)[13-16] are known to cause COPD on their own. Tobacco smoke and occupational exposures also appear to act additively to increase the risk of developing COPD. However this may reflect an inadequate data base from populations who are exposed to other risk factors, such as heavy exposures to indoor air pollution from poorly vented biomass cooking and heating.

Tobacco Smoke: Cigarette smoking is by far the most commonly encountered risk factor for COPD. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV_1, and a greater COPD mortality rate than nonsmokers. Pipe and cigar smokers have greater COPD morbidity and mortality rates than nonsmokers, although their rates are lower than those for cigarette smokers[11]. Other types of tobacco smoking popular in various countries are also risk factors for COPD[17,18], although their risk relative to cigarette smoking has not been reported. The risk for COPD in smokers is dose-related[12]. Age at starting to smoke, total pack-years smoked, and current smoking status are predictive of COPD mortality. Not all smokers develop clinically significant COPD, which suggests that genetic factors must modify each individual's risk[9].

Passive exposure to cigarette smoke (also known as environmental tobacco smoke or ETS) may also contribute to respiratory symptoms[19] and COPD[20] by increasing the lungs' total burden of inhaled particles and gases[21,22]. 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[23,24].

Figure 3-2. COPD Risk is Related to the Total Burden of Inhaled Particles



Occupational Dusts and Chemicals: Occupational exposures are an underappreciated risk factor for COPD[14-16,25]. These exposures include organic and inorganic dusts and chemical agents and fumes. An analysis of the large US population-based NHANES III survey of almost 10,000 adults aged 30-75 years, which included lung function tests, estimated the fraction of COPD attributable to work was 19.2% overall, and 31.1% among never smokers[16]. These estimates are consistent with a statement published by the American Thoracic Society that concluded that occupational exposures account for 10-20% of either symptoms or functional impairment consistent with COPD[26].

Indoor Air Pollution: Wood, animal dung, crop residues, and coal, typically burned in open fires or poorly functioning stoves, may lead to very high levels of indoor air pollution. The evidence that indoor pollution from biomass cooking and heating in poorly ventilated dwellings is an important risk factor for COPD (especially among women in developing countries) continues to grow[27-33], with case-control studies[32, 33] and other robustly designed studies now available.

Almost 3 billion people worldwide use biomass and coal as their main source of energy for cooking, heating, and other household needs, so the population at risk worldwide is very large. In these communities, indoor air pollution is responsible for a greater fraction of COPD risk than SO_2 or particulates from motor vehicle emissions, even in cities densely populated with people and cars. Biomass fuels used by women for cooking account for the high prevalence of COPD among nonsmoking women in parts of the Middle East, Africa, and Asia[34,35]. Indoor air pollution resulting from the burning of wood and other biomass fuels is estimated to kill two million women and children each year[36].

Outdoor Air Pollution: High levels of urban air pollution are harmful to individuals 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 that of cigarette smoking. It has also been difficult to assess the effects of single pollutants in long-term exposure to atmospheric pollution. However, air pollution from fossil fuel combustion, primarily from motor vehicle emissions in cities, is associated with decrements of respiratory function[37]. The relative effects of short-term, high-peak exposures and long-term, low-level exposures is a question yet to be resolved.

Lung Growth and Development

Lung growth is related to processes occurring during gestation, birth, and exposures during childhood[38-40]. Reduced maximal attained lung function (as measured by spirometry) may identify individuals who are at increased risk for the development of COPD[41]. Any factor that affects lung growth during gestation and childhood has the potential for increasing an individual's risk of developing COPD. For example, a large study and meta-analysis confirmed a positive association between birth weight and FEV_1 in adulthood[42].

Oxidative Stress

The lungs are continuously exposed to oxidants generated either endogenously from phagocytes and other cell types or exogenously from air pollutants or cigarette smoke. In addition, intracellular oxidants, such as those derived from mitochondrial electron transport, are involved in many cellular signaling pathways. Lung cells are protected against this oxidative challenge by well-developed enzymatic and nonenzymatic systems. When the balance between oxidants and antioxidants shifts in favor of the former—i.e., an excess of oxidants and/or a depletion of antioxidants—oxidative stress occurs. Oxidative stress not only produces direct injurious effects in the lungs but also activates molecular mechanisms that initiate lung inflammation. Thus, an imbalance between oxidants and antioxidants is considered to play a role in the pathogenesis of COPD[43].

Gender

The role of gender in determining COPD risk remains unclear[44]. In the past, most studies showed that COPD prevalence and mortality were greater among men than women. Studies from developed countries[45,46] show that the prevalence of the disease is now almost equal in men and women, which probably reflects changing patterns of tobacco smoking. Some studies have suggested that women are *more* susceptible to the effects of tobacco smoke than men[44,47,48]. This is an important question given the increasing rate of smoking among women in both developed and developing countries.

Infections

Infections (viral and bacterial) may contribute to the pathogenesis and progression of COPD[49], and the bacterial colonization associated with airway inflammation[50], and may also play a significant role in exacerbations[51]. A history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood[38,41,52]. There are several possible explanations for this association (which are not mutually exclusive). There may be an increased diagnosis of severe infections in children who have underlying airway hyperresponsiveness, itself considered a risk factor for COPD. Susceptibility to viral infections may be related to another factor, such as birth weight, that is related to COPD. HIV infection has been shown to accelerate the onset of smoking-related emphysema; HIV-induced pulmonary inflammation may play a role in this process[53].

Socioeconomic Status

There is evidence that the risk of developing COPD is inversely related to socioeconomic status[54]. 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 low socioeconomic status[55,56].

Nutrition

The role of nutrition as an independent risk factor for the development of COPD is unclear. Malnutrition and weight loss can reduce respiratory muscle strength and endurance, apparently by reducing both respiratory muscle mass and the strength of the remaining muscle fibers[57]. The association of starvation and anabolic/catabolic status with the development of emphysema has been shown in experimental studies in animals[58]. Lung CT scans of women chronically malnourished because of anorexia nervosa showed emphysema-like changes[59].

Asthma

Asthma may be risk factor for the development of COPD, although the evidence is not conclusive. In a report from a longitudinal cohort of the Tucson Epidemiological Study of Airway Obstructive Disease adults with asthma were found to have a twelvefold higher risk of acquiring COPD over time than those without asthma, after adjusting for smoking[60]. Another longitudinal study of people with asthma found that around 20% of subjects developed functional signs of COPD, irreversible airflow limitation, and reduced transfer coefficient[61].

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CHAPTER

4

PATHOLOGY, PATHOGENESIS, AND PATHOPHYSIOLOGY

CHAPTER 4: PATHOLOGY, PATHOGENESIS, AND PATHOPHYSIOLOGY

KEY POINTS:

- Pathological changes characteristic of COPD are found in the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature. These changes include chronic inflammation, and structural changes resulting from repeated injury and repair.
- Inhaled cigarette smoke and other noxious particles cause lung inflammation, a normal response which appears to be amplified in patients who develop COPD.
- There is a characteristic pattern of inflammation in the lungs of COPD patients, with increased numbers of neutrophils (in the airway lumen), macrophages (airway lumen, airway wall, and parenchyma), and $CD8^+$ lymphocytes (airway wall and parenchyma). The pattern is different from that seen in asthma.
- Lung inflammation is further amplified by oxidative stress and an excess of proteases in the lung.
- Physiological changes characteristic of the disease include mucus hypersecretion, airflow limitation and air trapping (leading to hyperinflation), gas exchange abnormalities, and cor pulmonale.
- Systemic features of COPD, particularly in patients with severe disease, include cachexia, skeletal muscle wasting, increased risk of cardiovascular disease, anemia, osteoporosis, and depression.
- Exacerbations represent a further amplification of the inflammatory response in the airways of patients with COPD, and may be triggered by infection with bacteria or viruses or by environmental pollutants.

INTRODUCTION

Inhaled cigarette smoke and other noxious particles cause lung inflammation, a normal response which appears to be amplified in patients who develop COPD. This abnormal inflammatory response may induce parenchymal tissue destruction (resulting in emphysema), and disrupt normal repair and defense mechanisms (resulting in small airway fibrosis). These pathological changes lead to air trapping and progressive airflow limitation. A brief overview follows of the pathologic changes in COPD, their cellular and molecular mechanisms, and how these underlie physiologic abnormalities and symptoms characteristic of the disease[1].

PATHOLOGY

Pathological changes characteristic of COPD are found in the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature[2] (**Figure 4-1**). The pathological changes include chronic inflammation, with increased numbers of specific inflammatory cell types in different parts of the lung, and structural changes resulting from

Figure 4-1. Pathological Changes in COPD

Proximal airways (trachea, bronchi > 2 mm internal diameter)
Inflammatory cells: ↑Macrophages, ↑$CD8^+$ (cytotoxic) T lymphocytes, few neutrophils or eosinophils
Structural changes: ↑Goblet cells, enlarged submucosal glands (both leading to mucus hypersecretion), squamous metaplasia of epithelium[3]

Peripheral airways (bronchioles < 2mm i.d.)
Inflammatory cells: ↑Macrophages, ↑T lymphocytes ($CD8^+$ > $CD4^+$), ↑B lymphocytes, lymphoid follicles, ↑fibroblasts, few neutrophils or eosinophils
Structural changes: Airway wall thickening, peribronchial fibrosis, luminal inflammatory exudate, airway narrowing (obstructive bronchiolitis) Increased inflammatory response and exudate correlated with disease severity[4]

Lung parenchyma (respiratory bronchioles and alveoli)
Inflammatory cells: ↑Macrophages, ↑$CD8^+$ T lymphocytes
Structural changes: Alveolar wall destruction, apoptosis of epithelial and endothelial cells[5]
- Centrilobular emphysema: dilatation and destruction of respiratory bronchioles; most commonly seen in smokers
- Panacinar emphysema: destruction of alveolar sacs as well as respiratory bronchioles; most commonly seen in alpha-1 antitrypsin deficiency

Pulmonary vasculature
Inflammatory cells: ↑Macrophages, ↑T lymphocytes
Structural changes: Thickening of intima, endothelial cell dysfunction, ↑smooth muscle → pulmonary hypertension[6].

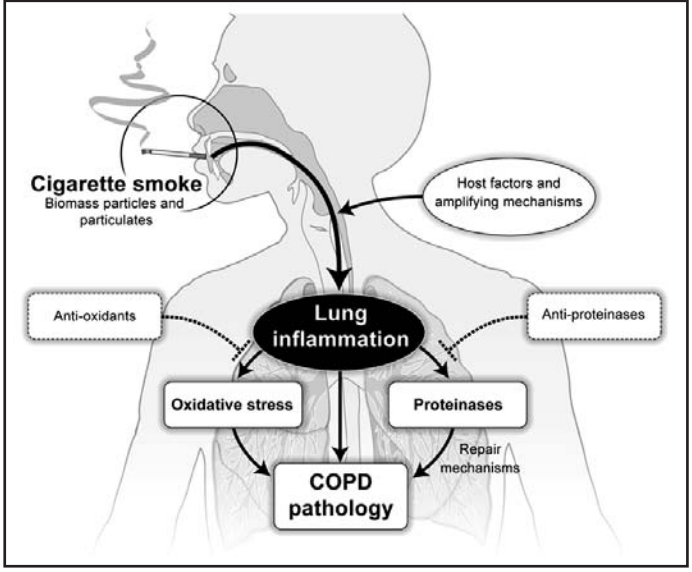
+Illustrations of many of the topics covered in this chapter can be found on the GOLD Website: http://www.goldcopd.org.

repeated injury and repair. In general, the inflammatory and structural changes in the airways increase with disease severity and persist on smoking cessation.

PATHOGENESIS

The inflammation in the respiratory tract of COPD patients appears to be an amplification of the normal inflammatory response of the respiratory tract to chronic irritants such as cigarette smoke. The mechanisms for this amplification are not yet understood but may be genetically determined. Some patients develop COPD without smoking, but the nature of the inflammatory response in these patients is unknown[7]. Lung inflammation is further amplified by oxidative stress and an excess of proteinases in the lung. Together, these mechanisms lead to the characteristic pathological changes in COPD (**Figure 4-2**).

Figure 4-2. Pathogenesis of COPD



Inflammatory Cells

COPD is characterized by a specific pattern of inflammation involving neutrophils, macrophages, and lymphocytes[1] (**Figure 4-3**). These cells release inflammatory mediators and interact with structural cells in the airways and lung parenchyma.

Inflammatory Mediators

The wide variety of inflammatory mediators that have been shown to be increased in COPD patients[10] attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (proinflammatory cytokines), and induce structural changes (growth factors). Examples of each type of mediator are listed in **Figure 4-4**.

Figure 4-3. Inflammatory Cells in COPD

Neutrophils: ↑ in sputum of normal smokers. Further ↑ in COPD and related to disease severity. Few neutrophils are seen in tissue. They may be important in mucus hypersecretion and through release of proteases[8].

Macrophages: Greatly ↑ numbers are seen in airway lumen, lung parenchyma, and bronchoalveolar lavage fluid. Derived from blood monocytes that differentiate within lung tissue. Produce increased inflammatory mediators and proteases in COPD patients in response to cigarette smoke and may show defective phagocytosis[9].

T lymphocytes: Both CD4+ and CD8+ cells are increased in the airway wall and lung parenchyma, with ↑CD8+:CD4+ ratio. ↑CD8+ T cells (Tc1) and Th1 cells which secrete interferon-γ and express the chemokine receptor CXCR3[9]. CD8+ cells may be cytotoxic to alveolar cells, contributing to their destruction.

B lymphocytes: ↑ in peripheral airways and within lymphoid follicles, possibly as a response to chronic colonization and infection of the airways[4].

Eosinophils: ↑ eosinophil proteins in sputum and ↑ eosinophils in airway wall during exacerbations.

Epithelial cells: May be activated by cigarette smoke to produce inflammatory mediators.

Figure 4-4. Inflammatory Mediators Involved in COPD

Chemotactic factors:

- **Lipid mediators:** e.g., leukotriene B_4 (LTB_4) attracts neutrophils and T lymphocytes
- **Chemokines:** e.g., interleukin-8 (IL-8) attracts neutrophils and monocytes.

Proinflammatory cytokines: e.g., tumor necrosis factor-α (TNF-α), IL-1β, and IL-6 amplify the inflammatory process and may contribute to some of the systemic effects of COPD.

Growth factors: e.g., transforming growth factor-ß (TGF-ß) may induce fibrosis in small airways.

Oxidative Stress

Oxidative stress may be an important amplifying mechanism in COPD[11]. Biomarkers of oxidative stress (e.g., hydrogen peroxide, 8-isoprostane) are increased in the exhaled breath condensate, sputum, and systemic circulation of COPD patients. Oxidative stress is further increased in exacerbations. Oxidants are generated by cigarette smoke and other inhaled particulates, and released from activated inflammatory cells such as macrophages and neutrophils[12]. There may also be a reduction in endogenous antioxidants in COPD patients. Oxidative stress has several adverse consequences in the lungs, including activation of inflammatory genes, inactivation of antiproteases, stimulation of mucus secretion, and stimulation of increased plasma exudation. Many of these adverse effects are mediated by peroxynitrite, which is formed via an interaction between

superoxide anions and nitric oxide. In turn, the nitric oxide is generated by inducible nitric oxide synthase, which is expressed in the peripheral airways and lung parenchyma of COPD patients. Oxidative stress may also account for a reduction in histone deacetylase activity in lung tissue from COPD patients, which may lead to enhanced expression of inflammatory genes and also a reduction in the anti-inflammatory action of glucocorticosteroids[13].

Protease-Antiprotease Imbalance

There is compelling evidence for an imbalance in the lungs of COPD patients between proteases that break down connective tissue components and antiproteases that protect against this. Several proteases, derived from inflammatory cells and epithelial cells, are increased in COPD patients. There is increasing evidence that they may interact with each other (**Figure 4-5**). Protease-mediated destruction of elastin, a major connective tissue component in lung parenchyma, is an important feature of emphysema and is likely to be irreversible.

Figure 4-5. Proteases and Antiproteases Involved in COPD

Increased Proteases	*Decreased Antiproteases*
Serine proteases	
Neutrophil elastase	alpha-1 antitrypsin
Cathepsin G	alpha-1 antichymotrypsin
Proteinase 3	Secretory leukoprotease inhibitor
	Elafin
Cysteine proteinases	
Cathepsins B, K, L, S	Cystatins
Matrix metalloproteinases (MMPs)	
MMP-8, MMP-9, MMP-12	Tissue inhibitors of MMP 1-4 (TIMP1-4)

Differences in Inflammation Between COPD and Asthma

Although both COPD and asthma are associated with chronic inflammation of the respiratory tract, there are marked differences in the inflammatory cells and mediators involved in the two diseases, which in turn account for differences in physiological effects, symptoms, and response to therapy (**Figure 4-6, Figure 4-7**). However, there are greater similarities between the lung inflammation in severe asthma and COPD. Some patients with COPD have features of asthma and may have a mixed inflammatory pattern with increased eosinophils. Finally, people with asthma who smoke develop pathological features similar to COPD[14].

PATHOPHYSIOLOGY

There is now a good understanding of how the underlying disease process in COPD leads to the characteristic physiologic abnormalities and symptoms. For example, decreased FEV_1 primarily results from inflammation and narrowing of peripheral airways, while decreased gas transfer arises from the parenchymal destruction of emphysema.

Airflow Limitation and Air Trapping

The extent of inflammation, fibrosis, and luminal exudates in small airways is correlated with the reduction in FEV_1 and FEV_1/FVC ratio, and probably with the accelerated decline in FEV_1 characteristic of COPD[4]. This peripheral airway obstruction progressively traps air during expiration, resulting in hyperinflation. Although emphysema is more associated with gas exchange abnormalities than with reduced FEV_1, it does contribute to air trapping during expiration. This is especially so as alveolar attachments to small airways are destroyed when the disease becomes more severe. Hyperinflation reduces inspiratory capacity such that functional residual capacity increases, particularly during exercise (when this abnormality is known as dynamic hyperinflation), and this results in dyspnea and limitation of exercise capacity. It is now thought that hyperinflation develops early in the disease and is the main mechanism for exertional dyspnea[15]. Bronchodilators acting on peripheral airways reduce air trapping, thereby reducing lung volumes and improving symptoms and exercise capacity.

Gas Exchange Abnormalities

Gas exchange abnormalities result in hypoxemia and hypercapnia, and have several mechanisms in COPD. In general, gas transfer worsens as the disease progresses. The severity of emphysema correlates with arterial PO_2 and other markers of ventilation-perfusion (V_A/Q) imbalance. Peripheral airway obstruction also results in V_A/Q imbalance, and combines with ventilatory muscle impaired function in severe disease to reduce ventilation, leading to carbon dioxide retention. The abnormalities in alveolar ventilation and a reduced pulmonary vascular bed further worsen the V_A/Q abnormalities.

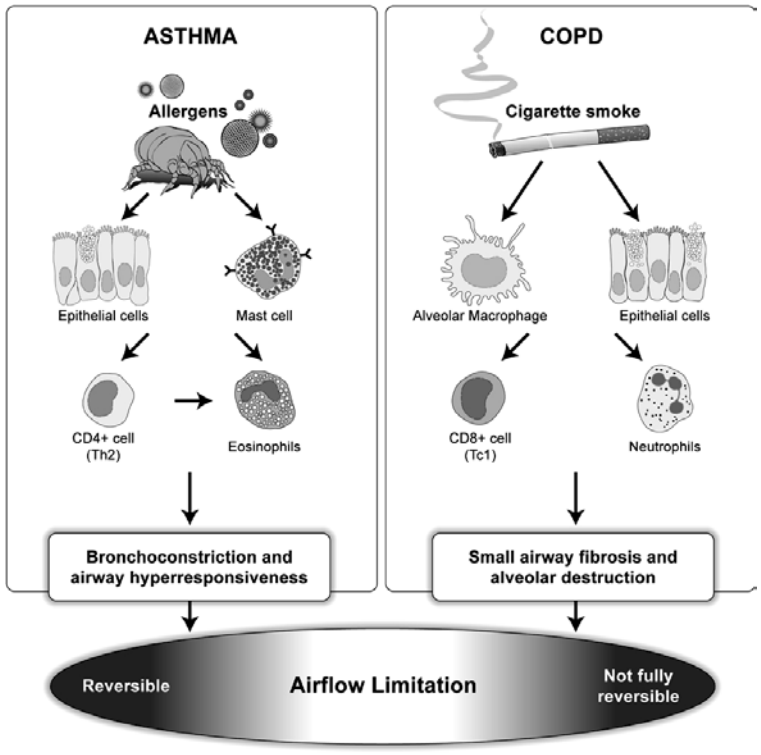
Mucus Hypersecretion

Mucus hypersecretion, resulting in a chronic productive cough, is a feature of chronic bronchitis and is not necessarily associated with airflow limitation. Conversely, not all patients with COPD have symptomatic mucus

Figure 4-6. Differences in Pulmonary Inflammation Between Asthma and COPD			
Cells	Neutrophils ++ Macrophages +++ CD8+ T cells (Tc1)	Eosinophils ++ Macrophages + CD4+ T cells (Th2)	Neutrophils + Macrophages CD4+ T cells (Th2), CD8+ T cells (Tc1)
Key mediators	IL-8 TNF-α, IL-1β, IL-6 NO +	Eotaxin IL-4, IL-5, IL-13 NO +++	IL-8 IL-5, IL-13 NO ++
Oxidative stress	+++	+	+++
Site of disease	Peripheral airways Lung parenchyma Pulmonary vessels	Proximal airways	Proximal airways Peripheral airways
Consequences	Squamous metaplasia Mucous metaplasia Small airway fibrosis Parenchymal destruction Pulmonary vascular remodeling	Fragile epithelium Mucous metaplasia ↑ Basement membrane Bronchoconstriction	
Response to therapy	Small b/d response Poor response to steroids	Large b/d response Good response to steroids	Smaller b/d response Reduced response to steroids

NO = nitric oxide, b/d = bronchodilator

Figure 4-7. Inflammatory Cascade in COPD and Asthma



hypersecretion. When present, it is due to mucous metaplasia with increased numbers of goblet cells and enlarged submucosal glands in response to chronic airway irritation by cigarette smoke and other noxious agents. Several mediators and proteases stimulate mucus hypersecretion and many of them exert their effects through the activation of epidermal growth factor receptor (EGFR)[16].

Pulmonary Hypertension

Mild to moderate pulmonary hypertension may develop late in the course of COPD and is due to hypoxic vaso-constriction of small pulmonary arteries, eventually resulting in structural changes that include intimal hyperplasia and later smooth muscle hypertrophy/hyperplasia[17]. There is an inflammatory response in vessels similar to that seen in the airways and evidence for endothelial cell dysfunction. The loss of the pulmonary capillary bed in emphysema may also contribute to increased pressure in the pulmonary circulation. Progressive pulmonary hypertension may lead to right ventricular hypertrophy and eventually to right-side cardiac failure (cor pulmonale).

Systemic features

It is increasingly recognized that COPD involves several systemic features, particularly in patients with severe disease, and that these have a major impact on survival and comorbid diseases[18,19] (**Figure 4-8**). Cachexia is commonly seen in patients with severe COPD. There may be a loss of skeletal muscle mass and weakness as a result of increased apoptosis and/or muscle disuse. Patients with COPD also have increased likeliness of having osteoporosis, depression and chronic anemia[20]. Increased concentrations of inflammatory mediators, including TNF-α, IL-6, and oxygen-derived free radicals, may mediate some of these systemic effects. There is an increase in the risk of cardiovascular diseases, which is correlated with an increase in C-reactive protein (CRP)[21].

Figure 4-8. Systemic Features of COPD

- Cachexia: loss of fat free mass
- Skeletal muscle wasting: apoptosis, disuse atrophy
- Osteoporosis
- Depression
- Normochromic normocytic anemia
- Increased risk of cardiovascular disease: associated with ↑ CRP

EXACERBATIONS

Exacerbations represent a further amplification of the inflammatory response in the airways of COPD patients, and may be triggered by infection with bacteria or viruses or by environmental pollutants. There is a relative lack of information about the inflammatory mechanisms involved in exacerbations of COPD. In mild and moderate exacerbations there is an increase in neutrophils and in some studies also eosinophils in sputum and the airway wall[22]. This is associated with increased concentrations of certain mediators, including TNF-α, LTB_4 and IL-8, and an increase in biomarkers of oxidative stress. There is even less information about severe exacerbations, although one study showed a marked increase in neutrophils in the airway wall and increased expression of chemokines[23]. During an exacerbation there is increased hyperinflation and air trapping, with reduced expiratory flow, thus accounting for the increased dyspnea[24]. There is also worsening of V_A/Q abnormalities resulting in severe hypoxemia.

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CHAPTER

5

MANAGEMENT

OF COPD

CHAPTER 5: MANAGEMENT OF COPD

INTRODUCTION

An effective COPD management plan includes four components: (1) Assess and Monitor Disease; (2) Reduce Risk Factors; (3) Manage Stable COPD; and (4) Manage Exacerbations. Management of Mild to Moderate COPD (*Stages I and II*) involves the avoidance of risk factors to prevent disease progression and pharmacotherapy as needed to control symptoms. Severe (*Stage III*) and Very Severe (*Stage IV*) COPD often require the integration of several different disciplines, a variety of treatment approaches, and a commitment of the clinician to the continued support of the patient as the illness progresses. In addition to patient education, health advice, and pharmacotherapy, COPD patients may require specific counseling about smoking cessation, instruction in physical exercise, nutritional advice, and continued nursing support. Not all approaches are needed for every patient, and assessing the potential benefit of each approach at each stage of the illness is a crucial aspect of effective disease management.

While disease prevention is the ultimate goal, once COPD has been diagnosed, effective management should be aimed at the following goals:

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

These goals should be reached with minimal side effects from treatment, a particular challenge in COPD patients because they commonly have comorbidities. 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 individual, his or her family, and the community must be considered.

Patients should be identified as early in the course of the disease as possible, and certainly before the end stage of the illness when disability is substantial. Access to spirometry is key to the diagnosis of COPD and should be available to health care workers who care for COPD patients. However, the benefits of community-based spirometric screening, of either the general population or smokers, are still unclear.

Educating patients, physicians, and the public 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 non-pharmacologic, 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.

Important differences exist between countries in the approach to chronic illnesses such as COPD and in the acceptability and affordability of particular forms of therapy. Ethnic differences in drug metabolism, especially for oral medications, may result in different patient preferences in different communities. Little is known about these important issues in relationship to COPD.

COMPONENT 1: ASSESS AND MONITOR DISEASE

KEY POINTS:

- A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease. The diagnosis should be confirmed by spirometry.
- 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. The presence of a postbronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 <$ 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.
- Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality, and the presence of complications.
- Measurement of arterial blood gas tensions should be considered in all patients with $FEV_1 < 50\%$ predicted or clinical signs suggestive of respiratory failure or right heart failure.
- COPD is usually a progressive disease and 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 to determine when to modify therapy and to identify any complications that may develop.
- Comorbidities are common in COPD and should be actively identified. Comorbidities often complicate the management of COPD, and vice versa.

INITIAL DIAGNOSIS

A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease (**Figure 5.1-1**). The diagnosis should be confirmed by spirometry. The presence of a postbronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted confirms the presence of airflow limitation that is not fully reversible.

Figure 5.1-1. Key Indicators for Considering a Diagnosis of COPD

Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic 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.

Dyspnea that is:	Progressive (worsens over time) Usually worse with exercise Persistent (present every day) Described by the patient as an "increased effort to breathe," "heaviness," "air hunger," or "gasping."
Chronic Cough	May be intermittent and may be unproductive.
Chronic sputum production:	Any pattern of chronic sputum production may indicate COPD.
History of exposure to risk factors, *especially:*	Tobacco smoke. Occupational dusts and chemicals Smoke from home cooking and heating fuels.

Assessment of Symptoms

Although exceptions occur, the general patterns of symptom development in COPD is well established. The main symptoms of patients in *Stage I: Mild COPD* are chronic cough and sputum production. These symptoms can be present for many years before the development of airflow limitation and are often ignored or discounted by patients and attributed to aging or lack of conditioning. As airflow limitation worsens in *Stage II: Moderate COPD*, patients often experience dyspnea, which may interfere with their daily activities[1]. Typically, this is the stage at which they seek medical attention and may be diagnosed with COPD. However, some patients do not experience cough, sputum production, or dyspnea in *Stage I: Mild COPD* or *Stage II: Moderate COPD*, and do not come to medical attention until their airflow limitation becomes more severe or their lung function is worsened acutely by a respiratory tract infection. As airflow limitation worsens and the patient enters *Stage III: Severe COPD*, the symptoms of cough and sputum production typically continue, dyspnea worsens, and additional symptoms heralding complications (such as respiratory failure, right heart failure, weight loss, and arterial hypoxemia) may develop. It is important to note that, since COPD

may be diagnosed at any stage, any of the symptoms described below may be present in a patient presenting for the first time.

Dyspnea. Dyspnea, the hallmark symptom of COPD, is the reason most patients seek medical attention and is a major cause of disability and anxiety associated with the disease. Typical COPD patients describe their dyspnea as a sense of increased effort to breathe, heaviness, air hunger, or gasping[2]. However, the terms used to describe dyspnea vary both by individual and by culture[3]. It is often possible to distinguish the breathlessness of COPD from that due to other causes by analysis of the terms used, although there is considerable overlap with descriptors of bronchial asthma. A simple way to quantify the impact of breathlessness on a patient's health status is the British Medical Research Council (MRC) questionnaire (**Figure 5.1-2**). This questionnaire relates well to other measures of health status[4] and predicts future mortality risk[5].

Figure 5.1-2: Modified Medical Research Council Questionnaire for Assessing the Severity of Breathlessness[4]

PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY)

I only get breathless with strenuous exercise.	☐
I get short of breath when hurrying on the level or walking up a slight hill.	☐
I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
I stop for breath after walking about 100 meters or after a few minutes on the level.	☐
I am too breathless to leave the house or I am breathless when dressing or undressing.	☐

Breathlessness in COPD is characteristically persistent and progressive. Even on "good days" COPD patients experience dyspnea at lower levels of exercise than unaffected people of the same age. Initially, breathlessness is only noted on unusual effort (e.g., walking or running up a flight of stairs) and may be avoided entirely by appropriate behavioral change (e.g., using an elevator). As lung function deteriorates, breathlessness becomes more intrusive, and patients may notice that they are unable to walk at the same speed as other people of the same age or carry out activities that require use of the accessory respiratory muscles (e.g., carrying grocery bags)[6]. Eventually, breathlessness is present during everyday activities (e.g., dressing, washing) or at rest, leaving the patient confined to the home.

Cough. Chronic cough, often the first symptom of COPD to develop[7], is often discounted by the patient as an expected consequence of smoking and/or environmental exposures. Initially, the cough may be intermittent, but later is present every day, often throughout the day. The chronic cough in COPD may be unproductive[8]. In some cases, significant airflow limitation may develop without the presence of a cough. **Figure 5.1-3** lists some of the other causes of chronic cough in individuals with a normal chest X-ray.

Figure 5.1-3. Causes of Chronic Cough with a Normal Chest X-ray

Intrathoracic
- Chronic obstructive pulmonary disease
- Bronchial asthma
- Central bronchial carcinoma
- Endobronchial tuberculosis
- Bronchiectasis
- Left heart failure
- Interstitial lung disease
- Cystic fibrosis

Extrathoracic
- Postnasal drip
- Gastroesophageal reflux
- Drug therapy (e.g., ACE inhibitors)

Sputum production. COPD patients commonly raise small quantities of tenacious sputum after coughing bouts. Regular production of sputum for 3 or more months in 2 consecutive years (in the absence of any other conditions that may explain it) is the epidemiological definition of chronic bronchitis[9], but this is a somewhat arbitrary definition that does not reflect the range of sputum production in COPD patients. Sputum production is often difficult to evaluate because patients may swallow sputum rather than expectorate it, a habit subject to significant cultural and gender variation. Patients producing large volumes of sputum may have underlying bronchiectasis. The presence of purulent sputum reflects an increase in inflammatory mediators[10], and its development may identify the onset of an exacerbation[11].

Wheezing and chest tightness. Wheezing and chest tightness are nonspecific symptoms that may vary between days, and over the course of a single day. These symptoms may be present in *Stage I: Mild COPD*, but are more characteristic of asthma or *Stage III: Severe COPD* and *Stage IV: Very Severe COPD*. Audible wheeze may arise at a laryngeal level and need not be accompanied by auscultatory abnormalities. Alternatively, widespread inspiratory or expiratory wheezes can be present on listening to the chest. Chest tightness often follows exertion, is poorly

localized, is muscular in character, and may arise from isometric contraction of the intercostal muscles. An absence of wheezing or chest tightness does not exclude a diagnosis of COPD, nor does their presence confirm a diagnosis of asthma.

Additional features in severe disease. Weight loss and anorexia are common problems in advanced COPD[12]. They are prognostically important[13] and can also be a sign of other diseases (e.g., tuberculosis, bronchial tumors), and therefore should always be investigated. Cough syncope occurs due to rapid increases in intrathoracic pressure during attacks of coughing. Coughing spells may also cause rib fractures, which are sometimes asymptomatic. Ankle swelling may be the only symptomatic pointer to the development of cor pulmonale. Finally, psychiatric morbidity, especially symptoms of depression and/or anxiety, is common in advanced COPD[14] and merits specific enquiry in the clinical history.

Medical History

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

- *Patient's exposure to risk factors,* such as smoking and occupational or environmental exposures
- *Past medical history*, including asthma, allergy, sinusitis, or nasal polyps; respiratory infections in childhood; other respiratory diseases
- *Family history of COPD or other chronic respiratory disease*
- *Pattern of symptom development:* COPD typically develops in adult life and most patients are conscious of increased breathlessness, more frequent "winter colds," and some social restriction for a number of years before seeking medical help.
- *History of exacerbations or previous hospitalizations for respiratory disorder:* Patients may be aware of periodic worsening of symptoms even if these episodes have not been identified as exacerbations of COPD.
- *Presence of comorbidities,* such as heart disease, malignancies, osteoporosis, and muscloskeletal disorders, which may also contribute to restriction of activity[15].
- *Appropriateness of current medical treatments:* For example, beta-blockers commonly prescribed for heart disease are usually contraindicated in COPD.
- *Impact of disease on patient's life*, including limitation of activity, missed work and economic impact, effect on family routines, 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 usually not present until significant impairment of lung function has occurred[16,17], and their detection has a relatively low sensitivity and specificity. A number of physical signs may be present in COPD, but their absence does not exclude the diagnosis.

Inspection.

- Central cyanosis, or bluish discoloration of the mucosal membranes, may be present but is difficult to detect in artificial light and in many racial groups.
- Common chest wall abnormalities, which reflect the pulmonary hyperinflation seen in COPD, include relatively horizontal ribs, "barrel-shaped" chest, and protruding abdomen.
- Flattening of the hemi-diaphragms may be associated with paradoxical in-drawing of the lower rib cage on inspiration, and widening of the xiphosternal angle.
- Resting respiratory rate is often increased to more than 20 breaths per minute and breathing can be relatively shallow[17].
- Patients commonly show pursed-lip breathing, which may serve to slow expiratory flow and permit more efficient lung emptying[18].
- COPD patients often have resting muscle activation while lying supine. Use of the scalene and sterno-cleidomastoid muscles is a further indicator of respiratory distress.
- Ankle or lower leg edema can be a sign of right heart failure.

Palpation and percussion.

- These are often unhelpful in COPD.
- Detection of the heart apex beat may be difficult due to pulmonary hyperinflation.
- Hyperinflation also leads to downward displacement of the liver and an increase in the ability to palpate this organ without it being enlarged.

Auscultation.

- Patients with COPD often have reduced breath sounds, but this finding is not sufficiently characteristic to make the diagnosis[19].

- The presence of wheezing during quiet breathing is a useful pointer to airflow limitation. However, wheezing heard only after forced expiration has not been validated as a diagnostic test for COPD.
- Inspiratory crackles occur in some COPD patients but are of little help diagnostically.
- Heart sounds are best heard over the xiphoid area.

Measurement of Airflow Limitation (Spirometry)[1]

Spirometry should be undertaken in all patients who may have COPD. It is needed to make a confident diagnosis of COPD and to exclude other diagnoses that may present with similar symptoms. Although spirometry does not fully capture the impact of COPD on a patient's health, it remains the gold standard for diagnosing the disease and monitoring its progression. It is the best standardized, most reproducible, and most objective measurement of airflow limitation available. Good quality spirometric measurement is possible and all health care workers who care for COPD patients should have access to spirometry. **Figure 5.1-4** summarizes some of the factors needed to achieve accurate test results.

Spirometry should measure the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC) and the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second, FEV_1), and the ratio of these two measurements (FEV_1/FVC) should be calculated. Spirometry measurements are evaluated by comparison with reference values[20] based on age, height, sex, and race (use appropriate reference values, e.g., see reference 20).

Figure 5.1-5 shows a normal spirogram and a spirogram typical of patients with mild to moderate COPD. Patients with COPD typically show a decrease in both FEV_1 and FVC. The degree of spirometric abnormality generally reflects the severity of COPD (**Figure 1-2**). The presence of airflow limitation is defined by a postbronchodilator $FEV_1/FVC < 0.70$. This approach to is a pragmatic one in view of the fact that universally applicable reference values for FEV_1 and FVC are not available. Spirometry should be performed after the administration of an adequate dose of a short-acting inhaled bronchodilator (e.g., 400 μg salbutamal) in order to minimize variability Where possible, values should be compared to age-related normal values to avoid over-diagnosis of COPD in the elderly[21]. Using the fixed ratio (FEV_1/FVC) is particularly problematic in older adults since the ratio declines with age leading to the potential for labeling healthy older adults as having COPD. Post- bronchodilator reference values in this population are urgently needed to avoid potential overdiagnosis.

Peak expiratory flow is sometimes used as a measure of airflow limitation, but in COPD may underestimate the degree of airways obstruction[22]. Data from the US National Health and Nutrition Examination Survey suggest that peak expiratory flow has good sensitivity, identifying over 90% of COPD cases that can be diagnosed with spirometry, but because its specificity is weaker it cannot be relied on as the only diagnostic test[23].

Figure 5.1-4. Considerations in Performing Spirometry

Preparation

- Spirometers need calibration on a regular basis.
- Spirometers should produce hard copy to permit detection of technical errors or have an automatic prompt to identify an unsatisfactory test and the reason for it.
- The supervisor of the test needs training in its effective performance.
- Maximal patient effort in performing the test is required to avoid errors in diagnosis and management.

Performance

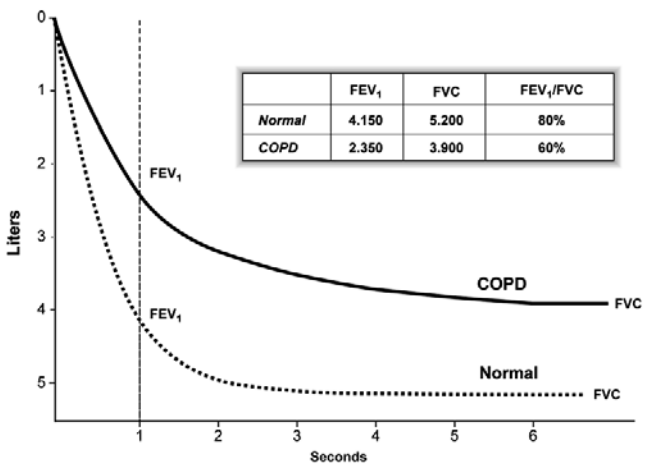
- pirometry should be performed using techniques that meet published standards[24].
- The expiratory volume/time traces should be smooth and free from irregularities.
- The recording should go on long enough for a volume plateau to be reached, which may take more than 15 seconds in severe disease.
- Both FVC and FEV_1 should be the largest value obtained from any of 3 technically satisfactory curves and the FVC and FEV_1 values in these three curves should vary by no more than 5% or 100 ml, whichever is greater.
- The FEV_1/FVC ratio should be taken from the technically acceptable curve with the largest sum of FVC and FEV_1.

Evaluation

- Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race (e.g., see reference 20).
- The presence of a postbronchodilator $FEV_1 < 80\%$ predicted together with an $FEV_1/FVC < 0.70$ confirms the presence of airflow limitation that is not fully reversible.

[1]Spirometry for Diagnosis of COPD: Insert for GOLD Pocket Guide available at http://www.goldcopd.org.

Figure 5.1-5. Normal Spirogram and Spirogram Typical of Patients with Mild to Moderate COPD*



	FEV_1	FVC	FEV_1/FVC
Normal	4.150	5.200	80%
COPD	2.350	3.900	60%

Postbronchodilator FEV_1 is recommended for the diagnosis and assessment of severity of COPD.

The role of screening spirometry in the general population or in a population at risk for COPD is controversial. Both FEV_1 and FVC predict all-cause mortality independent of tobacco smoking, and abnormal lung function identifies a subgroup of smokers at increased risk for lung cancer. This has been the basis of an argument that screening spirometry should be employed as a global health assessment tool[25]. However, there are no data to indicate that screening spirometry is effective in directing management decisions or in improving COPD outcomes in patients who are identified before the development of significant symptoms[26].

Assessment of COPD Severity

Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality (**Figure 1-2**), and the presence of complications such as respiratory failure, right heart failure, weight loss, and arterial hypoxemia.

Although the presence of airflow limitation is key to the assessment of COPD severity, it may be valuable from a public health perspective to identify individuals at risk for the disease before significant airflow limitation develops (**Figure 1-3**). A majority of people with early COPD identified in large studies complained of at least one respiratory symptom, such as cough, sputum production, wheezing, or breathlessness[27,28]. These symptoms may be present at a time of relatively minor or even no spirometric abnormality. While not all individuals with such symptoms will go on to develop COPD[29], the presence of these symptoms should help define a high-risk population that should be targeted for preventive intervention. Much depends on the success of convincing such people, as well as health care workers, that even minor respiratory symptoms are not normal and may be markers of future ill health.

When evaluating symptomatic patients presenting to a physician, the severity of the patient's symptoms and the degree to which they affect his or her daily life, not just the severity of airflow obstruction, are the major determinants of health status[30]. The severity of a patient's breathlessness is important and can be usefully gauged by the MRC scale (**Figure 5.1-2**). Other forms of symptom severity scoring have yet to be validated in different populations and commonly rely on individual clinical judgment, although a clinical COPD questionnaire has been validated in family practice[31].

Objectively measured exercise impairment, assessed by a reduction in self-paced walking distance[32] or during incremental exercise testing in a laboratory[33], is a powerful indicator of health status impairment and predictor of prognosis[30]. The ratio of inspiratory capacity to total lung capacity determined plethysmographically has also been found to be prognostically useful[34]. Similarly, weight loss and reduction in the arterial oxygen tension identify patients at increased risk for mortality[35,36].

A relatively simple approach to identifying disease severity using a combination of most of the above variables has been proposed. The BODE method gives a composite score (Body mass index, Obstruction, Dyspnea and Exercise) that is a better predictor of subsequent survival than any component singly[37], and its properties as a measurement tool are under investigation.

Additional Investigations

For patients diagnosed with *Stage II: Moderate COPD* and beyond, the following additional investigations may be considered:

Bronchodilator reversibility testing. Despite earlier hopes, neither bronchodilator nor oral glucocorticosteroid reversibility testing predicts disease progression, whether judged by decline in FEV_1, deterioration of health status, or frequency of exacerbations[38,39] in patients with a clinical diagnosis of COPD and abnormal spirometry[39]. Small changes in FEV_1 (e.g., < 400 ml) after administration of a bronchodilator do not reliably predict the patient's response to treatment (e.g., change in exercise capacity[40]). Minor variations in initial airway caliber can lead to different classification of reversibility status depending on the day

of testing[39], and the lower the pre-bronchodilator FEV_1, the greater the chance of a patient being classified as reversible even when the 200 ml volume criterion is included.

In some cases (e.g., a patient with an atypical history such as asthma in childhood and regular night waking with cough or wheeze) a clinician may wish to perform a bronchodilator and/or glucocorticosteroid reversibility test and a possible protocol is suggested in **Figure 5.1-6.**

Figure 5.1-6. Bronchodilator Reversibility Testing in COPD

Preparation

- Tests should be performed when patients are clinically stable and free from respiratory infection.
- Patients should not have taken inhaled short-acting bronchodilators in the previous six hours, long-acting bronchodilator n the previous 12 hours, or sustained-release theophylline in the previous 24 hours.

Spirometry

- FEV_1 should be measured before a bronchodilator is given.
- The bronchodilator should be given by metered dose inhaler through a spacer device or by nebulizer to be certain it has been inhaled.
- The bronchodilator dose should be selected to be high on the dose/response curve.
- Possible dosage protocols are 400 μg β_2-agonist, up to 160 μg anticholinergic, or the two combined[20]. FEV_1 should be measured again 10-15 minutes after a short-acting bronchodilator is given; 30-45 minutes after the combination.

Results

- An increase in FEV_1 that is both greater than 200 ml and 12% above the pre-bronchodilator FEV_1 is considered significant[20]. It is usually helpful to report the absolute change as well as the % change from baseline to set the improvement in a clinical context.

Chest X-ray. An abnormal chest X-ray is seldom diagnostic in COPD unless obvious bullous disease is present, but it is valuable in excluding alternative diagnoses and establishing the presence of significant comorbidities such as cardiac failure. Radiological changes associated with COPD include signs of hyperinflation (flattened diaphragm on the lateral chest film, and an increase in the volume of the retrosternal air space), hyperlucency of the lungs, and rapid tapering of the vascular markings. Computed tomography (CT) of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD, high resolution CT (HRCT) scanning might help in the differential diagnosis. In addition, if a surgical procedure such as lung volume reduction is contemplated, a chest CT scan is necessary since the distribution of emphysema is one of the most important determinants of surgical suitability[41].

Arterial blood gas measurement. In advanced COPD, measurement of arterial blood gases while the patient is breathing air is important. This test should be performed in stable patients with $FEV_1 < 50\%$ predicted or with clinical signs suggestive of respiratory failure or right heart failure. Several considerations are important to ensure accurate test results. The inspired oxygen concentration (FiO_2 – normally 21% at sea level) should be noted, a particularly important point if patient is using an O_2-driven nebulizer. Changes in arterial blood gas tensions take time to occur, especially in severe disease. Thus, 20-30 minutes should pass before rechecking the gas tensions when the FiO_2 has been changed, e.g., during an assessment for domiciliary oxygen therapy. Adequate pressure must be applied at the arterial puncture site for at least one minute, as failure to do so can lead to painful bruising.

Alpha-1 antitrypsin deficiency screening. In patients of Caucasian descent 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 or appropriate counseling. A serum concentration of alpha-1 antitrypsin below 15-20% of the normal value is highly suggestive of homozygous alpha-1 antitrypsin deficiency.

Differential Diagnosis

In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques, and it is assumed that asthma and COPD coexist in these patients. In these cases, current management is similar to that of asthma. Other potential diagnoses are usually easier to distinguish from COPD (**Figure 5.1-7**).

Figure 5.1-7. Differential Diagnosis of COPD

Diagnosis	Suggestive Features
COPD	Onset in mid-life. Symptoms slowly progressive. Long history of tobacco smoking. 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. 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.

ONGOING MONITORING AND ASSESSMENT

Visits to health care facilities will increase in frequency as COPD progresses. The type of health care workers seen, and the frequency of visits, will depend on the health care system. Ongoing monitoring and assessment in COPD ensures that the goals of treatment are being met and should include evaluation of: (1) exposure to risk factors, especially tobacco smoke; (2) disease progression and development of complications; (3) pharmacotherapy and other medical treatment; (4) exacerbation history; (5) comorbidities.

Suggested questions for follow-up visits are listed in **Figure 5.1-8**. The best way to detect changes in symptoms and overall health status is to ask the patient the same questions at each visit.

Figure 5.1-8. Suggested Questions for Follow-Up Visits*

Monitor exposure to risk factors:
- Has your exposure to risk factors changed since your last visit?
- Since your last visit, have you quit smoking, or are you still smoking?
- If you are still smoking, how many cigarettes/how much tobacco per day?
- Would you like to quit smoking?
- Has there been any change in your working environment?

Monitor disease progression and development of complications:
- How much can you do before you get short of breath? (Use an everyday example, such as walking up flights of stairs, up a hill, or on flat ground.)
- Has your breathlessness worsened, improved, or stayed the same since your last visit?
- Have you had to reduce your activities because of your breathing or any other symptom?
- Have any of your symptoms worsened since your last visit?
- Have you experienced any new symptoms since your last visit?
- Has your sleep been disrupted by breathlessness or other chest symptoms?
- Since your last visit, have you missed any work/had to see a doctor because of your symptoms?

Monitor pharmacotherapy and other medical treatment:
- What medicines are you taking?
- How often do you take each medicine?
- How much do you take each time?
- Have you missed or stopped taking any regular doses of your medicine for any reason?
- Have you had trouble filling your prescriptions (e.g., for financial reasons, not on formulary)?
- Please show me how you use your inhaler.
- Have you tried any other medicines or remedies?
- Has your treatment been effective in controlling your symptoms?
- Has your treatment caused you any problems?

Monitor exacerbation history:
- Since your last visit, have you had any episodes/times when your symptoms were a lot worse than usual?
- If so, how long did the episode(s) last? What do you think caused the symptoms to get worse? What did you do to control the symptoms?

**These questions are examples and do not represent a standardized*

assessment instrument. The validity and reliability of these questions have not been assessed.

Monitor Disease Progression and Development of Complications

COPD is usually a progressive disease. 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 to determine when to modify therapy and to identify any complications that may develop. As at the initial assessment, follow-up visits should include a physical examination and discussion of symptoms, particularly any new or worsening symptoms.

Pulmonary function. A patient's decline in lung function is best tracked by periodic spirometry measurements although useful information about lung function decline is unlikely from spirometry measurements performed more than once a year. Spirometry should be performed if there is a substantial increase in symptoms or a complication.

Other pulmonary function tests, such as flow-volume loops, diffusing capacity (D_{LCO}) measurements, inspiratory capacity, and measurement of lung volumes are not needed in a routine assessment but can provide information about the overall impact of the disease and can be valuable in resolving diagnostic uncertainties and assessing patients for surgery.

Arterial blood gas measurement. The development of respiratory failure is indicated by a PaO_2 < 8.0 kPa (60 mm Hg) with or without $PaCO_2$ > 6.7 kPa (50 mm Hg) in arterial blood gas measurements made while breathing air at sea level. Screening patients by pulse oximetry and assessing arterial blood gases in those with an oxygen saturation (SaO_2) < 92% is a useful way of selecting patients for arterial blood gas measurement[42]. However, pulse oximetry gives no information about CO_2 tensions.

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.

Assessment of pulmonary hemodynamics. Mild to moderate pulmonary hypertension (mean pulmonary artery pressure ≥ 30 mm Hg) is only likely to be important in patients who have developed respiratory failure. 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.

Diagnosis of right heart failure or cor pulmonale. Elevation of the jugular venous pressure and the presence of pitting ankle edema are often the most useful findings suggestive of cor pulmonale in clinical practice. However, the jugular venous pressure is often difficult to assess in patients with COPD, due to large swings in intrathoracic pressure. Firm diagnosis of cor pulmonale can be made through a number of investigations, including radiography, electrocardiography, echocardiography, radionucleotide scintigraphy, and magnetic resonance imaging. However, all of these measures involve inherent inaccuracies of diagnosis.

CT and ventilation-perfusion scanning. Despite the benefits of being able to delineate pathological anatomy, routine CT and ventilation-perfusion scanning are currently confined to the assessment of COPD patients for surgery. HRCT is currently under investigation as a way of visualizing airway and parenchymal pathology more precisely.

Hematocrit. Polycythemia can develop in the presence of arterial hypoxemia, especially in continuing smokers[43], and can be identified by hematocrit > 55%. Anemia is more prevalent than previously thought, affecting almost a quarter of COPD patients in one hospital series[44]. A low hematocrit indicates a poor prognosis in COPD patients receiving long-term oxygen treatment[45].

Respiratory muscle function. Respiratory muscle function is usually measured by recording the maximum inspiratory and expiratory mouth pressures. More complex measurements are confined to research laboratories. Measurement of inspiratory muscle force is useful in assessing patients when dyspnea or hypercapnia is not readily explained by lung function testing or when peripheral muscle weakness is suspected. This measurement may improve in COPD patients when other measurements of lung mechanics do not (e.g., after pulmonary rehabilitation)[46,47].

Sleep studies. Sleep studies may be indicated when hypoxemia or right heart failure develops in the presence of relatively mild airflow limitation or when the patient has symptoms suggesting the presence of sleep apnea.

Exercise testing. Several types of tests are available to measure exercise capacity, e.g., treadmill and cycle ergometry in the laboratory – or six-minute and shuttle walking tests , but these are primarily used in conjunction with pulmonary rehabilitation programs.

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

During periodic assessments, health care workers should question the patient and evaluate any records of exacerbations, both self-treated and those treated by other health care providers. 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. Specific inquiry into unscheduled visits to providers, telephone calls for assistance, and use of urgent or emergency care facilities may be helpful. 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. The clinician then can request summaries of all care received to facilitate continuity of care.

Monitor Comorbidities

Comorbidities are common in COPD. Some may be an indirect result of COPD, arising independently but more likely to occur when COPD is present, e.g., ischemic heart disease, bronchial carcinoma, osteoporosis. Other comorbid conditions may coexist with COPD because they become prevalent as part of the aging process, e.g., arthritis, diabetes, reflux esophagitis. All comorbid conditions become harder to manage when COPD is present, either because COPD adds to the total level of disability or because COPD therapy adversely affects the comorbid disorder. All comorbid conditions amplify the disability associated with COPD and can potentially complicate its management. Until more integrated guidance about disease management for specific comorbid problems becomes available, the focus should be on identification and management of these individual problems in line with local treatment guidance.

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 in most people to reduce the risk of developing COPD and stop its progression (**Edivence A**).
- Comprehensive tobacco control policies and programs with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel.
- Efforts to reduce smoking through public health initiatives should also focus on passive smoking to minimize risks for nonsmokers.
- 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.
- Reducing the risk from indoor and outdoor air pollution is feasible and requires a combination of public policy and protective steps taken by individual patients.

INTRODUCTION

Identification, reduction, and control of risk factors are important steps toward prevention and treatment of any disease. In the case of COPD, these factors include tobacco smoke, occupational exposures, and indoor and outdoor air pollution and irritants. Since cigarette smoking is the most commonly encountered risk factor for COPD worldwide, tobacco control (smoking prevention) programs should be implemented and smoking cessation programs should be readily available and encouraged for all individuals who smoke. Reduction of total personal exposure to occupational dusts, fumes, and gases and to indoor and outdoor air pollutants is also an important goal to prevent the onset and progression of COPD.

TOBACCO SMOKE

Smoking Prevention

Comprehensive tobacco control policies and programs with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel, including health care providers, community activities, schools, and radio, television, and print media. National and local campaigns should be undertaken to reduce exposure to tobacco smoke in public forums. Such bans are proving to be workable and to result in measurable gains in respiratory health[48]. Legislation to establish smoke-free schools, public facilities, and work environments should be developed and implemented by government officials and public health workers, and encouraged by the public. Smoking prevention programs should target all ages, including young children, adolescents, young adults, and pregnant women. Interventions to prevent smoking uptake and maximize cessation should be implemented at every level of the health care system. Physicians and public health officials should encourage smoke-free homes.

An important step toward a collective international response to tobacco-caused death and disease was taken in 1996 by the World Health Organization with the implementation of an International Framework Convention on Tobacco Control (**Figure 5.2-1**).

Figure 5.2-1. World Health Organization: International Framework Convention on Tobacco Control

In May, 1996, to address the global tobacco pandemic, the Forty-ninth World Health Assembly requested the Director-General of the World Health Organization (WHO) to initiate the development of an international framework convention for tobacco control. Included as part of this framework convention is a strategy to encourage Member States to move progressively towards the adoption of comprehensive tobacco control policies and to deal with aspects of tobacco control that transcend national boundaries.

Information about the work of the WHO tobacco control program can be found at http://www.who.int/tobacco/resources/publications/fctc/en/index.html

Environmental tobacco smoke exposure is also an important cause of respiratory symptoms and increased risk for COPD, especially in partners and children of smokers[49]. Long-term indoor exposure, combined with crowded living conditions in poorly ventilated homes, adds to the total burden of particulate exposure and increases the risk of developing COPD[50]. Efforts to reduce smoking through public health initiatives should also focus on passive smoking to minimize risks for nonsmokers. Partners and parents should not smoke in the immediate vicinity of nonsmokers or children, nor in enclosed spaces such as cars and poorly ventilated rooms that expose others to increased risk.

The first exposure to cigarette smoke may begin in utero when the fetus is exposed to blood-borne metabolites from the mother[51]. Education to reduce *in utero* risks for unborn children is also of great importance to prevent the effects of maternal smoking in reducing lung growth and causing airways disease in early and later life[52,53]. Neonates and infants may also be exposed passively to tobacco smoke in the home if a family member smokes. Children less than 2 years old who are passively exposed to cigarette smoke have an increased prevalence of respiratory infections, and are at a greater risk of developing chronic respiratory symptoms later in life[53,54].

Smoking Cessation

Smoking cessation is the single most effective—and cost effective—way to reduce exposure to COPD risk factors. Quitting smoking can prevent or delay the development of airflow limitation, or reduce its progression[55], and can have a substantial effect on subsequent mortality[56]. All smokers—including those who may be at risk for COPD as well as those who already have the disease—should be offered the most intensive smoking cessation intervention feasible.

Smoking cessation interventions are effective in both sexes, in all racial and ethnic groups, and in pregnant women. Age influences quit rates, with young people less likely to quit, but nevertheless smoking cessation programs can be effective in all age groups. International data on the economic impact of smoking cessation are strikingly consistent: *investing resources in smoking cessation programs is cost effective in terms of medical and societal costs per life-year gained.* Effective interventions include nicotine replacement with transdermal patches, gums, and nasal sprays; counseling from physicians and other health professionals (with or without nicotine replacement therapy); self-help and group programs; and community-based stop-smoking challenges.

A review of data from a number of countries estimated the median societal cost of various smoking cessation interventions at $990 to $13,000 (US) per life-year gained[57]. Smoking cessation programs are a particularly good value for the UK National Health Service, with costs from £212 to £873 (US $320 to $1,400) per life-year gained[58].

The role of health care providers in smoking cessation. A successful smoking cessation strategy requires a multifaceted approach, including public policy, information dissemination programs, and health education through the media and schools[59]. However, health care providers, including physicians, nurses, dentists, psychologists, pharmacists, and others, are key to the delivery of smoking cessation messages and interventions. Involving as many of these individuals as possible will help. Health care workers should encourage all patients who smoke to quit, even those patients who come to the health care provider for unrelated reasons and do not have symptoms of COPD, evidence of airflow limitation, or other smoking-related disease. Guidelines for smoking cessation entitled *Treating Tobacco Use and Dependence: A Clinical Practice Guideline* were published by the US Public Health Service[60]. The major conclusions are summarized in **Figure 5.2-2.**

Figure 5.2-2. US Public Health Service Report: Treating Tobacco Use and Dependence: A Clinical Practice Guideline—Major Findings and Recommendations[60]

1. Tobacco dependence is a chronic condition that warrants repeated treatment until long-term or permanent abstinence is achieved.
2. Effective treatments for tobacco dependence exist and all tobacco users should be offered these treatments.
3. Clinicians and health care delivery systems must institutionalize the consistent identification, documentation, and treatment of every tobacco user at every visit.
4. Brief smoking cessation counseling is effective and every tobacco user should be offered such advice at every contact with health care providers.
5. There is a strong dose-response relation between the intensity of tobacco dependence counseling and its effectiveness.
6. Three types of counseling were found to be especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment.
7. Five first-line pharmacotherapies for tobacco dependence—bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch—are effective and at least one of these medications should be prescribed in the absence of contraindications.
8. Tobacco dependence treatments are cost effective relative to other medical and disease prevention interventions.

The Public Health Service Guidelines recommend a five-step program for intervention (**Figure 5.2-3**), which provides a strategic framework helpful to health care providers interested in helping their patients stop smoking[60-63]. The guidelines emphasize that tobacco dependence is a chronic disease (**Figure 5.2-4**)[60] and urge clinicians to recognize that relapse is common and reflects the chronic nature of dependence and addiction, not failure on the part of the clinician or the patient.

Most individuals go through several stages before they stop smoking (**Figure 5.2-5**)[59]. It is often helpful for the clinician to assess a patient's readiness to quit in order to determine the most effective course of action at that time. The clinician should initiate treatment if the patient is ready to quit. For a patient not ready to make a quit attempt, the clinician should provide a brief intervention designed to promote the motivation to quit.

Figure 5.2-3. Brief Strategies to Help the Patient Willing to Quit[60-63]

1. ASK: Systematically identify all tobacco users at every visit.

Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented.

2. ADVISE: Strongly urge all tobacco users to quit.

In a clear, strong, and personalized manner, urge every tobacco user to quit.

3. ASSESS: Determine willingness to make a quit attempt.

Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).

4. ASSIST: Aid the patient in quitting.

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.

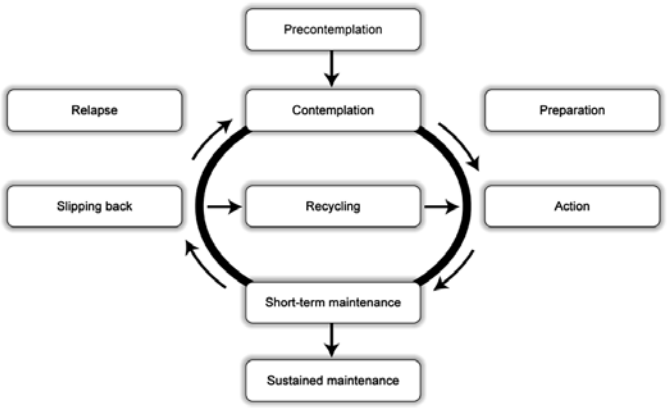
5. ARRANGE: Schedule follow-up contact.

Schedule follow-up contact, either in person or via telephone.

Figure 5.2-4. Tobacco Dependence as a Chronic Disease[10]

- For most people, tobacco dependence results in true drug dependence comparable to dependence caused by opiates, amphetamines, and cocaine.
- Tobacco dependence is almost always a chronic disorder that warrants long-term clinical intervention as do other addictive disorders. Failure to appreciate the chronic nature of tobacco dependence may impair the clinician's motivation to treat tobacco use consistently in a long-term fashion.
- Clinicians must understand that tobacco dependence is a chronic condition requiring sustained effort focused on simple counseling advice, support, and appropriate pharmacotherapy, and ongoing support for recent quitters to prevent relapse.
- Relapse is common, which is the nature of dependence and not the failure of the clinician or the patient.

Figure 5.2-5. Stages of Change Model



Counseling. Counseling delivered by physicians and other health professionals significantly increases quit rates over self-initiated strategies[64]. Even a brief (3-minute) period of counseling to urge a smoker to quit results in smoking cessation rates of 5-10%[65]. At the very least, this should be done for every smoker at every health care provider visit[65,66]. Education in how to offer optimal smoking cessation advice and support should be a mandatory element of curricula for health professionals.

There is a strong dose-response relationship between counseling intensity and cessation success[18,19]. Ways to intensify treatment include increasing the length of the treatment session, the number of treatment sessions, and the number of weeks over which the treatment is delivered. Sustained quit rates of 10.9% at 6 months have been achieved when clinician tutorials and feed-back are linked to counseling sessions[67]. With more complex interventions (for example, controlled clinical trials that include skills training, problem solving, and psychosocial support), quit rates can reach 20-30%[68]. In a multicenter controlled clinical trial, a combination of physician advice, group support, skills training, and nicotine replacement therapy achieved a quit rate of 35% at 1 year and a sustained quit rate of 22% at 5 years[55].

Both individual and group counseling are effective formats for smoking cessation programs. Several particular items of counseling content seem to be especially effective, including problem solving, general skills training, and provision of intra-treatment support. The important elements in the support aspect of successful treatment programs are shown in **Figure 5.2-6**[59,60]. The common subjects covered in successful problem solving/skills training programs include:

- Recognition of danger signals likely to be associated with the risk of relapse, such as being around other smokers, psychosocial stress, being under time pressure, getting into an argument, drinking alcohol, and negative moods
- Enhancement of skills needed to handle these situations, such as learning to anticipate and manage or avoid a particular stress
- Basic information about smoking and successful quitting, such as the nature and time course of withdrawal, the addictive nature of smoking, and the fact that any return to smoking, including even a single puff, increases the likelihood of a relapse

Systematic programs to sustain smoking cessation should be implemented in health care settings[17].

Pharmacotherapy. Numerous effective pharmacotherapies for smoking cessation now exist[59-61], and pharmacotherapy is recommended when counseling is not sufficient to help patients quit smoking. 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.

Nicotine replacement products. 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[60,69]. Nicotine replacement therapy is more effective when combined with counseling and behavior therapy[70], although nicotine patch or nicotine gum consistently increases smoking cessation rates regardless of the level of additional behavioral or psychosocial interventions. Medical contraindications to nicotine replacement therapy include unstable coronary artery disease, untreated peptic ulcer disease, and recent myocardial infarction or stroke[59]. Specific studies do not support the use of nicotine replacement therapy for longer than 8 weeks, although some patients may require extended use to prevent relapse and, in some studies, use of multiple nicotine replacement therapy modalities has been shown to be more effective than only one[60,71].

All forms of nicotine replacement therapy are significantly more effective than placebo. Every effort should be made to tailor the choice of replacement therapy to the individual's culture and lifestyle to improve adherence. The patch is generally favored over the gum because it requires less training for effective use and is associated with fewer compliance problems. No data are available to help clinicians tailor nicotine patch regimens to the intensity of cigarette smoking. In all cases it seems generally appropriate to start with the higher dose patch. For most patches, which come in three different doses, patients should use the highest dose for the first four weeks and drop to progressively lower doses over an eight-week period. Where only two doses are available, the higher dose should be used for the first four weeks and the lower dose for the second four weeks.

When using nicotine gum, the patient needs to be advised that absorption occurs through the buccal mucosa. For this reason, the patient should be advised to chew the gum for a while and then put the gum against the inside of the cheek to allow absorption to occur and prolong the release of nicotine. Continuous chewing produces secretions that are swallowed rather than absorbed through the buccal mucosa, results in little absorption, and can cause nausea. Acidic beverages, particularly coffee, juices, and soft drinks, interfere with the absorption of nicotine. Thus, the patient needs to be advised that eating or drinking anything except water should be avoided for 15 minutes before and during chewing. Although nicotine gum is an effective smoking cessation treatment, problems with compliance, ease of use, social acceptability, risk of developing temporomandibular joint symptoms, and unpleasant taste have been noted. In highly dependent smokers, the 4 mg gum is more effective than the 2 mg gum[72].

Other pharmacotherapy. The antidepressants bupropion[73] and nortriptyline have also been shown to increase long-term quit rates[59,69,74], but should always be used as one element in a supportive intervention program rather than on their own. Although more studies need to be conducted with these medications, a randomized controlled trial with counseling and support showed quit rates at one year of 30% with sustained-release bupropion alone and 35% with sustained-release bupropion plus nicotine patch[73]. The effectiveness of the antihypertensive drug clonidine is limited by side effects[69].

Varenicline, a nicotinic acetylcholine receptor partial agonist that aids smoking cessation by relieving nicotine withdrawal symptoms and reducing the rewarding properties of nicotine has been demonstrated to be safe and efficacious[75-77].

OCCUPATIONAL EXPOSURES

In the United States, it has been estimated that up to 19% of COPD in smokers and up to 31% of COPD in nonsmokers may be attributable to occupational dust and fume exposure[78-81], and the burden may be higher in countries where there is higher exposure to inhaled particles, fumes and gases. Many occupations have been shown to be associated with increased risk of developing COPD, particularly those that involve exposure

to fumes and mineral and biological dusts. 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[82-84]:

- Implement, monitor and enforce strict, legally mandated control of airborne exposure in the workplace.
- Initiate intensive and continuing education of exposed workers, industrial managers, health care workers, primary care physicians, and legislators.
- Educate employers, workers, and policymakers on how cigarette smoking aggravates occupational lung diseases and why efforts to reduce smoking where a hazard exists are important.

The main 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 surveillance and early case detection, is also of great importance. Both approaches are necessary to improve the present situation and to reduce the burden of lung disease. Although studies as yet have not been done to demonstrate reduced burden of disease, it is the logical consequence of effective strategies to reduce workplace exposure to respiratory irritants and toxic inhalants.

INDOOR AND OUTDOOR AIR POLLUTION

Individuals experience diverse indoor and outdoor environments throughout the day, each of which has its own unique set of air contaminants and particulates that cause adverse effects on lung function[80].

Although outdoor and indoor air pollution are generally considered separately, the concept of total personal exposure may be more relevant for COPD. Reducing the risk from indoor and outdoor air pollution is feasible and requires a combination of public policy and protective steps taken by individual patients. Reduction of exposure to smoke from biomass fuel, particularly among women and children, is a crucial goal to reduce the prevalence of COPD worldwide. Although efficient non-polluting cooking stoves have been developed, their adoption has been slow due to social customs and cost.

Regulation of Air Quality

At the national level, achieving a set level of air quality standards should be a high priority; this goal will normally require legislative action. Details on setting and maintaining air quality goals are beyond the scope of this document, but public policy to reduce vehicle and industrial emissions to safe levels is an urgent priority to reduce the development of COPD as well as symptoms, exacerbations, and hospital admissions in those with disease. Understanding health risks posed by local air pollution sources may be difficult and requires skills in community health, toxicology, and epidemiology. Local physicians may become involved through concerns about the health of their patients or as advocates for the community's environment.

Steps for Health Care Providers/Patients

The health care provider should consider COPD risk factors including smoking history, family history, exposure to indoor/outdoor pollution) and socioeconomic status for each individual patient. Some steps to consider:

Individuals at risk for COPD:

- Patients should be counseled concerning the nature and degree of their risk for COPD.
- If various solid fuels are used for cooking and heating, adequate ventilation should be encouraged.
- Respiratory protective equipment has been developed for use in the workplace in order to minimize exposure to toxic gases and particles. Under most circumstances, vigorous attempts should be made to reduce exposure through reducing workplace emissions and improving ventilation measures, rather than simply by using respiratory protection to reduce the risks of ambient air pollution.
- Ventilation and interventions to meet safe air quality standards in the workplace offer the greatest opportunity to reduce worker exposure to known atmospheric pollutants and reduce the risk of developing COPD, although to date there are no studies to quantify these benefits.

Patients who have been diagnosed with COPD:

- Persons with advanced COPD should monitor public announcements of air quality and be aware that staying indoors when air quality is poor may help reduce their symptoms.
- The use of medication should follow the usual clinical indications; therapeutic regimens should not be adjusted because of the occurrence of a pollution episode without evidence of worsening of symptoms or lung function.
- Those who are at high risk should avoid vigorous exercise outdoors during pollution episodes.
- Air cleaners have not been shown to have health benefits, whether directed at pollutants generated by indoor sources or at those brought in with outdoor air.

COMPONENT 3: MANAGE STABLE COPD

KEY POINTS:

- The overall approach to managing stable COPD should be individualized to address symptoms and improve quality of life.
- For patients with COPD, health education plays an important role in smoking cessation (**Evidence A**) and can also play a role in improving skills, ability to cope with illness and health status.
- None of the existing medications for COPD have 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 and exacerbations.
- The principal bronchodilator treatments are β_2-agonists, anticholinergics, and methylxanthines used singly or in combination (**Evidence A**).
- Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (**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**).
- In COPD patients influenza vaccines can reduce serious illness (**Evidence A**). Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older and for COPD patients younger than age 65 with an FEV_1 < 40% predicted (**Evidence B**).
- 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 an increase in treatment, depending on the severity of the disease and the clinical status of the patient. The step-down approach used in the chronic treatment of asthma is not applicable to COPD since COPD is usually stable and very often progressive. Management of COPD involves several objectives (*see Chapter 5, Introduction*) that should be met with minimal side effects from treatment. It is based on an individualized assessment of disease severity (**Figure 5.3-1**) and response to various therapies.

Figure 5.3-1. Factors Affecting the Severity of COPD

- Severity of symptoms
- Severity of airflow limitation
- Frequency and severity of exacerbations
- Presence of one or more complications
- Presence of respiratory failure
- Presence of comorbid conditions
- General health status
- Number of medications needed to manage the disease

The classification of severity of stable COPD incorporates an individualized assessment of disease severity and therapeutic response into the management strategy. The severity of airflow limitation (**Figure 1-2**) provides a general guide to the use of some treatments, but the selection of therapy is predominantly determined by the patient's symptoms and clinical presentation. Treatment also 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 is generally regarded as an essential component of care for any chronic disease, the role of education in COPD has been poorly studied. Assessment of the value of education in COPD may be difficult because of the relatively long time required to achieve improvements in objective measurements of lung function.

Studies that have been done indicate that patient education alone does not improve exercise performance or lung function[85-88] (**Evidence B**), but it can play a role in improving skills, ability to cope with illness, and health status[89]. These outcomes are not traditionally measured in clinical trials, but they may be most important in COPD where even pharmacologic interventions generally confer only a small benefit in terms of lung function.

Patient education regarding smoking cessation has the greatest capacity to influence the natural history of COPD. Evaluation of the smoking cessation component in a long-term, multicenter study indicates that if effective resources and time are dedicated to smoking cessation, 25% long-term quit rates can be maintained[55] (**Evidence A**). Education also improves patient response to exacerbations[90,91] (**Evidence B**). Prospective end-of-life discussions can lead to understanding of advance directives and effective therapeutic decisions at the end of life[92] (**Evidence B**).

Ideally, educational messages should be incorporated into all aspects of care for COPD and may take place in many settings: consultations with physicians or other health care workers, home-care or outreach programs, and comprehensive pulmonary rehabilitation programs.

Goals and Educational Strategies

It is vital for patients with COPD to understand the nature of their disease, risk factors for progression, and their role and the role of health care workers in achieving optimal management and health outcomes. Education should be tailored to the needs and environment of the individual 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 caregivers.

In managing COPD, open communication between patient and physician is essential. In addition to being empathic, attentive and communicative, health professionals should pay attention to patients' fears and apprehensions, focus on educational goals, tailor treatment regimens to each individual patient, anticipate the effect of functional decline, and optimize patients' practical skills.

Several specific education strategies have been shown to improve patient adherence to medication and management regimens. In COPD, adherence does not simply refer to whether patients take their medication appropriately. It also covers a range of nonpharmacologic treatments, e.g., maintaining an exercise program after pulmonary rehabilitation, undertaking and sustaining smoking cessation, and using devices such as nebulizers, spacers, and oxygen concentrators properly.

Components of an Education Program

The topics that seem most appropriate for an education program 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 during exacerbations; and advance directives and end-of-life issues (**Figure 5.3-2**). Education should be part of consultations with health care workers beginning at the time of first assessment for COPD and continuing with each follow-up visit. The intensity and content of these educational messages should vary depending on the severity of the patient's disease. In practice, a patient often poses a series of questions to the physician (**Figure 5.3-3**). It is important to answer these questions fully and clearly, as this may help make treatment more effective.

Figure 5.3-2. Topics for Patient Education

For all patients:

- Information and advice about reducing risk factors

Stage I: Mild COPD through Stage III: Severe COPD
Above topic, plus:

- Information about the nature of COPD
- Instruction on how to use inhalers and other treatments
- Recognition and treatment of exacerbations
- Strategies for minimizing dyspnea

Stage IV: Very Severe COPD
Above topics, plus:

- Information about complications
- Information about oxygen treatment
- Advance directives and end-of-life decisions

Figure 5.3-3. Examples of Patient Questions

- *What is COPD?*
- *What causes COPD?*
- *How will it affect me?*
- *Can it be treated?*
- *What will happen if my disease gets worse?*
- *What will happen if I need to be admitted to the hospital?*
- *How will I know when I need oxygen at home?*
- *What if I do not wish to be admitted to intensive care for ventilation?*

Answers to these questions can be developed from this document and will depend on local circumstances. In all cases, it is important that answers are clear and use terminology that the patient understands.

There are several different types of educational programs, ranging from simple distribution of printed materials, to teaching sessions designed to convey information about COPD, to workshops designed to train patients in specific skills (e.g., self-management). In general, case-management approaches to medical problems have been somewhat disappointing[93]. However, COPD patients recruited to a comprehensive COPD education program in Canada had significantly fewer exacerbations and hospitalizations. and used fewer health care resources[94]. These encouraging results require replication in other health care systems and patient groups.

Although printed materials may be a useful adjunct to other educational messages, passive dissemination of printed materials alone does not improve skills or health outcomes. Education is most effective when it is interactive and conducted in small workshops[88] (**Evidence B**) designed to improve both knowledge and skills. Behavioral approaches such as cognitive therapy and behavior modification lead to more effective self-management skills and maintenance of exercise programs.

Cost Effectiveness of Education Programs for COPD Patients

The cost effectiveness of education programs for COPD patients is highly dependent on local factors that influence the cost of access to medical services and that will vary substantially between countries. In one cost-benefit analysis of education provided to hospital inpatients with COPD[95], an information package resulted in increased knowledge of COPD and reduced use of health services, including reductions of hospital readmissions and general practice consultations. The education package involved training patients to increase knowledge of COPD, medication usage, precautions for exacerbations, and peak flow monitoring technique. However, this study was undertaken in a heterogeneous group of patients—65% were smokers and 88% were judged to have an asthmatic component to their disease—and these findings may not hold true for a "pure" COPD population. In a study of mild to moderate COPD patients at an outpatient clinic, patient education involving one 4-hour group session followed by one to two individual sessions with a nurse and physiotherapist improved patient outcomes and reduced costs in a 12-month follow-up[96].

Although a healthy lifestyle is important, and should be encouraged, additional studies are needed to identify specific components of self-management programs that are effective[97].

PHARMACOLOGIC TREATMENT

Overview of the Medications

Pharmacologic therapy 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 have been shown to modify the long-term decline in lung function that is the hallmark of this disease[55,98-100] (**Evidence A**). However, this should not preclude efforts to use medications to control symptoms. Since COPD is usually progressive, recommendations for the pharmacological treatment of COPD reflect the following general principles:

- Treatment tends to be cumulative with more medications being required as the disease state worsens.
- Regular treatment needs to be maintained at the same level for long periods of time unless significant side effects occur or the disease worsens.
- Individuals differ in their response to treatment and in the side effects they report during therapy. Careful monitoring is needed over an appropriate period to ensure that the specific aim of introducing a therapy has been met without an unacceptable cost to the patient. The effect of therapy in COPD may occur sooner after treatment with bronchodilators and inhaled glucocorticosteroids than previously thought[101], although at present, there is no effective way to predict whether or not treatment will reduce exacerbations.

The medications are presented in the order in which they would normally be introduced in patient care, based on the level of disease severity and clinical symptoms. However, each treatment regimen needs to be patient-specific as the relationship between the severity of symptoms and the severity of airflow limitation is influenced by other factors, such as the frequency and severity of exacerbations, the presence of one or more complications, the presence of respiratory failure, comorbidities (cardiovascular disease, sleep-related disorders, etc.), and general health status.

The classes of medications commonly used in treating COPD are shown in **Figure 5.3-4.** The choice within each class depends on the availability of medication and the patient's response.

Figure 5-3-4. Commonly Used Formulations of Drugs used in COPD					
Drug	**Inhaler (μg)**	**Solution for Nebulizer (mg/ml)**	**Oral**	**Vials for Injection (mg)**	**Duration of Action (hours)**
β_2-agonists					
Short-acting					
Fenoterol	100-200 (MDI)	1	0.05% (Syrup)		4-6
Salbutamol (albuterol)	100, 200 (MDI & DPI)	5	5mg (Pill) Syrup 0.024%	0.1, 0.5	4-6
Terbutaline	400, 500 (DPI)	–	2.5, 5 (Pill)	0.2, 0.25	4-6
Long-acting					
Formoterol	4.5–12 (MDI & DPI)				12+
Salmeterol	25-50 (MDI & DPI)				12+
Anticholinergics					
Short-acting					
Ipratropium bromide	20, 40 (MDI)	0.25-0.5			6-8
Oxitropium bromide	100 (MDI)	1.5			7-9
Long-acting					
Tiotropium	18 (DPI)				24+
Combination short-acting β_2-agonists plus anticholinergic in one inhaler					
Fenoterol/Ipratropium	200/80 (MDI)	1.25/0.5			6-8
Salbutamol/Ipratropium	75/15 (MDI)	0.75/4.5			6-8
Methylxanthines					
Aminophylline			200-600 mg (Pill)	240 mg	Variable, up to 24
Theophylline (SR)			100-600 mg (Pill)		Variable, up to 24
Inhaled glucocorticosteroids					
Beclomethasone	50-400 (MDI & DPI)	0.2-0.4			
Budesonide	100, 200, 400 (DPI)	0.20, 0.25, 0.5			
Fluticasone	50-500 (MDI & DPI)				
Triamcinolone	100 (MDI)	40		40	
Combination long-acting β_2-agonists plus glucocorticosteroids in one inhaler					
Formoterol/Budesonide	4.5/160, 9/320 (DPI)				
Salmeterol/Fluticasone	50/100, 250, 500 (DPI) 25/50, 125, 250 (MDI)				
Systemic glucocorticosteroids					
Prednisone			5-60 mg (Pill)		
Methyl-prednisolone			4, 8, 16 mg (Pill)		

Bronchodilators

Medications that increase the FEV_1 or change other spirometric variables, usually by altering airway smooth muscle tone, are termed bronchodilators[102], since the improvements in expiratory flow reflect widening of the airways rather than changes in lung elastic recoil. Such drugs improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise[103], and improve exercise performance. The extent of these changes, especially in more advanced disease, is not easily predictable from the improvement in FEV_1[104,105]. Regular bronchodilation with drugs that act primarily on airway smooth muscle does not modify the decline of function in *Stage I: Mild COPD* or, by inference, the prognosis of the disease[6] (**Evidence B**).

Bronchodilator medications are central to the symptomatic management of COPD[106-109] (**Evidence A**) (**Figure 5.3-5**). 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. The side effects of bronchodilator therapy are pharmacologically predictable and dose dependent. Adverse effects are less likely, and resolve more rapidly after treatment withdrawal, with inhaled than with oral treatment. However, COPD patients tend to be older than asthma patients and more likely to have comorbidities, so their risk of developing side effects is greater.

When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential. The choice of inhaler device will depend on availability, cost, the prescribing physician, and the skills and ability of the patient. COPD patients may have more problems in effective coordination and find it harder to use a simple metered-dose inhaler (MDI) than do healthy volunteers or younger asthmatics. It is essential to ensure that inhaler technique is correct and to re-check this at each visit.

Alternative breath-activated or spacer devices are available for most formulations. Dry powder inhalers (DPIs) may be more convenient and possibly provide improved drug deposition, although this has not been established in COPD. In general, particle deposition will tend to be more central with the fixed airflow limitation and lower inspiratory flow rates in COPD[110,111]. Wet nebulizers are not recommended for regular treatment because they are more expensive and require appropriate maintenance[112].

Figure 5.3-5. Bronchodilators in Stable COPD

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

Dose-response relationships using the FEV_1 as the outcome are relatively flat with all classes of bronchodilators[106-109]. Toxicity is also dose related. Increasing the dose of either a β_2-agonist or an anticholinergic by an order of magnitude, especially when given by a wet nebulizer, appears to provide subjective benefit in acute episodes[113] (**Evidence B**) but is not necessarily helpful in stable disease[114] (**Evidence C**).

All categories of bronchodilators have been shown to increase exercise capacity in COPD, without necessarily producing significant changes in FEV_1[115-118] (**Evidence A**). Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators[119-122] (**Evidence A**).

Regular use of a long-acting β_2-agonist[120] or a short- or long-acting anticholinergic improves health status[119-121]. Treatment with a long-acting inhaled anti-cholinergic drug reduces the rate of COPD exacerbations[123] and improves the effectiveness of pulmonary rehabilitation[124]. Theophylline is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred when available. All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations.

β_2-agonists. The principal action of β_2-agonists is to relax airway smooth muscle by stimulating β_2-adrenergic receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. Oral therapy is slower in onset and has more side effects than inhaled treatment[125] (**Evidence A**).

Inhaled β_2-agonists have a relatively rapid onset of bronchodilator effect although this is probably slower in COPD than in asthma. The bronchodilator effects of short-acting β_2-agonists usually wear off within 4 to 6 hours[126,127] (**Evidence A**). For single-dose, as-needed use in COPD, there appears to be no advantage in using levalbuterol over conventional nebulized bronchodilators[128]. Long-acting inhaled β_2-agonists, such as salmeterol and formoterol, show a duration of effect of 12 hours or more with no loss of effectiveness overnight or with regular use in COPD patients[129-132] (**Evidence A**).

Adverse effects. Stimulation of β_2-adrenergic receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in very susceptible patients, although this appears to be a remarkably rare event with inhaled therapy. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of β_2-agonists, whatever the route of administration, and this limits the dose that can be tolerated. Although hypokalemia can occur, especially

when treatment is combined with thiazide diuretics[133], and oxygen consumption can be increased under resting conditions[134], these metabolic effects show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO_2 occur after administration of both short-and long-acting β_2-agonists[135], but the clinical significance of these changes is doubtful. Despite the concerns raised some years ago, further detailed study has found no association between β_2-agonist use and an accelerated loss of lung function or increased mortality in COPD.

Anticholinergics. The most important effect of anticholinergic medications, such as ipratropium, oxitropium and tiotropium bromide, in COPD patients appears to be blockage of acetylcholine's effect on M3 receptors. Current short-acting drugs also block M2 receptors and modify transmission at the pre-ganglionic junction, although these effects appear less important in COPD[136]. The long-acting anticholinergic tiotropium has a pharmacokinetic selectivity for the M3 and M1 receptors[137]. The bronchodilating effect of short-acting inhaled anticholinergics lasts longer than that of short-acting β_2-agonists, with some bronchodilator effect generally apparent up to 8 hours after administration[126] (**Evidence A**). Tiotropium has a duration of action of more than 24 hours[119,138,139] (**Evidence A**).

Adverse effects. Anticholinergic drugs are poorly absorbed which limits the troublesome systemic effects seen with atropine. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of the mouth. Twenty-one days of inhaled tiotropium, 18 μg/day as a dry powder, does not retard mucus clearance from the lungs[140]. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal relationship. A bitter, metallic taste is reported by some patients using ipratropium. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported and requires further investigation[141].

Use of wet nebulizer solutions with a face mask has been reported to precipitate acute glaucoma, probably by a direct effect of the solution on the eye. Mucociliary clearance is unaffected by these drugs, and respiratory infection rates are not increased.

Methylxanthines. Controversy remains about the exact effects of xanthine derivatives. They may act as non-selective phosphodiesterase inhibitors, but have also been reported to have a range of non-bronchodilator actions, the significance of which is disputed[142-146].

Data on duration of action for conventional, or even slow-release, xanthine preparations are lacking in COPD. Changes in inspiratory muscle function have been reported in patients treated with theophylline[142], but whether this reflects changes in dynamic lung volumes or a primary effect on the muscle is not clear (**Evidence B**). All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations. Theophylline is effective in COPD but, due to its potential toxicity, inhaled bronchodilators are preferred when available.

Adverse effects. Toxicity is dose related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given[144,145] (**Evidence A**). Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include the development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). More common and less dramatic side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum theophylline. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental).

Theophylline, the most commonly used methylxanthine, is metabolized by cytochrome P450 mixed function oxidases. Clearance of the drug declines with age. Many other physiological variables and drugs modify theophylline metabolism; some of the potentially important interactions are listed in **Figure 5.3-6.**

Figure 5.3-6. Drugs and Physiological Variables that Affect Theophylline Metabolism in COPD

Increased
- Tobacco smoking
- Anticonvulsant drugs
- Rifampicin
- Alcohol

Decreased
- Old age
- Arterial hypoxemia (PaO_2 < 6.0 kPa, 45 mm Hg)
- Respiratory acidosis
- Congestive cardiac failure
- Liver cirrhosis
- Erythromycin
- Quinolone antibiotics
- Cimetidine (not ranitidine)
- Viral infections
- Herbal remedies (St. John's Wort)

Combination bronchodilator therapy. Combining broncho- dilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects. For example, a combination of a short-acting β_2-agonist and an anticholinergic produces greater and more sustained improvements in FEV_1 than either drug alone and does not produce evidence of tachyphylaxis over 90 days of treatment[126,147,148] (**Evidence A**).

The combination of a β_2-agonist, an anticholinergic, and/or theophylline may produce additional improvements in lung function[126,146-151] and health status[126,152]. 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.

Glucocorticosteroids

The effects of oral and inhaled glucocorticosteroids in COPD are much less dramatic than in asthma, and their role in the management of stable COPD is limited to specific indications. The use of glucocorticosteroids for the treatment of acute exacerbations is described in *Component 4: Manage Exacerbations.*

Oral glucocorticosteroids: short-term. 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. This recommendation is based on evidence[153] that short-term effects predict long-term effects of oral glucocorticosteroids on FEV_1, and evidence that asthma patients with airflow limitation might not respond acutely to an inhaled bronchodilator but do show significant bronchodilation after a short course of oral 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[38,100]. For this reason, there appears to be insufficient evidence to recommend a therapeutic trial with oral glucocorticosteroids in patients with *Stage II: Moderate COPD, Stage III: Severe COPD,* or *Stage IV: Very Severe COPD* and poor response to an inhaled bronchodilator.

Oral glucocorticosteroids: long-term. Two retrospective studies[154,155] analyzed the effects of treatment with oral glucocorticosteroids on long-term FEV_1 changes in clinic populations of patients with moderate to very severe COPD. The retrospective nature of these studies, their lack of true control groups, and their imprecise definition of COPD are reasons for a cautious interpretation of the data and conclusions.

A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy[156-158], which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced COPD. In view of the well-known toxicity of long-term treatment with oral glucocorticosteroids, prospective studies on the long-term effects of these drugs in COPD are limited[159,160].

Therefore, based on the lack of evidence of benefit, and the large body of evidence on side effects, long-term treatment with oral glucocorticosteroids is not recommended in COPD (**Evidence A**).

Inhaled glucocorticosteroids. Regular treatment with inhaled glucocorticosteroids does not modify the long-term decline of FEV_1 in patients with COPD[98-100,161]. However, regular treatment with inhaled glucocorticosteroids 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 (for example, 3 in the last 3 years)[162-165] (**Evidence A**). This treatment has been shown to reduce the frequency of exacerbations and thus improve health status[140] (**Evidence A**), and withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients[166]. Re-analysis of pooled data from several longer studies of inhaled glucocorticosteroids in COPD suggests that this treatment reduces all-cause mortality[167], but this conclusion requires confirmation in prospective studies before leading to a change in current treatment recommendations. An inhaled glucocorticosteroid combined with a long-acting β_2-agonist is more effective than the individual components[162,164,165,168,169] (**Evidence A**).

The dose-response relationships and long-term safety of inhaled glucocorticosteroids in COPD are not known. Only moderate to high doses have been used in long-term clinical trials. Two studies showed an increased incidence of skin bruising in a small percentage of the COPD patients[98,100]. One long-term study showed no effect of budesonide on bone density and fracture rate[98,170], while another study showed that treatment with triamcinolone acetonide was associated with a decrease in bone density[161]. The efficacy and side effects of inhaled glucocorticosteroids in asthma are dependent on the dose and type of glucocorticosteroid[171]. This pattern can also be expected in COPD and needs documentation in this patient population. Treatment with inhaled glucocorticosteroids can be recommended for patients with more advanced COPD and repeated exacerbations.

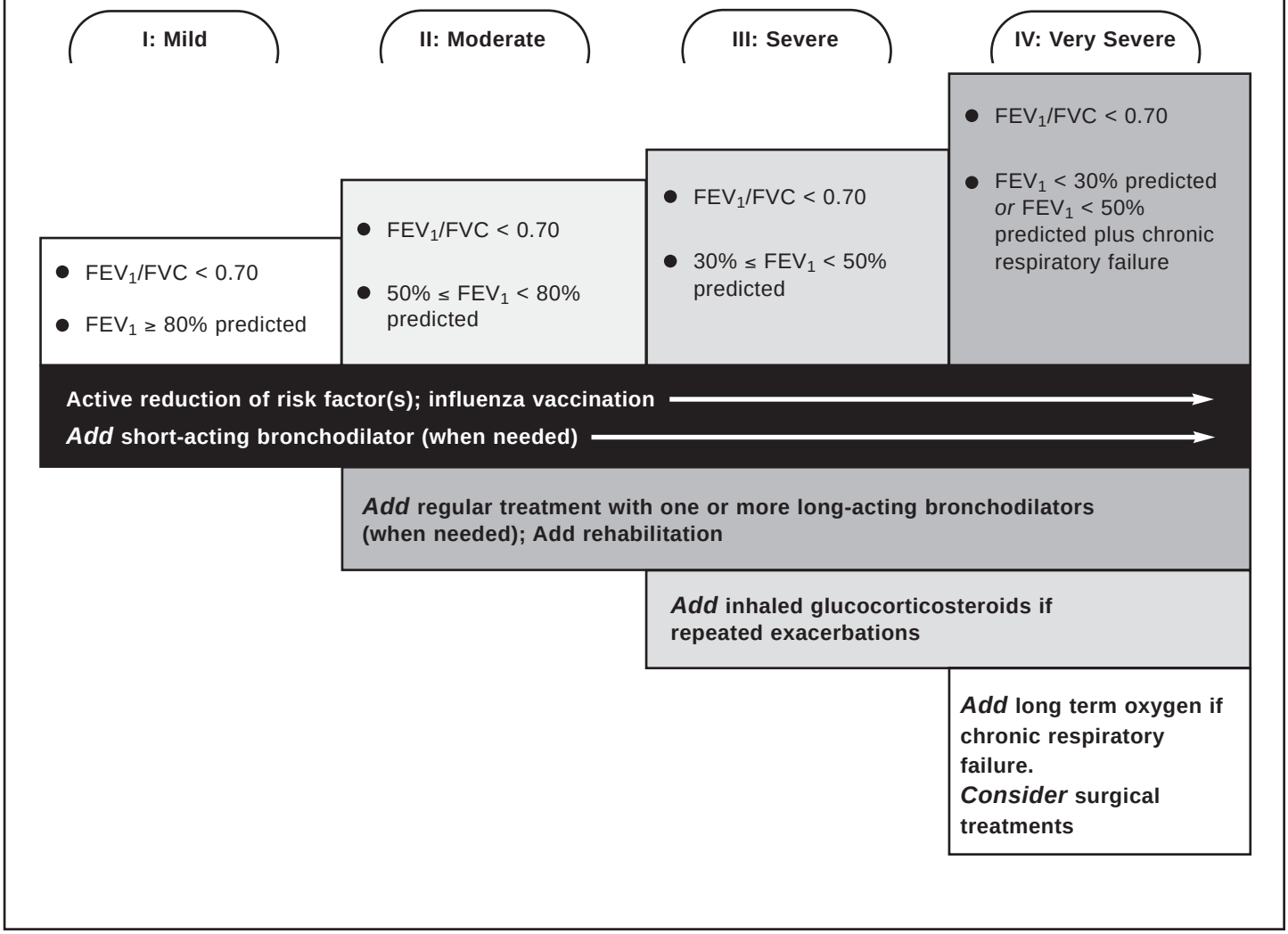
Pharmacologic Therapy by Disease Severity

Figure 5.3-7 provides a summary of recommended treatment at each stage of COPD. For patients with few or intermittent symptoms (*Stage I: Mild COPD*), use of a short-acting inhaled bronchodilator as needed to control dyspnea is sufficient. If inhaled bronchodilators are not available, regular treatment with slow-release theophylline should be considered.

In patients with *Stage II: Moderate COPD* to *Stage IV: Very Severe COPD*) whose dyspnea during daily activities is not relieved despite treatment with as-needed short-acting bronchodilators, adding regular treatment with a long-acting inhaled bronchodilator is recommended (**Evidence A**). Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (**Evidence A**). There is insufficient evidence to favor one long-acting bronchodilator over others. For patients on regular long-acting bronchodilator therapy who need additional symptom control, adding theophylline may produce additional benefits (**Evidence B**).

Patients with *Stage II: Moderate COPD* to *Stage IV: Very Severe COPD* who are on regular short- or long-acting bronchodilator therapy may also use a short-acting bronchodilator as needed.

Figure 5.3-7. Therapy at Each Stage of COPD*



Postbronchodilator FEV_1 is recommended for the diagnosis and assessment of severity of COPD.

Some patients may request regular treatment with high-dose nebulized bronchodilators, especially if they have experienced subjective benefit from this treatment during an acute exacerbation. Clear scientific evidence for this approach is lacking, but one suggested option is to examine the improvement in mean daily peak expiratory flow recording during two weeks of treatment in the home and continue with nebulizer therapy if a significant change occurs[112]. In general, nebulized therapy for a stable patient is not appropriate unless it has been shown to be better than conventional dose therapy.

In patients with a postbronchodilator FEV_1 < 50% predicted (*Stage III: Severe COPD* to *Stage IV: Very Severe COPD*) and a history of repeated exacerbations (for example, 3 in the last 3 years), regular treatment with inhaled glucocorticosteroids reduces the frequency of exacerbations and improves health status. In these patients, regular treatment with an inhaled glucocorticosteroid should be added to long-acting inhaled bronchodilators. Chronic treatment with oral glucocorticosteroids should be avoided.

Other Pharmacologic Treatments

Vaccines. Influenza vaccines can reduce serious illness[172] and death in COPD patients by about 50%[173,174] (**Evidence A**). Vaccines containing killed or live, inactivated viruses are recommended[175] as they are more effective in elderly patients with COPD[176]. The strains are adjusted each year for appropriate effectiveness and should be given once each year[177]. Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older[178,179]. In addition, this vaccine has been shown to reduce the incidence of community-acquired pneumonia in COPD patients younger than age 65 with an FEV_1 < 40% predicted[180] (**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 patients with COPD that is unrelated to alpha-1 antitrypsin deficiency (**Evidence C**).

Antibiotics. Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD[181-183] and a study that examined the efficacy of winter chemoprophylaxis over a period of 5 years, concluded that there was no benefit[184]. There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful[185,186] (**Evidence A**).

Mucolytic (mucokinetic, mucoregulator) agents (ambroxol, erdosteine, carbocysteine, iodinated glycerol). The regular use of mucolytics in COPD has been evaluated in a number of long-term studies with controversial results[187-189]. Although a few patients with viscous sputum may benefit from mucolytics[190,191], the overall benefits seem to be very small, and the widespread use of these agents cannot be recommended at present (**Evidence D**).

Antioxidant agents. Antioxidants, in particular N-acetylcysteine, have been reported in small studies to reduce the frequency of exacerbations, leading to speculation that these medications could have a role in the treatment of patients with recurrent exacerbations[192-195] (**Evidence B**). However, a large randomized controlled trial found no effect of N-acetylcysteine on the frequency of exacerbations, except in patients not treated with inhaled glucocorticosteroids[196].

Immunoregulators (immunostimulators, immunomodulators). Studies using an immunoregulator in COPD show a decrease in the severity and frequency of exacerbations[197,198]. However, additional studies to examine the long-term effects of this therapy are required before its regular use can be recommended[199].

Antitussives. Cough, although sometimes a troublesome symptom in COPD, has a significant protective role[200]. Thus the regular use of antitussives is not recommended in stable COPD (**Evidence D**).

Vasodilators. The belief that pulmonary hypertension in COPD is associated with a poorer prognosis has provoked many attempts to reduce right ventricular afterload, increase cardiac output, and improve oxygen delivery and tissue oxygenation. Many agents have been evaluated, including inhaled nitric oxide, but the results have been uniformly disappointing. In patients with COPD, in whom hypoxemia is caused primarily by ventilation-perfusion mismatching rather than by increased intrapulmonary shunt (as in noncardiogenic pulmonary edema), inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-perfusion balance[201,202]. Therefore, based on the available evidence, nitric oxide is contraindicated in stable COPD.

Narcotics (morphine). 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[203]. However, some clinical studies suggest that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects[204-208].

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

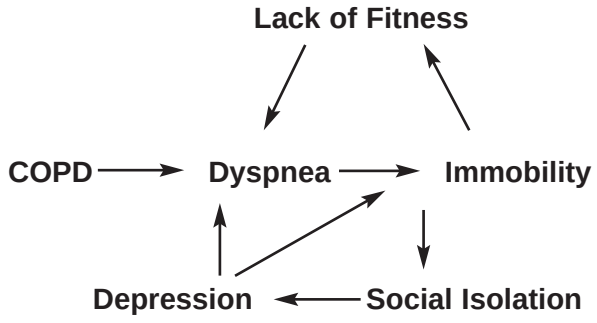
NON-PHARMACOLOGIC TREATMENT

Rehabilitation

The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities. To accomplish these goals, pulmonary rehabilitation covers a range of non-pulmonary problems that may not be adequately addressed by medical therapy for COPD. Such problems, which especially affect patients with *Stage II: Moderate COPD, Stage III: Severe COPD,* and *Stage IV: Very Severe COPD*, include exercise de-conditioning, relative social isolation, altered mood states (especially depression), muscle wasting, and weight loss. These problems have complex interrelationships and improvement in any one of these interlinked processes can interrupt the "vicious circle" in COPD so that positive gains occur in all aspects of the illness (**Figure 5.3-9**). A comprehensive statement on pulmonary rehabilitation has been prepared by the ATS/ERS[209].

Pulmonary rehabilitation has been carefully evaluated in a large number of clinical trials; the various benefits are summarized in **Figure 5.3-10**[89,210-220]. On average, rehabilitation increases peak workload by 18%, peak oxygen consumption by 11%, and endurance time time by 87% of baseline. This translates into a 49 m improvement in 6-minute walking distance[221]. Rehabilitation has been shown to be at least additive to other forms of therapy such as bronchodilator treatment[124].

Figure 5.3-9. The Cycle of Physical, Social, and Psychosocial Consequences of COPD



Patient selection and program design. Although more information is needed on criteria for patient selection for pulmonary rehabilitation programs, COPD patients at all stages of disease appear to benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue[222] (**Evidence A**). Data suggest that these benefits can be sustained even after a single pulmonary rehabilitation program[223-225].

Figure 5.3-10. Benefits of Pulmonary Rehabilitation in COPD

- Improves exercise capacity (**Evidence A**).
- Reduces the perceived intensity of breathlessness (**Evidence A**).
- Improves health-related quality of life (**Evidence A**).
- Reduces the number of hospitalizations and days in the hospital (**Evidence A**).
- Reduces anxiety and depression associated with COPD (**Evidence A**).
- Strength and endurance training of the upper limbs improves arm function (**Evidence B**).
- Benefits extend well beyond the immediate period of training (**Evidence B**).
- Improves survival (**Evidence B**).
- Respiratory muscle training is beneficial, especially when combined with general exercise training (**Evidence C**).
- Psychosocial intervention is helpful (**Evidence C**).

Benefit does wane after a rehabilitation program ends, but if exercise training is maintained at home the patient's health status remains above pre-rehabilitation levels (**Evidence B**). To date there is no consensus on whether repeated rehabilitation courses enable patients to sustain the benefits gained through the initial course.

Ideally, pulmonary rehabilitation should involve several types of health professionals. Significant benefits can also occur with more limited personnel, as long as dedicated professionals are aware of the needs of each patient. Benefits have been reported from rehabilitation programs conducted in inpatient, outpatient, and home settings[214,215,226]. Considerations of cost and availability most often determine the choice of setting. The educational and exercise training components of rehabilitation are usually conducted in groups, normally with 6 to 8 individuals per class (**Evidence D**).

The following points summarize current knowledge of considerations important in choosing patients:

Functional status: Benefits have been seen in patients with a wide range of disability, although those who are chair-bound appear unlikely to respond even to home visiting programs[227] (**Evidence A**).

Severity of dyspnea: Stratification by breathlessness intensity using the MRC questionnaire (**Figure 5.1-3**) may be helpful in selecting patients most likely to benefit from rehabilitation. Those with MRC grade 5 dyspnea may not benefit[227] (**Evidence B**).

Motivation: Selecting highly motivated participants is especially important in the case of outpatient programs[224].

Smoking status: There is no evidence that smokers will benefit less than nonsmokers, but many clinicians believe that inclusion of a smoker in a rehabilitation program should be conditional on their participation in a smoking cessation program. Some data indicate that continuing smokers are less likely to complete pulmonary rehabilitation programs than nonsmokers[224] (**Evidence B**).

Components of pulmonary rehabilitation programs. The components of pulmonary rehabilitation vary widely from program to program but a comprehensive pulmonary rehabilitation program includes exercise training, nutrition counseling, and education.

Exercise training. Exercise tolerance can be assessed by either bicycle ergometry or treadmill exercise with the measurement of a number of physiological variables, including maximum oxygen consumption, maximum heart rate, and maximum work performed. A less complex approach is to use a self-paced, timed walking test (e.g., 6-minute walking distance). These tests require at least one practice session before data can be interpreted. Shuttle walking tests offer a compromise: they provide more complete information than an entirely self-paced test, but are simpler to perform than a treadmill test[228].

Exercise training ranges in frequency from daily to weekly, in duration from 10 minutes to 45 minutes per session, and in intensity from 50% peak oxygen consumption (VO_2 max) to maximum tolerated[229]. The optimum length for an exercise program has not been investigated in randomized controlled trials but most studies involving fewer than 28 exercise sessions show inferior results compared to those with longer treatment periods[221]. In practice, the length depends on the resources available and usually ranges from 4 to 10 weeks, with longer programs resulting in larger effects than shorter programs[213].

Participants are often encouraged to achieve a pre-determined target heart rate[230], but this goal may have limitations in COPD. In many programs, especially those using simple corridor exercise training, the patient is encouraged to walk to a symptom-limited maximum, rest, and then continue walking until 20 minutes of exercise have been completed. Where possible, endurance exercise training to 60-80% of the symptom-limited maximum is preferred. Endurance training can be accomplished through continuous or interval exercise programs. The latter involve the patient doing the same total work but divided into briefer periods of high-intensity exercise, which is useful when performance is limited by other comorbidities[231,232]. Use of a simple wheeled walking aid seems to improve walking distance and reduces breathlessness in severely disabled COPD patients[233-235] (**Evidence C**). Other approaches to improving outcomes such as use of oxygen during exercise[236], exercising while breathing heliox gas mixtures[237], unloading the ventilatory muscles while exercising, or use of pursed lip breathing remain experimental at present. Specific strength training is possible but its benefits remain uncertain, as do the effects of supplementation with anabolic steroids and the use of neuromuscular electrical stimulation.

The minimum length of an effective rehabilitation program is 6 weeks; the longer the program continues, the more effective the results[238-240] (**Evidence B**). However, as yet, no effective program has been developed to maintain the effects over time[241]. Many physicians advise patients unable to participate in a structured program to exercise on their own (e.g., walking 20 minutes daily). The benefits of this general advice have not been tested, but it is reasonable to offer such advice to patients if a formal program is not available.

Some programs also include upper limb exercises, usually involving an upper limb ergometer or resistive training with weights. There are no randomized clinical trial data to support the routine inclusion of these exercises, but they may be helpful in patients with comorbidities that restrict other forms of exercise and those with evidence of respiratory muscle weakness[242,243]. The addition of upper limb exercises or other strength training to aerobic training is effective in improving strength, but does not improve quality of life or exercise tolerance[244].

Nutrition counseling. Nutritional state is an important determinant of symptoms, disability, and prognosis in COPD; both overweight and underweight can be a problem. Specific nutritional recommendations for patients with COPD are based on expert opinion and some small randomized clinical trials[209]. Approximately 25% of patients with *Stage II: Moderate COPD* to *Stage IV: Very Severe COPD* show a reduction in both their body mass index and fat free mass[12,245,246]. A reduction in body mass index is an independent risk factor for mortality in COPD patients[13,247,248] (**Evidence A**).

Health care workers should identify and correct the reasons for reduced calorie intake in COPD patients. Patients who become breathless while eating should be advised to take small, frequent meals. Poor dentition should be corrected and comorbidities (pulmonary sepsis, lung tumors, etc.) should be managed appropriately. Improving the nutritional state of COPD patients who are losing weight can lead to improved respiratory muscle strength[249-251]. However, controversy remains as to whether this additional effort is cost effective[249,250].

Present evidence suggests that nutritional supplementation alone may not be a sufficient strategy. Increased calorie intake is best accompanied by exercise regimes that have a nonspecific anabolic action, and there is some evidence this also helps even in those patients without severe nutritional depletion[252]. Specific nutritional supplements (e.g., creatine) may improve body compo-sition, but further studies in large numbers of subjects are required before the routine use of these supplements can be recommended[253]. Anabolic steroids in COPD patients with weight loss increase body weight and lean body mass but have little or no effect on exercise capacity[254,255].

Education. Most pulmonary rehabilitation programs include an educational component, but the specific contributions of education to the improvements seen after pulmonary rehabilitation remain unclear.

Assessment and follow-up. Baseline and outcome assessments of each participant in a pulmonary rehabilitation program should be made to quantify individual gains and target areas for improvement. Assessments should include:

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

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. Several detailed questionnaires for assessing health status are available, including some that are specifically designed for patients with respiratory disease (e.g., Chronic Respiratory Disease Questionnaire[152], St. George Respiratory Questionnaire[256]), and there is increasing evidence that these questionnaires may be useful in a clinical setting. Health status can also be assessed by generic questionnaires, such as the Medical Outcomes Study Short Form (SF36)[257], to enable comparison of quality of life in different diseases. The Hospital Anxiety and Depression Scale (HADS) has been used to improve identification and treatment of anxious and depressed patients[258].

Economic cost of rehabilitation programs. A Canadian study showing statistically significant improvements in dyspnea, fatigue, emotional health, and mastery found that the incremental cost of pulmonary rehabilitation was $11,597 (CDN) per person[259]. A study from the United Kingdom provided evidence that an intensive (6-week, 18-visit) multidisciplinary rehabilitation program was effective in decreasing use of health services[225] (**Evidence B**). Although there was no difference in the number of hospital admissions between patients with disabling COPD in a control group and those who participated in the rehabilitation program, the number of days the rehabilitation group spent in the hospital was significantly lower. The rehabilitation group had more primary-care consultations at the general practitioner's premises than did the control group, but fewer primary-care home visits. Compared with the control group, the rehabilitation group also showed greater improvements in walking ability and in general and disease-specific health status.

Oxygen Therapy

Oxygen therapy, one of the principal nonpharmacologic treatments for patients with *Stage IV: Very Severe COPD*[190,260], can be administered in three ways: long-term continuous therapy, during exercise, and to relieve acute dyspnea. The primary goal of oxygen therapy is to increase the baseline PaO_2 to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce an SaO_2 at least 90%, which will preserve vital organ function by ensuring adequate delivery of oxygen.

The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival[261,262]. It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state[263]. Continuous oxygen therapy decreased resting pulmonary artery pressure in one study[261] but not in another study[262]. Prospective studies have shown that the primary hemodynamic effect of oxygen therapy is preventing the progression of pulmonary hypertension[264,265]. Long-term oxygen therapy improves general alertness, motor speed, and hand grip, although the data are less clear about changes in quality of life and emotional state. The possibility of walking while using some oxygen

devices may help to improve physical conditioning and have a beneficial influence on the psychological state of patients[266].

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

- PaO_2 at or below 7.3 kPa (55 mm Hg) or SaO_2 at or below 88%, with or without hypercapnia (**Evidence B**); *or*

- PaO_2 between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg), or SaO2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%) (**Evidence D**).

A decision about the use of long-term oxygen should be based on the waking PaO_2 values. The prescription should always include the source of supplemental oxygen (gas or liquid), method of delivery, duration of use, and flow rate at rest, during exercise, and during sleep. A detailed review of the uses of oxygen in COPD, together with possible assessment algorithms and information about methods of delivery, is available from http://www.thoracic.org/.

Oxygen is usually delivered by a facemask, with appropriate inspiratory flow rates varying between 24% and 35%. The facemask permits accurate titration of oxygen, which is particularly valuable in patients who are prone to CO_2 retention. However, facemasks are easily dislodged and restrict eating and conversation, so many patients prefer oxygen delivered by nasal cannulae. Oxygen delivery by this route requires additional blood gas monitoring to ensure that it is satisfactory, and may require individual titration. Other, more specialized methods of oxygen delivery (e.g., transtracheally) are available but should only be used in specialized centers familiar with the indications and complications of these delivery methods.

Long-term oxygen is usually provided from a fixed oxygen concentrator with plastic piping allowing the patient to use oxygen in their living area and bedroom. Treatment should be for at least 15 hours per day and preferably longer. In addition, a supply of oxygen should be provided that will allow the patient to leave the house for an appropriate period of time and to exercise without their oxygen saturation falling below 90%.

A number of physiological studies have shown that delivering oxygen during exercise can increase the duration of endurance exercise and/or reduce the intensity of end-exercise breathlessness[267,268] (**Evidence A**). This reflects a reduction in the rate at which dynamic hyperinflation occurs, which may be secondary to the documented reduction in ventilatory demand and chemoreceptor activation while breathing oxygen during exercise[269,270]. These changes occur whether or not patients are hypoxemic at rest and can translate into improved health status if the treatment is used as an outpatient[271]. However, good data about the use of ambulatory oxygen in representative patient populations are presently lacking, although a small randomized trial has suggested that compliance is not high[272]. Patients need encouragement to understand how and when to use ambulatory oxygen and overcome any anxieties or concerns about using this more conspicuous treatment.

Oxygen therapy reduces the oxygen cost of breathing and minute ventilation, a mechanism that although still disputed helps to minimize the sensation of dyspnea. This has led to the use of short burst therapy to control severe dyspnea such as occurs after climbing stairs. However, there is no benefit from using short burst oxygen for symptomatic relief before or after exercise[273,274] (**Evidence B**).

Cost considerations. Supplemental home oxygen is usually the most costly component of outpatient therapy for adults with COPD who require this therapy[275]. Studies of the cost effectiveness of alternative outpatient oxygen delivery methods in the US and Europe suggest that oxygen concentrator devices may be more cost effective than cylinder delivery systems[276,277].

Oxygen use in air travel. Although air travel is safe for most patients with chronic respiratory failure who are on long-term oxygen therapy, patients should be instructed to increase the flow by 1-2 L/min during the flight[278]. Ideally, patients who fly should be able to maintain an in-flight PaO_2 of at least 6.7 kPa (50 mm Hg). Studies indicate that this can be achieved in those with moderate to severe hypoxemia at sea level by supplementary oxygen at 3 L/min by nasal cannulae or 31% by Venturi facemask[279]. Those with a resting PaO_2 at sea level of > 9.3 kPa (70 mm Hg) are likely to be safe to fly without supplementary oxygen[278,280], although it is important to emphasize that a resting PaO_2 > 9.3 kPa (70 mm Hg) at sea level does not exclude the development of severe hypoxemia when travelling by air (**Evidence C**). Careful consideration should be given to any comorbidity that may impair oxygen delivery to tissues (e.g., cardiac impairment, anemia). Also, walking along the aisle may profoundly aggravate hypoxemia[281].

Ventilatory Support

Noninvasive ventilation (using either negative or positive pressure devices) is now widely used to treat acute exacerbations of COPD (*see Component 4*). Negative pressure ventilation is not indicated for the chronic management of *Stage IV: Very Severe COPD* patients, with or without CO_2 retention. It has been demonstrated to have no effect on shortness of breath, exercise tolerance, arterial blood gases, respiratory muscle strength, or quality of life in a large randomized trial in COPD patients with chronic respiratory failure[282].

Although preliminary studies suggested that combining noninvasive intermittent positive pressure ventilation (NIPPV) with long-term oxygen therapy could improve some outcome variables, current data do not support the routine use of this combination[283]. However, compared with long-term oxygen therapy alone, the addition of NIPPV can lessen carbon dioxide retention and improve shortness of breath in some patients[284]. Thus, although at present long-term NIPPV cannot be recommended for the routine treatment of patients with chronic respiratory failure due to COPD, the combination of NIPPV with long-term oxygen therapy may be of some use in a selected subset of patients, particularly in those with pronounced daytime hypercapnia[285].

Surgical Treatments

Bullectomy. Bullectomy is an older surgical procedure for bullous emphysema. Removal of a large bulla that does not contribute to gas exchange decompresses the adjacent lung parenchyma. Bullectomy can be performed thoracoscopically. In carefully selected patients, this procedure is effective in reducing dyspnea and improving lung function[286] (**Evidence C**).

Bullae may be removed to alleviate local symptoms such as hemoptysis, infection, or chest pain, and to allow re-expansion of a compressed lung region. This is the usual indication in patients with COPD. In considering the possible benefit of surgery it is crucial to estimate the effect of the bulla on the lung and the function of the nonbullous lung. A thoracic CT scan, arterial blood gas measurement, and comprehensive respiratory function tests are essential before making a decision regarding suitability for resection of a bulla. Normal or minimally reduced diffusing capacity, absence of significant hypoxemia, and evidence of regional reduction in perfusion with good perfusion in the remaining lung are indications a patient will likely benefit from surgery[287]. However, pulmonary hypertension, hypercapnia, and severe emphysema are not absolute contraindications for bullectomy. Some investigators have recommended that the bulla must occupy 50% or more of the hemithorax and produce definite displacement of the adjacent lung before surgery is performed[288].

Lung volume reduction surgery (LVRS). LVRS is a surgical procedure in which parts of the lung are resected to reduce hyperinflation[289], making respiratory muscles more effective pressure generators by improving their mechanical efficiency (as measured by length/tension relationship, curvature of the diaphragm, and area of apposition)[290,291]. In addition, LVRS increases the elastic recoil pressure of the lung and thus improves expiratory flow rates[292].

A large multicenter study of 1,200 patients comparing LVRS with medical treatment has shown that after 4.3 years, patients with upper-lobe emphysema and low exercise capacity who received the surgery had a greater survival rate than similar patients who received medical therapy (54% vs. 39.7%)[293]. In addition, the surgery patients experienced greater improvements in their maximal work capacity and their health-related quality of life. The advantage of surgery over medical therapy was less significant among patients who had other emphysema distribution or high exercise capacity prior to treatment.

Hospital costs associated with LVRS in 52 consecutive patients[294] ranged from US$11,712 to $121,829. Hospital charges in 23 consecutive patients admitted for LVRS at a single institution[295] ranged from US$20,032 to $75,561 with a median charge of $26,669. A small number of individuals incurred extraordinary costs because of complications. Advanced age was a significant factor leading to higher expected total hospital costs.

Although the results of the large multicenter study showed some very positive results of surgery in a select group of patients[41,293], LVRS is an expensive palliative surgical procedure and can be recommended only in carefully selected patients.

Lung transplantation. In appropriately selected patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity[296-299] (**Evidence C**), although the Joint United Network for Organ Sharing in 1998 found that lung transplantation does not confer a survival benefit in patients with end-stage emphysema after two years[298]. Criteria for referral for lung transplantation include $FEV_1 < 35\%$ predicted, $PaO_2 < 7.3$-8.0 kPa (55-60 mm Hg), $PaCO_2 > 6.7$ kPa (50 mm Hg), and secondary pulmonary hypertension[300,301].

Lung transplantation is limited by the shortage of donor organs, which has led some centers to adopt the single-lung technique. The common complications seen in COPD patients after lung transplantation, apart from operative mortality, are acute rejection and bronchiolitis obliterans, CMV, other opportunistic fungal (*Candida, Aspergillus, Cryptococcus, Carinii*) or bacterial (*Pseudomonas, Staphylococcus* species) infections, lymphoproliferative disease, and lymphomas[297].

Another limitation of lung transplantation is its cost. In the United States, hospitalization costs associated with lung transplantation have ranged from US$110,000 to well over $200,000. Costs remain elevated for months to years after surgery due to the high cost of complications and the immunosuppressive regimens[302-305] that must be initiated during or immediately after surgery.

Special Considerations

Surgery in COPD. Postoperative pulmonary complications are as important and common as postoperative cardiac complications and, consequently, are a key component of the increased risk posed by 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 post-operative 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[306-311].

The incidence of increased risk of postoperative pulmonary complications in COPD patients may vary according to the definition of postoperative pulmonary complications and the severity of COPD, with relative ranges of the order of 2.7 to 4.7[306]. The surgical site is the most important predictor, and risk increases as the incision approaches the diaphragm. Upper abdominal and thoracic surgery represents the greatest risk, the latter being uncommon after interventions outside the thorax or abdomen. Most reports conclude that epidural or spinal anesthesia have a lower risk than general anesthesia, although the results are not totally uniform.

Individual patient risk factors are identified by careful history, physical examination, chest radiography, and pulmonary function tests. Although the value of pulmonary function tests remains contentious, there is consensus that all COPD candidates for lung resection should undergo a complete battery, including forced spirometry with bronchodilator response, static lung volumes, diffusing capacity, and arterial blood gases at rest. One theoretical rationale behind the assessment of pulmonary function measurement is the identification of COPD patients in whom the risk is so elevated that surgery should be contraindicated.

Several studies in high-risk COPD patients suggest that there is a threshold beyond which the risk of surgery is prohibitive. The risk of postoperative respiratory failure appears to be in patients undergoing pneumonectomy with a preoperative FEV_1 < 2 L or 50% predicted and/or a DLCO < 50% predicted[310]. COPD patients at high risk due to poor lung function should undergo further lung function assessment, for example, tests of regional distribution of perfusion and exercise capacity[311]. To prevent postoperative pulmonary complications, stable COPD patients clinically symptomatic and/or with limited exercise capacity should be treated, before surgery, intensely with all the measures already well established for stable COPD patients who are not about to have surgery. Surgery should be postponed if an exacerbation is present.

Surgery in patients with COPD needs to be differentiated from that aimed to improve lung function and symptoms of COPD. This includes bullectomy, lung volume reduction surgery, and lung transplantation[311].

COMPONENT 4: MANAGE EXACERBATIONS

KEY POINTS:

- An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.
- The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified (**Evidence B**).
- Inhaled bronchodilators (particularly inhaled β_2-agonists with or without anticholinergics) and oral glucocorticosteroids are effective treatments for exacerbations of COPD (**Evidence A**).
- Patients experiencing COPD exacerbations with clinical signs of airway infection (e.g., increased sputum purulence) may benefit from antibiotic treatment (**Evidence B**).
- Noninvasive mechanical ventilation in exacerbations improves respiratory acidosis, increases pH, decreases the need for endotracheal intubation, and reduces $PaCO_2$, respiratory rate, severity of breathlessness, the length of hospital stay, and mortality (**Evidence A**).
- Medications and education to help prevent future exacerbations should be considered as part of follow-up, as exacerbations affect the quality of life and prognosis of patients with COPD.

INTRODUCTION

COPD is often associated with exacerbations of symptoms[312-316]. An exacerbation of COPD is defined as *an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD*[317,318]. Exacerbations are categorized in terms of either clinical presentation (number of symptoms[314]) and/or heath-care resources utilization[317]. The impact of exacerbations is significant and a patient's symptoms and lung function may both take several weeks to recover to the baseline values[319].

Exacerbations affect the quality of life and prognosis of patients with COPD. Hospital mortality of patients admitted for a hypercarbic COPD exacerbation is approximately 10%, and the long-term outcome is poor[320]. Mortality reaches 40% at 1 year in those needing mechanical support, and all-cause mortality is even higher (up to 49%) 3 years after hospitalization for a COPD exacerbation[316,320-325]. In addition, exacerbations of COPD have serious negative impacts on patients' quality of life[140], lung function[326,327], and socioeconomic costs[325]. Thus, prevention, early detection, and prompt treatment of exacerbations may impact their clinical progression by ameliorating the effects on quality of life and minimizing the risk of hospitalization[328].

The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution[329], but the cause of about one-third of severe exacerbations cannot be identified. The role of bacterial infections is controversial, but recent investigations with newer research techniques have begun to provide important information. Bronchoscopic studies have shown that at least 50% of patients have bacteria in high concentrations in their lower airways during exacerbations[330-332]. However, a significant proportion of these patients also have bacteria colonizing their lower airways in the stable phase of the disease.

There is some indication that the bacterial burden increases during exacerbations[330], and that acquisition of strains of the bacteria that are new to the patient is associated with exacerbations[332]. Development of specific immune responses to the infecting bacterial strains, and the association of neutrophilic inflammation with bacterial exacerbations, also support the bacterial causation of a proportion of exacerbations[333-336].

DIAGNOSIS AND ASSESSMENT OF SEVERITY

Medical History

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 tachycardia and tachypnea, 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 prior history of chronic sputum production[314,336].

Assessment of Severity

Assessment of the severity of an exacerbation is based on the patient's medical history before the exacerbation, preexisting comorbidities, symptoms, physical examination, arterial blood gas measurements, and other laboratory tests (**Figure 5.4-1**). Specific information is required on the frequency and severity of attacks of breathlessness and cough, sputum volume and color, and limitation of daily activities. When available, prior arterial blood gas measurements 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. Thus, where possible, physicians should instruct their patients to bring the summary of their last evaluation when they come to the hospital with an exacerbation. In patients with *Stage IV: Very Severe COPD*, the most important sign of a severe exacerbation is a change in the mental status of the patient and this signals a need for immediate evaluation in the hospital.

Figure 5.4-1. Assessment of COPD Exacerbations: Medical History and Signs of Severity

Medical History	Signs of Severity
• Severity of FEV_1	• Use of accessory respiratory muscles
• Duration of worsening or new symptoms	• Paradoxical chest wall movements
• Number of previous episodes (exacerbations/ hospitalizations)	• Worsening or new onset central cyanosis
• Comordibities	• Development of peripheral edema
• Present treatment regimen	• Hemodynamic instability
	• Signs of right heart failure
	• Reduced alertness

Spirometry and PEF. Even simple spirometric tests can be difficult for a sick patient to perform properly. These measurements are not accurate during an acute exacerbation; therefore their routine use is not recommended.

Pulse oximetry and arterial blood gas measurement. Pulse oximetry can be used to evaluate a patient's oxygen saturation and need for supplemental oxygen therapy. For patients that require hospitalization, measurement of arterial blood gases is important to assess the severity of an exacerbation. A PaO_2 < 8.0 kPa (60 mm Hg) and/or SaO_2 < 90% with or without $PaCO_2$ > 6.7 kPa (50 mmHg) when breathing room air indicate respiratory failure. In addition, moderate-to-severe acidosis (pH < 7.36) plus hypercapnia ($PaCO_2$ > 6-8 kPa, 45-60 mm Hg) in a patient with respiratory failure is an indication for mechanical ventilation[311,337].

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. Although the history and physical signs can be confusing, especially when pulmonary hyperinflation masks coexisting cardiac signs, most problems are resolved by the chest X-ray and ECG. An ECG aids in the diagnosis of right heart hypertrophy, arrhythmias, and ischemic episodes. Pulmonary embolism can be very difficult to distinguish from an exacerbation, especially in advanced COPD, because right ventricular hypertrophy and large pulmonary arteries lead to confusing ECG and radiographic results. A low systolic blood pressure and an inability to increase the PaO_2 above 8.0 kPa (60 mm Hg) despite high-flow oxygen also suggest pulmonary embolism. If there are strong indications that pulmonary embolism has occurred, it is best to treat for this along with the exacerbation.

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 empirical antibiotic treatment[33]. *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 the initial antibiotic treatment, a sputum culture and an antibiogram should be performed. Bio- chemical test abnormalities can be associated with an exacerbation and include electrolyte disturbance(s) (e.g., hyponatremia, hypokalemia), poor glucose control, metabolic acid-base disorder. These abnormalities can also be due to associated co-morbid conditions (see below "Differential Diagnoses").

Differential Diagnoses

Ten to 30% of patients with apparent exacerbations of COPD do not respond to treatment[319,338]. In such cases the patient should be re-evaluated for other medical

conditions that can aggravate symptoms or mimic COPD exacerbations[190]. These conditions include pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, and cardiac arrhythmia. Non-compliance with the prescribed medication regimen can also cause increased symptoms that may be confused with a true exacerbation. Elevated serum levels of brain-type natriuretic peptide, in conjunction with other clinical information, identifies patients with acute dyspnea secondary to congestive heart failure and enables them to be distinguished from patients with COPD exacerbations[339,340].

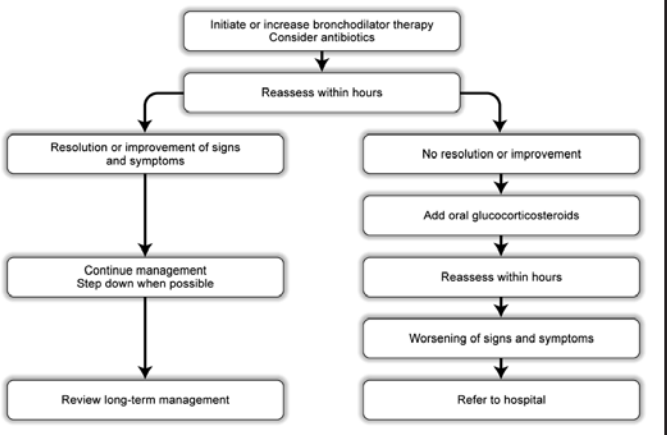
HOME MANAGEMENT

There is increasing interest in home care for end-stage COPD patients, although economic studies of home-care services have yielded mixed results. Four randomized clinical trials have shown that nurse-administered home care (also known as "hospital-at-home" care) represents an effective and practical alternative to hospitalization in selected patients with exacerbations of COPD without acidotic respiratory failure. However, the exact criteria for this approach as opposed to hospital treatment remain uncertain and will vary by health care setting[341-344].

The algorithm reported in **Figure 5.4-2** may assist in the management of an exacerbation at home; a stepwise therapeutic approach is recommended[190,311,345].

Figure 5.4-2. Algorithm for the Management of an Exacerbation of COPD at Home (adapted from ref[346])

The exact criteria for home vs, hospital treatment remain uncertain and will vary by health care setting. If it is determined that care can be initiated at home, this algorithm provides a stepwise therapeutic approach.



Bronchodilator Therapy

Home management of COPD exacerbations involves increasing the dose and/or frequency of existing short-acting bronchodilator therapy, preferably with a β_2-agonist (**Evidence A**). There is not sufficient evidence, however, to indicate a difference in efficacy between the different classes of short-acting bronchodilators[347], or to indicate additional benefit of combinations of short-acting bronchodilators[348]. However, if not already used, an anticholinergic can be added until the symptoms improve. There is no difference in the clinical response between bronchodilator therapy delivered by MDI with a spacer and by hand held nebulizer.

Glucocorticosteroids

Systemic glucocorticosteroids are beneficial in the management of exacerbations of COPD. They shorten recovery time, improve lung function (FEV_1) and hypoxemia (PaO_2)[349-352] (**Evidence A**), and may reduce the risk of early relapse, treatment failure, and length of hospital stay[353]. They should be considered in addition to bronchodilators if the patient's baseline FEV_1 is < 50% predicted. A dose of 30-40 mg prednisolone per day for 7-10 days is recommended[346,349,350]. One large study indicates that nebulized budesonide may be an alternative (although more expensive) to oral glucocorticosteroids in the treatment of non-acidotic exacerbations[351]. Randomized clinical trials in the outpatient office set-up are not available.

Antibiotics

The use of antibiotics in the management of COPD exacerbations is discussed above in the section on assessment of severity and below in the hospital management section.

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[320]. Patients lacking these features are not at high risk of dying, but those with severe underlying COPD often require hospitalization in any case. Attempts at managing such patients entirely in the community have met with only limited success[354], but returning them to their homes with increased social support and a supervised medical care package after initial emergency room assessment has been much more successful[355]. Savings on inpatient expenditures[356] offset the additional costs of maintaining a community-based COPD nursing team. However, detailed cost-benefit analyses of these approaches are awaited.

A range of criteria to consider for hospital assessment/admission for exacerbations of COPD are shown in **Figure 5.4-3**. Some patients need immediate admission to an intensive care unit (ICU) (**Figure 5.4-4**). Admission of patients with severe COPD exacerbations to intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment exist to identify and manage acute respiratory failure successfully.

Figure 5.4-3. Indications for Hospital Assessment or Admission for Exacerbations of COPD*

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

**Local resources need to be considered.*

Figure 5.4-4. Indications for ICU Admission of Patients with Exacerbations of COPD*

- Severe dyspnea that responds inadequately to initial emergency therapy
- Changes in mental status (confusion, lethargy, coma)
- Persistent or worsening hypoxemia (PaO_2 < 5.3 kPa, 40 mmHg), and/or severe/worsening hypercapnia ($PaCO_2$ > 8.0 kPa, 60 mmHg), and/or severe/worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and noninvasive ventilation
- Need for invasive mechanical ventilation
- Hemodynamic instability—need for vasopressors

**Local resources need to be considered.*

Emergency Department or Hospital

The first actions when a patient reaches the emergency department are to provide supplemental oxygen therapy and to determine whether the exacerbation is life threatening (**Figure 5.4-4**). 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 **Figure 5.4-5.**

Figure 5.4-5. Management of Severe but Not Life-Threatening Exacerbations of COPD in the Emergency Department or the Hospital[346]*

- Assess severity of symptoms, blood gases, chest X-ray
- Administer controlled oxygen therapy and repeat arterial blood gas measurement after 30-60 minutes

- Bronchodilators:
  - Increase doses and/or frequency
  - Combine β_2-agonists and anticholinergics
  - Use spacers or air-driven nebulizers
  - Consider adding intravenous mehylxanthines, if needed

- Add oral or intravenous glucocorticosteroids
- Consider antibiotics (oral or occasionally intravenous) when signs of bacterial infection
- Consider noninvasive mechanical ventilation
- At all times:
  - Monitor fluid balance and nutrition
  - Consider subcutaneous heparin
  - Identify and treat associated conditions (e.g., heart failure, arrhythmias)
  - Closely monitor condition of the patient

**Local resources need to be considered.*

Controlled oxygen therapy. Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Supplemental oxygen should be titrated to improve the patient's hypoxemia. Adequate levels of oxygenation (PaO_2 > 8.0 kPa, 60 mm Hg, or SaO_2 > 90%) are easy to achieve in uncomplicated exacerbations, but CO_2 retention can occur insidiously with little change in symptoms. Once oxygen is started, arterial rrr blood gases should be checked 30-60 minutes later to ensure satisfactory oxygenation without CO_2 retention or acidosis. Venturi masks (high-flow devices) offer more accurate delivery of controlled oxygen than do nasal prongs but are less likely to be tolerated by the patient[311].

Bronchodilator therapy. Short-acting inhaled β_2-agonists are usually the preferred bronchodilators for treatment of exacerbations of COPD[190,311,357] (**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. Despite its widespread clinical use, the role of methylxanthines in the treatment of exacerbations of COPD remains controversial. Methylxanthines (theophylline or aminohylline) is currently considered

second-line intravenous therapy, used when there is inadequate or insufficient response to short-acting bronchodilators[358-362] (**Evidence B**). Possible beneficial effects in terms of lung function and clinical endpoints are modest and inconsistent, whereas adverse effects are significantly increased[363,364]. There are no clinical studies that have evaluated the use of inhaled long-acting bronchodilators (either β_2-agonists or anticholinergics) with or without inhaled glucocorticosteroids during an acute exacerbation.

Glucocorticosteroids. Oral or intravenous glucocorticosteroids are recommended as an addition to other therapies in the hospital management of exacerbations of COPD[350,351] (**Evidence A**). The exact dose that should be recommended is not known, but high doses are associated with a significant risk of side effects. Thirty to 40 mg of oral prednisolone daily for 7-10 days is effective and safe (**Evidence C**). Prolonged treatment does not result in greater efficacy and increases the risk of side effects (e.g., hyperglycemia, muscle atrophy).

Antibiotics. Randomized placebo-controlled studies of antibiotic treatment in exacerbations of COPD have demonstrated a small beneficial effect of antibiotics on lung function[365], and a randomized 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, and sputum purulence[314]. 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[11], 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 antibiotic treatment of exacerbations of COPD have not been validated in other studies. A study in COPD patients with exacerbations requiring mechanical ventilation (invasive or noninvasive) indicated that not giving antibiotics was associated with increased mortality and a greater incidence of secondary nosocomial pneumonia[366]. Based on the current available evidence[311,62], antibiotics should be given to:

- Patients with exacerbations of COPD with the following three cardinal symptoms: increased dyspnea, increased sputum volume, and 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 mechanical ventilation (invasive or noninvasive) (**Evidence B**).

The infectious agents in COPD exacerbations can be viral or bacterial[177,367]. The predominant bacteria recovered from the lower airways of patients with COPD exacerbations are *H. influenzae, S. pneumoniae, and M. catarrhalis*[177,330,331,368]. So-called atypical pathogens, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*[368,369], have been identified in patients with COPD exacerbations, but because of diagnostic limitations the true prevalence of these organisms is not known.

Studies in patients with severe underlying COPD who require mechanical ventilation[370,371] 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[372,373]. In patients with mild COPD exacerbations , *S. pneumoniae* is predominant. As FEV_1 declines and patients have more frequent exacerbations and/or comorbid diseases , *H. influenzae* and *M. catarrhalis* become more frequent, and *P. aeruginosa* may appear in patients with severe airway limitation (**Figure 5-4-6**)[177,311]. The risk factors for *P. aeruginosa* infection are recent hospitalization, frequent administration of antibiotics (4 courses in the last year), severe COPD exacerbations, and isolation of *P. aeruginosa* during a previous exacerbation or colonization during a stable period[372,373].

Figure 5.4-7[177,311,332] provides recommended antibiotic treatment for exacerbations of COPD, although it must be emphasized that most of the published studies related to the use of antibiotics were done in chronic bronchitis patients. The route of administration (oral or intravenous) depends on the ability of the patient to eat and the pharmacokinetics of the antibiotic. The oral route is preferred; if the IV route must be used, switching to the oral route is recommended when clinical stabilization permits. Based on studies of the length of use of antibiotics for chronic bronchitis[374-376], antibiotic treatment in patients with COPD exacerbations could be given for 3 to 7 days (**Evidence D**).

Figure 5.4-6: Stratification of patients with COPD exacerbated for antibiotic treatment and potential microorganisms involved in each group[177,311]

Group	Definition[a]	Microorganisms
Group A	Mild exacerbation: No risk factors for poor outcome	*H. influenzae* *S. pneumoniae* *M. catarrhalis* *Chlamydia pneumoniae* Viruses
Group B	Moderate exacerbation with risk factor(s) for poor outcome	Group A plus, presence of resistant organisms (β-lactamase producing, penicillin-resistant *S. pneumoniae*), Enterobacteriaceae (*K.pneumoniae, E. coli, Proteus, Enterobacter,* etc)
Group C	Severe exacerbation with risk factors for *P. aeruginosa* infection	Group B plus: *P. aeruginosa*

a. Risk factors for poor outcome in patients with COPD exacerbation: presence of comorbid diseases, severe COPD, frequent exacerbations (>3 /yr), and antimicrobial use within last 3 months)[177,311,372].

Respiratory Stimulants. Respiratory stimulants are not recommended for acute respiratory failure[357]. Doxapram, a nonspecific but relatively safe respiratory stimulant available in some countries as an intravenous formulation, should be used only when noninvasive intermittent ventilation is not available or not recommended[377].

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

Noninvasive mechanical ventilation. Noninvasive intermittent ventilation (NIV) has been studied in several randomized controlled trials in acute respiratory failure, consistently providing positive results with success rates of 80-85%[285,378-380]. These studies provide evidence that NIV improves respiratory acidosis (increases pH, and decreases $PaCO_2$) , decreases respiratory rate, severity of breathlessness, and length of hospital stay (**Evidence A**). More importantly, mortality—or its surrogate, intubation rate—is reduced by this intervention[380-383]. However, NIV is not appropriate for all patients, as summarized in **Figure 5.4-8**[285].

5.4-7: Antibiotic treatment in exacerbations of COPD[a,b] (ref. 177,311,332)

	Oral Treatment *(No particular order)*	Alternative Oral Treatment *(No particular order)*	Parenteral Treatment *(No particular order)*
Group A	***Patients with only one cardinal symptom[c] should not receive antibiotics*** If indication then: • β-lactam (Penicillin, Ampicillin/ Amoxicillin[d]) • Tetracycline • Trimethoprim/ Sulfameth-oxazole	• β-lactam/ β-lactamase inhibitor (Co-amoxiclav) • Macrolides (Azithromycin, Clarithromycin, Roxithromycin[e]) • Cephalosporins - 2nd or 3rd generation • Ketolides (Telithromycin)	
Group B	• β-lactam/ β-lactamase inhibitor (Co-amoxiclav)	• Fluoroquinol-ones[e] (Gemifloxacin, Levofloxacin, Moxifloxacin)	• β-lactam/ β-lactamase inhibitor (Co-amoxiclav, ampicillin/ sulbactam) • Cephalosporins - 2nd or 3rd generation • Fluoroquinol-ones[e] (Levofloxacin, Moxifloxacin)
Group C	In patients at risk for *pseudomonas* infections: • Fluoroquinol-ones[e] (Ciprofloxacin, Levofloxacin - high dose[f])		• Fluoroquinol-ones[e] (Ciprofloxacin, Levofloxacin - high dose[f]) or • β-lactam with *P.aeruginosa* activity

a. All patients with symptoms of a COPD exacerbation should be treated with additional bronchodilators ± 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 Figure 5-4-6 for definition of Groups A, B, and C.)
c. Cardinal symptoms are increased dyspnea, sputum volume, and sputum purulence.
d. This antibiotic is not appropriate in areas where there is increased prevalence of β-lactamase producing *H. influenzae* and *M. catarrhalis* and/or of *S. pneumoniae* resistant to penicillin.
e. Not available in all areas of the world.
f. Dose 750 mg effective against *P. aeruginosa*

Figure 5.4-8. Indications and Relative Contraindications for NIV[311,378,384,385]

Selection criteria

- Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Moderate to severe acidosis (pH ≤ 7.35) and/ or hypercapnia ($PaCO_2$ > 6.0 kPa, 45 mm Hg)[386]
- Respiratory frequency > 25 breaths per minute

Exclusion criteria (any may be present)

- Respiratory arrest
- Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
- Change in mental status; uncooperative patient
- High aspiration risk
- Viscous or copious secretions
- Recent facial or gastroesophageal surgery
- Craniofacial trauma
- Fixed nasopharyngeal abnormalities
- Burns
- Extreme obesity.

Invasive mechanical ventilation. During exacerbations of COPD the events occurring within the lungs include bronchoconstriction, airway inflammation, increased mucus secretion, and loss of elastic recoil, all of which prevent the respiratory system from reaching its passive functional residual capacity at the end of expiration, enhancing dynamic hyperinflation and increasing the work of breathing[387,388]. The indications for initiating invasive mechanical ventilation during exacerbations of COPD are shown in **Figure 5.4-9**, including failure of an initial trial of NIV[389]. As experience is being gained with the generalized clinical use of NIV in COPD, several of the indications for invasive mechanical ventilation are being successfully treated with NIV. **Figure 5.4-10** details some other factors that determine the use of invasive ventilation.

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. 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. Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation.

Contrary to some opinions, acute mortality among COPD patients with respiratory failure is lower than mortality among patients ventilated for non-COPD causes[324]. A study of a large number of COPD patients with acute respiratory failure reported in-hospital mortality of 17-49%[316]. Further deaths were reported over the next 12 months, particularly among those patients who had poor lung function before ventilation (FEV_1 < 30% predicted), had a non-respiratory comorbidity, or were housebound. Patients who did not have a previously diagnosed comorbid condition, had respiratory failure due to a potentially reversible cause (such as an infection), or were relatively mobile and not using long-term oxygen did surprisingly well with ventilatory support.

Figure 5.4-9. Indications for Invasive Mechanical Ventilation

- Unable to tolerate NIV or NIV failure (or exclusion criteria, see **Figure 5.4-8**)
- Severe dyspnea with use of accessory muscles and paradoxical abdominal motion.
- Respiratory frequency > 35 breaths per minute
- Life-threatening hypoxemia
- Severe acidosis (pH < 7.25) and/or hypercapnia ($PaCO_2$ > 8.0 kPa, 60 mm Hg)
- Respiratory arrest
- Somnolence, impaired mental status
- Cardiovascular complications (hypotension, shock)
- Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion)

Figure 5.4-10. Factors Determining the Decision to Initiate Invasive Mechanical Ventilation

- Cultural attitudes toward chronic disability
- Expectations of therapy
- Financial resources (especially the provision of ICU facilities)
- Perceived likelihood of recovery
- Customary medical practice
- Wishes, if known, of the patient

Weaning or discontinuation from mechanical ventilation can be particularly difficult and hazardous in patients with COPD. The most influential determinant of mechanical ventilatory dependency in these patients is the balance between the respiratory load and the capacity of the respiratory muscles to cope with this load[390]. By contrast, pulmonary gas exchange by itself is not a major difficulty in patients with COPD[391-393]. Weaning patients from the ventilator can be a very difficult and prolonged process and the best method (pressure support or a T-piece trial) remains a matter of debate[394-396]. In COPD patients that failed extubation, noninvasive ventilation facilitates weaning and prevents reintubation, but does not reduce

mortality[89,92]. A report that included COPD and non-COPD patients showed that noninvasive mechanical ventilation in patients that failed extubation was not effective in averting the need for reintubation and did not reduce mortality[397].

Other measures. Further treatments that can be used in the hospital include: fluid administration (accurate monitoring of fluid balance is essential); nutrition (supplementary when needed); deep venous thrombosis prophylaxis (mechanical devices, heparins, etc.) in immobilized, polycythemic, or dehydrated patients with or without a history of thromboembolic disease; and 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. There are no data to support the routine use of inhaled N-acetylcysteine or any other measures to increase mucus clearance. Pulmonary rehabilitation by itself is not indicated in COPD exacerbations but may be useful in patients after they recover from the acute event.

Hospital Discharge and Follow-Up

Insufficient clinical data exist to establish the optimal duration of hospitalization in individual patients developing an exacerbation of COPD[312,398,399]. Consensus and limited data support the discharge criteria listed in **Figure 5.4-11**. **Figure 5.4-12** 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[355]. Home visits by a community nurse may permit earlier discharge of patients hospitalized with an exacerbation of COPD, without increasing readmission rates[190,400-402].

In patients hypoxemic during a COPD exacerbation, arterial blood gases and/or pulse oximetry should be evaluated prior to hospital discharge and in the following 3 months. If the patient remains hypoxemic, long-term supplemental oxygen therapy may be required.

Opportunities for prevention of future exacerbations should be reviewed before discharge, with particular attention to smoking cessation, current vaccination (influenza, pneumococcal vaccines), knowledge of current therapy including inhaler technique[32,403,404], and how to recognize symptoms of exacerbations.

Figure 5.4-11. Discharge Criteria for Patients with Exacerbations of COPD

- Inhaled β_2-agonist therapy is required no more frequently than every 4 hrs.
- Patient, if previously ambulatory, is able to walk across room.
- Patient is able to eat and sleep without frequent awakening by dyspnea.
- Patient has been clinically stable for 12-24 hrs.
- Arterial blood gases have been stable for 12-24 hrs.
- Patient (or home caregiver) fully understands correct use of medications.
- Follow-up and home care arrangements have been completed (e.g., visiting nurse, oxygen delivery, meal provisions).
- Patient, family, and physician are confident patient can manage successfully at home.

Figure 5.4-12. Items to Assess at Follow-Up Visit 4-6 Weeks After Discharge from Hospital for Exacerbations of COPD

- Ability to cope in usual environment
- Measurement of FEV_1
- Reassessment of inhaler technique
- Understanding of recommended treatment regimen
- Need for long-term oxygen therapy and/or home nebulizer (for patients with *Stage IV: Very Severe COPD*)

Pharmacotherapy known to reduce the number of exacerbations and hospitalizations and delay the time of first/next hospitalization, such as long-acting inhaled bronchodilators, inhaled glucocorticosteroids, and combination inhalers, should be specifically considered. Early outpatient pulmonary rehabilitation after hospitalization for a COPD exacerbation is safe and results in clinically significant improvements in exercise capacity and health status at 3 months[405]. Social problems should be discussed and principal caregivers identified if the patient has a significant persisting disability.

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CHAPTER

6

TRANSLATING GUIDELINE RECOMMENDATIONS TO THE CONTEXT OF (PRIMARY) CARE

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KEY POINTS:

- There is considerable evidence that management of COPD is generally not in accordance with current guidelines. Better dissemination of guidelines and their effective implementation in a variety of health care settings is urgently required.
- In many countries, primary care practitioners treat the vast majority of patients with COPD and may be actively involved in public health campaigns and in bringing messages about reducing exposure to risk factors to both patients and the public.
- Spirometric confirmation is a key component of the diagnosis of COPD and primary care practitioners should have access to high quality spirometry.
- Older patients frequently have multiple chronic health conditions. Comorbidities can magnify the impact of COPD on a patient's health status, and can complicate the management of COPD.

INTRODUCTION

The recommendations provided in Chapters 1 through 5 define—from a *disease* perspective—best practices in the diagnosis, monitoring, and treatment of COPD. However, (primary) medical care is based on an engagement with *patients*, and this engagement determines the success or failure of pursuing best practice. For this reason, medical practice requires a translation of disease-specific recommendations to the circumstances of individual patients – the local communities in which they live, and the health systems from which they receive medical care. This chapter summarizes a number of key factors in the application of the recommendations in clinical practice, particularly primary care. These factors will determine to a large extent the success with which the GOLD-proposed best practices will be implemented.

It is recognized that the scope of this chapter is limited. It does not cover the wide range of health care workers that provide care for COPD patients, nor the ever increasing need to develop educational curricula that will lead to better skills for COPD diagnosis and management, nor does it explore the essential role of national/regional Medical Societies from many disciplines working together, and in collaboration with public health officials to coordinate key messages to increase COPD awareness and reduce the burden of this disease. These topics are very important and will receive increasing attention in the years to come.

DIAGNOSIS

Early diagnosis and implementation of treatment—especially smoking cessation—have been demonstrated to prevent or delay the onset of airflow limitation or reduce its progression. In pursuing early diagnosis, a policy of identifying patients at high risk of COPD, followed by watchful surveillance of these patients, is advised.

Respiratory Symptoms

Of the chronic symptoms characteristic of COPD (dyspnea, cough, sputum production), dyspnea is the symptom that interferes most with a patient's daily life and health status. When taking the medical history of the patient, it is therefore important to explore the impact of dyspnea and other symptoms on daily activities, work, and social activities, and provide treatment accordingly. History taking is as much listening to the patient as asking questions, and active listening will often reveal the impact of signs/symptoms on the patient's health status. If this process yields insufficient clarity, it can be helpful to use a short questionnaire such as the British Medical Research Council (MRC) questionnaire[1], which measures the impact of dyspnea on daily activities, the Clinical COPD Questionnaire (CCQ)[2], which measures COPD-related symptoms, functional status, and mental health, or the International Primary Care Airways Group (IPAG) Questionnaire which measures COPD-related symptoms and risk factors (http://www.ipag.org).

Spirometry

COPD is both *under*-diagnosed and *over*-diagnosed in most countries. To avoid this, the use and availability of high-quality spirometry should be encouraged. High-quality spirometry in primary care is possible[3,4], provided that good skills training and an ongoing quality assurance program are provided. An alternative is to ensure that high quality spirometry is available in the community, for example, within the primary care practice itself, in a primary care laboratory, or in a hospital setting, depending on the structure of the local health care system[5]. Ongoing

collaboration between primary care and respiratory care also helps assure quality control.

Although confirmation of the diagnosis of COPD and assessment of disease severity are established by spirometry, in many countries primary care practitioners diagnose COPD on clinical grounds alone[6]. Several factors are responsible for this situation, including poor recognition of the essential role of spirometry in the diagnosis of COPD, and lack of adequate training in its use and interpretation[6-8]. There is a clear necessity for further education initiatives targeted to all primary care practitioners in order to address these factors.

However, in many areas practitioners lack access to spirometry, especially state-of-the-art spirometry. Under such conditions it is not possible to fully apply the recommendations in this report, and diagnosis of COPD has to be made with the tools available. Use of peak flow meters may be considered, provided that the limited (positive and negative) predictive value of peak flow meters for the diagnosis of COPD is clearly understood. Low peak flow is consistent with COPD but has poor specificity, since it can be caused by other lung diseases or by poor performance. The use peak flow should not impede the implementation of spirometry.

COMORBIDITIES

Older patients frequently have multiple chronic health conditions. It has been estimated that worldwide, 25% of people over age 65 suffer from two of the five most common chronic diseases (which include COPD), and 10% suffer from three or more. These figures rise to 40% and 25%, respectively, among those 75 and older[9].

The severity of comorbid conditions and their impact on a patient's health status will vary between patients and in the same patient over time. Comorbidities can be categorized in various ways to aid in the better understanding of their impact on the patient, and their impact on disease management[10].

- *Common pathway comorbidities:* diseases with a common pathophysiology—for instance, in the case of COPD, other smoking-related diseases such as ischemic heart disease and lung cancer
- *Complicating comorbidities:* conditions that arise as a complication of a specific preexisting disease—in the case of COPD, pulmonary hypertension and consequent heart failure. Early intervention is directed at preventing complications and the effectiveness of these early interventions should be monitored.
- *Co-incidental comorbidities:* Coexisting chronic conditions with unrelated pathogenesis. Particularly in diseases like COPD that are related to aging, there is a high chance of co-incidental comorbidity such as bowel or prostate cancer, depression, diabetes mellitus, Parkinson's disease, dementia, and arthritis. Such conditions may make COPD management more difficult.
- *Inter-current comorbidities:* Acute illnesses that may have a more severe impact in patients with a given chronic disease. For example, upper respiratory tract infections are the most frequent health problem in all age groups, but they may have a more severe impact or require different treatment in patients with COPD.

REDUCING EXPOSURE TO RISK FACTORS

Reduction of total personal exposure to tobacco smoke, occupational dusts and chemicals, and indoor and outdoor air pollutants, including smoke from cooking over biomass fueled fires, are important goals to prevent the onset and progression of COPD. In many health care systems, primary care practitioners may be actively involved in public health campaigns and can play an important part in bringing messages about reducing exposure to risk factors to patients and the public. Primary care practitioners can also play a very important role in reinforcing the dangers of passive smoking and the importance of implementing smoke-free work environments.

Smoking cessation: Smoking cessation is the most effective intervention to reduce the risk of developing COPD, and simple smoking cessation advice from health care professionals has been shown to make patients more likely to stop smoking. Primary care practitioners often have many contacts with a patient over time, which provides the opportunity to discuss smoking cessation, enhance motivation for quitting, and identify the need for supportive pharmacological treatment. It is very important to align the advice given by individual practitioners with public health campaigns in order to send a coherent message to the public.

IMPLEMENTATION OF COPD GUIDELINES

GOLD has developed a network of individuals, the GOLD National Leaders, who are playing an essential role in the dissemination of information about prevention, early diagnosis, and management of COPD in health systems around the world. A major GOLD program activity that has helped to bring together health care teams at the local level is World COPD Day, held

annually on the third Wednesday in November (http://www.goldcopd.org/WCDIndex.asp). GOLD National Leaders, often in concert with local physicians, nurses, and health care planners, have hosted many types of activities to raise awareness of COPD. WONCA (the World Organization of Family Doctors) is also an active collaborator in organizing World COPD Day activities. Increased participation of a wide variety of health care professionals in World COPD Day activities in many countries would help to increase awareness of COPD.

GOLD is a partner organization in a program launched in March 2006 by the World Health Organization, the Global Alliance Against Chronic Respiratory Diseases (GARD). The goal is to raise awareness of the burden of chronic respiratory diseases in all countries of the world, and to disseminate and implement recommendations from international guidelines. Information about the GARD program can be found at http://www.who.int/respiratory/gard/en/.

Although awareness and dissemination of guidelines are important goals, the actual implementation of a comprehensive care system in which to coordinate the management of COPD will be important to pursue. Evidence is increasing that a chronic disease management program for COPD patients that incorporates a variety of interventions, includes pulmonary rehabilitation, and is implemented by primary care reduce hospital admissions and bed days. Key elements are patient participation and information sharing among health care providers[11].

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