Medical Education Systems, Inc.

COPD: THE GOLD REPORT

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COPD: The Gold Report

Learning Objectives

Upon successful completion of this CEU, you will be able to:

- Explain what the Gold Report is, and discuss its importance to health care professionals treating COPD.
- Identify the “working” definition of COPD as provided by the Gold Report.
- Explain the prevalence COPD and the impact it is having on worldwide health.
- Discuss the *etiology* and *epidemiology* of COPD, and explain how it is diagnosed.
- Describe the latest international standards presented by the Gold Report regarding prevention, management, and treatment protocols for COPD.
- Identify and discuss the usefulness and side effects of medications currently in use for COPD patients.

Global Initiative for Chronic Obstructive Lung Disease (GOLD)

The condition known as COPD has been associated with considerable confusion and disagreement among health care professionals. Even defining the term has been somewhat controversial—much less determining how to diagnose and manage the condition. Given the relative confusion and disagreement among health care professionals regarding the topic of “COPD,” it was an historic breakthrough that on April 4, 2001, the medical world was greeted with the following important news release:

Latest update: 2017

International Guidelines Released on Chronic Obstructive Lung Disease (COPD)
Fourth Leading Cause of Death in US and Worldwide

The first international guidelines for the diagnosis, management, and prevention of Chronic Obstructive Lung Disease (COPD) — currently the fourth leading cause of death in the US and worldwide — were released today by an international team of scientists from the Global Initiative for Chronic Obstructive Lung Disease (GOLD). The *GOLD Workshop Report*, which provides evidence-based recommendations for the clinical management of COPD, is the first step in an international effort to boost awareness of COPD and improve the way it is treated. GOLD was created by the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health and the World Health Organization.

According to NHLBI Director Dr. Claude Lenfant, "COPD has become a major public health problem worldwide. That's why we, with the WHO, initiated this program. We hope that this report will increase worldwide awareness of COPD and help the millions of people who suffer from this disease."

COPD, a term used to describe chronic bronchitis and emphysema, is a slowly progressive airways disease characterized by a gradual loss of lung function. In the US, it is caused primarily by cigarette smoking. There is no known cure, but smoking cessation can slow disease progression.

COPD has been on the increase in the US, and in 2017, an estimated 11 million Americans had COPD. The number of deaths attributed to COPD has also increased substantially in the past 40 years, with over 130,000 deaths from COPD in 2010. The highest rate of increase in deaths has been seen in white women.

It is expected that by 2020, COPD will rank as the third leading cause of death, surpassing stroke. In 2010, the annual cost of COPD to the US economy is estimated at nearly $32 billion in direct costs, and 20.4 billion in indirect costs.

The GOLD Report, which was reviewed extensively by medical societies in more than 100 countries throughout both the developed and developing world, emphasizes the need for clinicians and patients to recognize cough and sputum production as early signs of possible COPD and calls for the use of spirometry, a simple test of lung function, to confirm the diagnosis. It also provides a general scheme for classifying COPD by severity to help clinicians determine how best to manage the condition. Practical recommendations for reducing risk factors and for managing both stable COPD and exacerbations are also provided.

Said Lenfant, "A concerted effort by government officials, health care workers, biomedical researchers, industry, and patients throughout the world is required to improve the way COPD is diagnosed and managed and to increase research into improved treatments and ultimately a cure. This effort has begun with the launch of the GOLD Initiative today."

Subsequent to the issuance of this press release, the report itself was made available, and we present the most relevant sections of that report here:

The Report

Preface

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

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

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

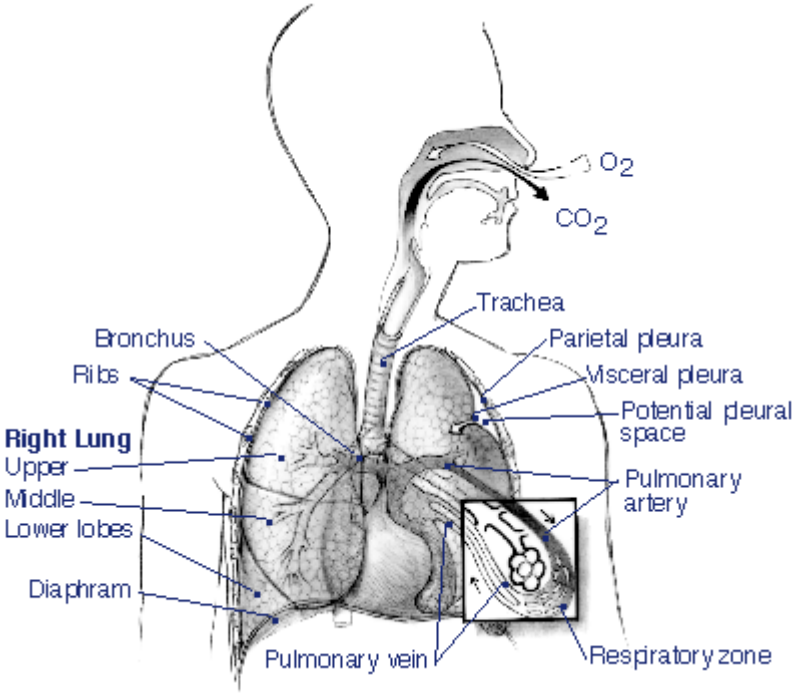
I would like to acknowledge the dedicated individuals who prepared the Workshop Report and the effective leadership of the Workshop Chair, Professor Romain Pauwels. It is a privilege for the National Heart, Lung, and Blood Institute to serve as one of the cosponsors. We look forward to working with the World Health Organization, and all other interested organizations and individuals, to meet the goals of the GOLD Initiative.

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

Claude Lenfant, MD
Director
National Heart, Lung, and Blood Institute

Introduction

Human Respiratory System



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 currently the fourth leading cause of death in the world, and further increases in its prevalence and mortality can be predicted in the coming decades. A unified international effort is needed to reverse these trends.

The **G**lobal Initiative for Chronic **O**bstructive **L**ung **D**isease (**GOLD**) is conducted in collaboration with the US National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO). Its goals are to increase awareness of COPD and decrease morbidity and mortality from 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 a renewed research interest in this highly prevalent disease.

A nihilistic attitude toward COPD has arisen 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. The GOLD project will work toward combating this nihilistic attitude by disseminating information about available treatments, both pharmacologic and non-pharmacologic.

Tobacco smoking is a major cause of COPD, as well as of many other diseases. A 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 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, investigation of COPD risk factors and ways to reduce exposure to these factors is also an important area for future research. New research tools have recently revealed that inflammation plays a prominent role in COPD pathogenesis, but this inflammation is different than that involved in asthma. Further study of the molecular and cellular mechanisms involved in COPD pathogenesis should lead to effective treatments that slow or halt the course of the disease.

GOLD WORKSHOP REPORT: *GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD*

One strategy to help achieve GOLD's objectives 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 Workshop 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 has been developed by individuals with expertise in COPD research and patient care and extensively reviewed by many experts and scientific societies. It provides state-of-the-art information about COPD for pulmonary specialists and other interested physicians. The document will also serve as a source for the production of various communications during the implementation of the GOLD program, including a practical guide for primary care physicians and a document for use in developing countries.

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 *Pathogenesis, Pathology, 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 lungs characteristic of the disease.

A major part of the GOLD Workshop 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 Acute Exacerbations*. Management recommendations are largely symptom driven and 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.

The final chapter identifies critical gaps in knowledge requiring *Further Research* and provides a summary of proposed directions for the development of new therapeutic approaches.

METHODS USED TO DEVELOP THIS REPORT

In January, 1997, COPD experts from several countries met in Brussels, Belgium to explore the development of a Global Initiative for Chronic Obstructive Lung Disease. Dr. Romain Pauwels served as Chair; representatives of the NHLBI and WHO attended. Participants agreed that the project was timely and important, and recommended the establishment of a panel with expertise on a wide variety of COPD-related topics to prepare an evidence-based document on diagnosis, management, and prevention of COPD. NHLBI and WHO staff, in concert with Dr. Pauwels, identified individuals from many regions of the world to serve on the Expert Panel, which included health professionals in the areas of respiratory medicine, epidemiology, pathology, socio-economics, public health, and health education.

The first step toward developing the Workshop Report was to review the multiple COPD guidelines already published. The NHLBI collected these guidelines and prepared a summary table of similarities and differences between the documents. Where agreement existed, the Expert Panel drew on these existing documents for use in the Workshop Report. Where major differences existed, the Expert Panel agreed to carefully examine the scientific evidence to reach an independent conclusion.

In September, 1997, several members of the Expert Panel met with a consultant to develop a comprehensive set of terms to build a database of COPD literature. The database and a computer program to search the world literature on COPD have been developed, and they will be placed on the Internet and cross-referenced with the Workshop Report to help keep the Report current as new literature is published.

In April, 1998, the NHLBI and WHO cosponsored a workshop to begin the development of the Report. Workshop participants were divided into three groups: definition and natural history, chaired by Dr. Sonia Buist; pathophysiology, risk factors, diagnosis, and classification of severity, chaired by Dr. Leonardo Fabbri; and management, chaired by Dr. Romain Pauwels. A table of contents was developed and writing assignments were made. The Panel agreed that clinical recommendations would require scientific evidence, or would be clearly labeled as "expert opinion." Each chapter would contain a set of the most current and representative references.

In September, 1998, the Panel met to evaluate its progress. Members reviewed a variety of evidence tables and chose to assign levels of evidence to statements using the system developed by the NHLBI (**Figure A**). Levels of evidence are assigned to management recommendations where appropriate in *Chapter 5, Management of COPD*, and 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 (e.g., a meta-analysis of a number of smaller studies was considered to be evidence level B). The panel met in May, 1999, September, 1999, and May, 2000 in conjunction with meetings of the American Thoracic Society (ATS) and the European Respiratory Society (ERS). Symposia were held at these meetings to present the developing program and to solicit opinion and comments. The meeting in May, 2000 was the final consensus workshop.

After this workshop, the document was submitted for review to individuals and medical societies interested in the management of COPD. The reviewers' comments were incorporated, as appropriate, into the final document by the Chair in cooperation with members of the Expert Panel. Prior to its release for publication, the Report was reviewed by the NHLBI and the WHO. A workshop was held in September, 2000 to begin implementation of the GOLD program.

In 2015 and 2016, while preparing the annual updated reports (www.goldcopd.org) Gold science committee reviewed literature and modified all their information on COPD, making it more relevant and available to health practitioners around the world.

Figure A

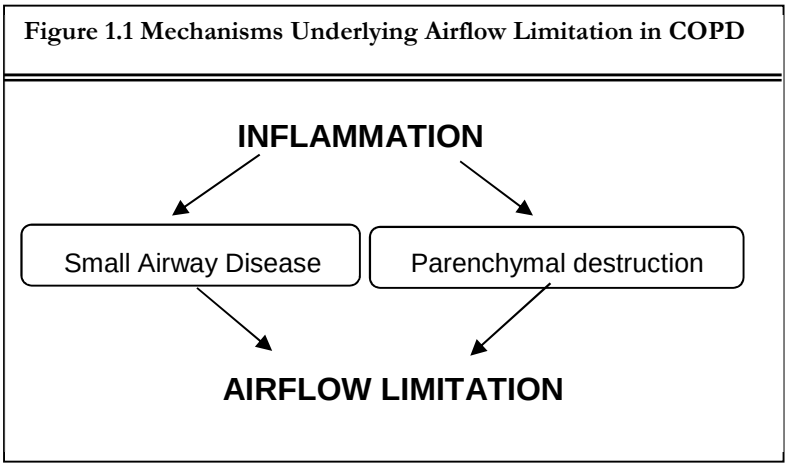
EVIDENCE QUALITY GRADES FOR THE BODY OF EVIDENCE

Grade	Evidence
A	Well-designed randomized controlled trials or diagnostic studies performed on a population similar to the guideline's target population
B	Randomized controlled trials or diagnostic studies with minor limitations; genetic natural history studies; overwhelmingly consistent evidence from observational studies
C	Observational studies (case-control and cohort design)
D	Expert opinion, case reports, or reasoning from first principles (bench research or animal studies)

Chapter 1: Definition

KEY POINTS:

Figure 1.1 Mechanisms Underlying Airflow Limitation in COPD



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

• The four-stage classification of COPD severity used throughout this report provides an educational tool and a general indication of the approach to management. This conceptual framework also emphasizes that COPD is usually progressive if exposure to the noxious agent is continued.

• The characteristic symptoms of COPD are cough, sputum production, and dyspnea upon exertion.

• Chronic cough and sputum production often precede the development of airflow limitation by many years and these symptoms identify individuals at risk of developing COPD.

• The focus of this Workshop Report is primarily on COPD caused by inhaled particles and gases, the most common of which worldwide is tobacco smoke.

• COPD can coexist with asthma, the other major chronic obstructive airway disease characterized by an underlying airway inflammation. However, the inflammation characteristic of COPD is distinct from that of asthma.

• Pulmonary tuberculosis may affect lung function and symptomatology and, in areas where tuberculosis is prevalent, can lead to confusion in the diagnosis of COPD.

DEFINITION

For years, clinicians, physiologists, pathologists, and epidemiologists have struggled with the definitions of disorders associated with chronic airflow limitation, including chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), and asthma.

The definitions of these terms variably emphasize structure and function and are often based on whether the term is used for clinical or research purposes. For example, epidemiologists have created terminology and

criteria, based on functional status that can be monitored in population-based studies or studies of physicians' diagnoses.

A working definition of Chronic Obstructive Pulmonary Disease (COPD) is: ***a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.*** Symptoms, functional abnormalities, and complications of COPD can all be explained on the basis on this underlying inflammation and the resulting pathology.

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. Chronic inflammation causes remodeling 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 measured by spirometry, as this is the most widely available, reproducible test of lung function.

Many previous definitions of COPD have emphasized the terms "emphysema" and "chronic bronchitis," which are no longer included in the definition of COPD used in this report. 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.

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. If exposure is stopped, the disease may still progress due to the decline in lung function that normally occurs with aging. Nevertheless, stopping exposure to noxious agents, even after significant airflow limitation is present, can result in some improvement in function and will certainly slow or even halt the progression of the disease.

Classification of Severity: Stages of COPD

For educational reasons, a simple classification of disease severity into four stages is recommended (**Figure 1-2**). The staging is based on airflow limitation as measured by spirometry, which is essential for diagnosis and provides a useful description of the severity of pathological changes in COPD. Specific FEV_1 cut-points (e.g.,< 80% predicted) are used for purposes of simplicity: these cut-points have not been clinically validated.

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) and complications of the disease. 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.

The characteristic symptoms of COPD are cough, sputum production, and dyspnea upon exertion. Chronic cough and sputum production often precede the development of airflow limitation by many years, although not all individuals with cough and sputum production go on to develop COPD. This pattern offers a unique opportunity to identify those at risk for COPD and intervene when the disease is not yet a health problem. A major objective of GOLD is to increase awareness among health care providers and the general public of the significance of these symptoms.

Chronic Obstructive Pulmonary Disease (COPD) is usually assessed by considering the specific COPD Symptoms exhibited, and a quantifiable parameter known as Lung Function.

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

Stage I: Mild COPD—Characterized by mild airflow limitation ($FEV_1/FVC < 70\%$ but $FEV_1 > 80\%$ predicted) and usually, but not always, by chronic cough and sputum production. At this stage, the individual may not even be aware that his or her lung function is abnormal. This underscores the importance of health care providers doing spirometry in all smokers so that their lung function can be observed and recorded over time.

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

Stage III—Severe COPD: Characterized by severe airflow limitation ($FEV_1 < 30\%$ predicted) or the presence of respiratory failure or clinical signs of right heart failure. Respiratory failure is defined as an arterial partial pressure of oxygen (PaO2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO2 (PaCO2) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level. 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 severe (Stage III) 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 exacerbations may be life threatening.

Stage IV—Very Severe COPD: Characterized by severe airflow limitation (FEV_1 FVC < 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 O2 (PaO2) less than 8.0 kPa (60 mm Hg), with or without arterial partial pressure of CO1 (PaCo2) greater than 6.7 kPa (50 mm Hg) while lead to effects on the heart such as cor pulmonale (right heart failure). Patients may have Stage IV even if the FEV_1 is < 30% predicted, whenever these complications are present. At this stage, quality of like ifs very appreciably impaired and exacerbations may be life threatening.

Figure 1.2 - Classification of COPD by Severity

Stage	Characteristics
I: Mild COPD	**COPD Stage 1** is considered *mild COPD* or *early stage COPD*. **Lung Function FEV_1%** is measured in the range 80 - 100% for Stage 1 COPD. The **Major Symptom of Stage 1 COPD** is a *chronic cough* that produces mucus from the lungs.
II: Moderate COPD	**COPD Stage 2** is considered as *moderately progressed COPD*. **Lung Function FEV_1%** is measured in the range 50 - 79% for Stage 2 COPD. **Major Symptoms for Stage 2 COPD** include: • A *chronic cough* that produces considerable mucus from the lungs • *Breathlessness*, especially when exercising • *COPD Exacerbations* have occurred
III: Severe COPD	**COPD Stage 3** is considered as *severely progressed COPD*. **Lung Function FEV_1%** is measured in the range 30 - 49% for Stage 3 COPD. **Major Symptoms for Stage 3 COPD** include: • A *chronic cough* that produces considerable mucus from the lungs • *Breathlessness and fatigue* that reduces the patients' ability to exercise • *Multiple COPD Exacerbations* have occurred, including severe exacerbations.
IV: Very Severe COPD	**COPD Stage 4** is considered as *very severely progressed COPD*. In Stage 4 COPD, **Lung Function FEV_1%** is measured below 30%, or below 50% with chronic respiratory failure due to retention of carbon dioxide. **Major Symptoms for Stage 4 COPD** include • A *chronic cough* that produces considerable mucus from the lungs • *Severe breathlessness and fatigue* that considerably reduces the patients' ability to exercise • *More frequent COPD Exacerbations*, including life-threatening exacerbations.

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

Variable Course of COPD

The common statement that only 15-20% of smokers develop clinically significant COPD is misleading. A much higher proportion develops abnormal lung function at some point if they continue to smoke. 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.

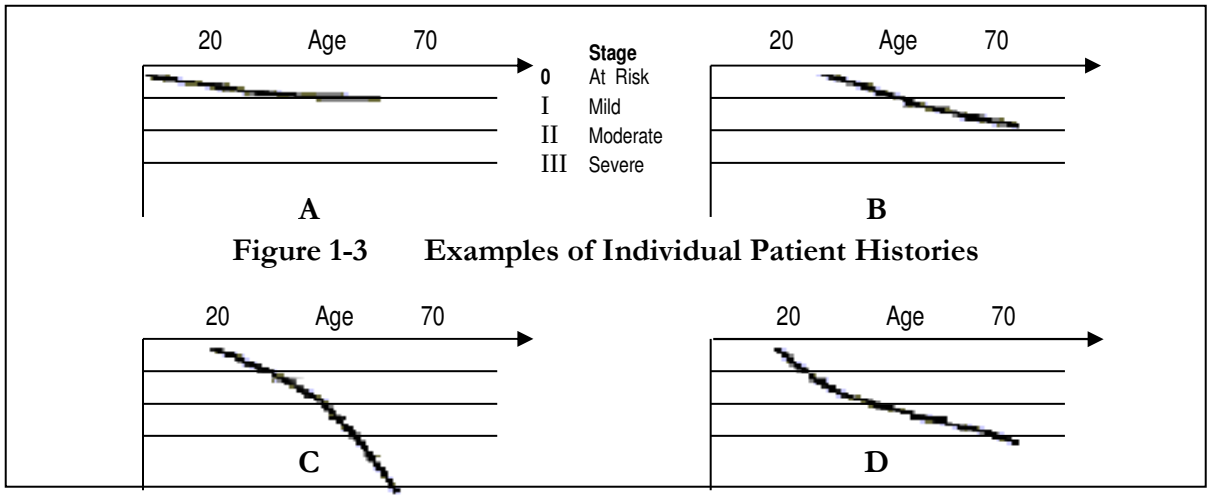


Figure 1-3 Examples of Individual Patient Histories

Figure 1-3 shows four examples of the various courses that individual COPD patients may follow. Panel A illustrates an individual who has cough and sputum production, but never develops abnormal lung function (as defined in this Report). Panel B illustrates an individual who develops abnormal lung function but who may never come to diagnosis. Panel C illustrates a person who develops abnormal lung function around age 50, then progressively deteriorates over about 15 years and dies of respiratory failure at age 65. Panel D illustrates an individual who develops abnormal lung function in mid-adult life and continues to deteriorate gradually but never develops respiratory failure and does not die as a result of COPD.

SCOPE OF THE REPORT

The focus of this Report is primarily on COPD caused by inhaled particles and gases, the most common of which worldwide is tobacco smoke. Poorly reversible airflow limitation associated with bronchiectasis, cystic fibrosis, tuberculosis, or asthma is not included 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. Asthma and COPD have their major symptoms in common, but these are generally more variable in asthma than in COPD. The underlying chronic airway inflammation is also very different (Figure 1-4): that in asthma is mainly eosinophilic and driven by CD4+ T lymphocytes, while that in COPD is neutrophilic and characterized by the presence of increased numbers of macrophages and CD8+ T lymphocytes. In addition, airflow limitation in asthma is often completely reversible, either spontaneously or with treatment, while in COPD it is never fully reversible and is usually progressive if exposure to noxious agents continues. Finally, the responses to treatment of asthma and COPD are dramatically different, in terms of both the overall magnitude of the achievable response and the qualitative effects of specific treatments such as anticholinergics and corticosteroids. However, there is undoubtedly an overlap between asthma and COPD. Individuals with asthma who are exposed to noxious agents that cause COPD may develop a mixture of "asthma-like" inflammation and "COPD-like" inflammation. There is also evidence that longstanding asthma

on its own can lead to airway remodeling and partly irreversible airflow limitation. Asthma can usually be distinguished from COPD, but until the causal mechanisms and pathognomonic markers of these diseases are better understood it will remain difficult to differentiate the two diseases in some individual patients. Given the current state of medical and scientific knowledge, an attempt to determine an absolutely rigid definition of COPD or asthma is bound to end up in semantics.

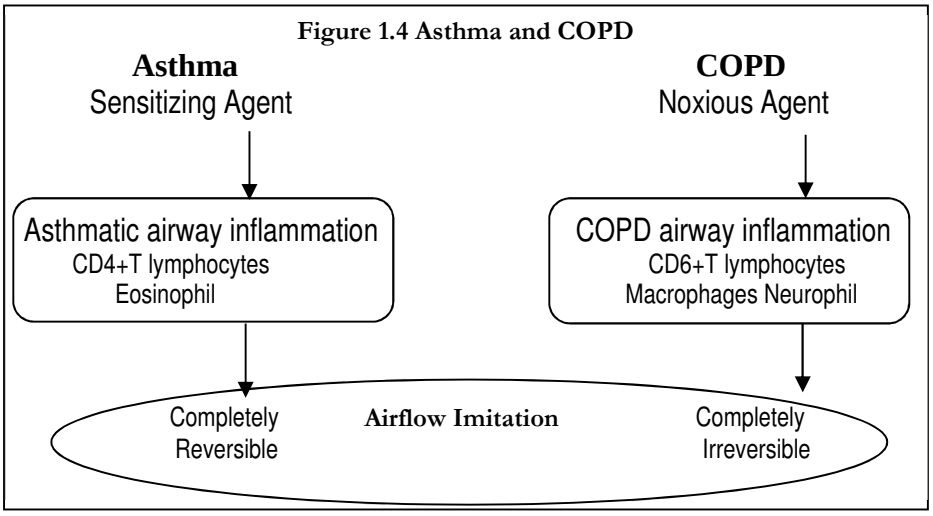


Figure 1.4 Asthma and COPD

Pulmonary Tuberculosis and COPD

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

Chronic bronchitis/bronchiolitis and emphysema often occur as complications of pulmonary tuberculosis and are important contributors to the mixed lung function changes characteristic of tuberculosis. The degree of obstructive airway changes in treated patients with pulmonary tuberculosis increases with age, the amount of cigarettes smoked, and the extent of the initial tuberculous disease. In patients with both diseases, COPD adds to the disability of pulmonary tuberculosis, and vice versa.

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. Investigations to exclude tuberculosis should be a routine part of COPD diagnosis, the intensity of the diagnostic procedures depending on the degree of suspicion. Chest radiograph and sputum culture are helpful in making the differential diagnosis.

Chapter 2: The Burden of COPD

KEY POINTS:

• COPD prevalence and morbidity data that are available probably greatly underestimate the total burden of the disease because it is not usually recognized and diagnosed until it is clinically apparent and moderately advanced.

• Prevalence, morbidity, and mortality vary appreciably across countries, but in all countries where data are available COPD is a significant health problem in both men and women.

• The substantial increase in the global burden of COPD projected over the next twenty years reflects, in large part, the increasing use of tobacco worldwide, and the changing age structure of populations in developing countries.

• Medical expenditures for treating COPD and the indirect costs of morbidity can represent a substantial economic and social burden for societies and public and private payers worldwide. Nevertheless, very little economic information concerning COPD is available**.**

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 appreciably across countries and across different groups within countries, but in general are directly related to the prevalence of tobacco smoking. Most epidemiological studies have found that COPD prevalence, morbidity, and mortality have increased over time and are greater in men than in women. Very few studies have quantified the economic and social burden of COPD. In developed countries, the direct medical costs of COPD are substantial because the disease is both chronic and highly prevalent. In developing countries, the indirect cost of COPD from loss of work and productivity may be more important than the direct costs of medical care.

EPIDEMIOLOGY

Most of the information available on COPD prevalence, morbidity, and mortality comes from developed countries. Even in these countries, accurate epidemiological data on COPD are difficult and expensive to collect. Prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced. The imprecise and variable definitions of COPD have made it hard to quantify the morbidity and mortality of this disease in developed and developing countries. Mortality data also underestimate COPD as a cause of death because the disease is more likely to be cited as a contributory than as an underlying cause of death, or may not be cited at all[2].

Prevalence

Available estimates of COPD prevalence have been developed by determining either the proportion of the population that reports having respiratory symptoms and/or airflow limitation, or the proportion that reports having been diagnosed with COPD, chronic bronchitis, or emphysema by a physician. Each of these approaches will yield a different estimate, and may be useful for different purposes.

For example, studies that ask about the full range of COPD symptoms from early to advanced disease are useful to estimate the *total* societal burden of the disease. Data on doctor diagnoses of COPD are useful to

estimate the prevalence of *clinically significant* disease that is of sufficient severity to require health services, and therefore is likely to incur significant costs.

The population surveys necessary to develop accurate estimates of COPD prevalence are costly to do and therefore have not been conducted in many countries. Obtaining reliable prevalence data for COPD in each country should be a priority in order to alert those responsible for planning prevention services and health care delivery to the high prevalence and cost of the disease. The prevalence of COPD is likely to vary appreciably depending on the prevalence of risk factor exposure, age distribution, and prevalence of susceptibility genes in different countries.

Until recently, virtually all population-based studies in developed countries showed a markedly greater prevalence and mortality of COPD among men compared to women. Gender-related differences in exposure to risk factors, mostly cigarette smoking, probably explain this pattern. In developing countries, some studies report a slightly higher prevalence of COPD in women than men. This likely reflects exposure to indoor air pollution from cooking and heating fuels (greater among women) as well as exposure to tobacco smoke (greater among men). Recent large population-based studies in the US show a different pattern emerging, with the prevalence of COPD almost equal in men and women. This likely reflects the changing pattern of exposure to the most important risk factor, tobacco smoke.

Estimates based on self-report of respiratory symptoms. COPD prevalence data based on self-report of respiratory symptoms (chronic cough, sputum production, wheezing, and shortness of breath) include people at risk for COPD (*Stage 0*) as well as those with airflow limitation, and thus yield maximum prevalence estimates. These studies reveal sizable variations in the prevalence of respiratory symptoms depending on smoking status, age, occupational and environmental exposures, country or region, and, to a lesser extent, gender and race. The data also reveal appreciable variations over time, reflecting important temporal changes in populations' exposure to risk factors such as smoking, outdoor air pollution, and occupational exposures.

The third National Health and Nutrition Examination Survey (NHANES 3), a large national survey conducted in the US, included self-report questions about respiratory symptoms. The prevalence of respiratory symptoms varied markedly by smoking status (current>ex>never). Among white males, chronic cough was reported by 24% of smokers, 4.7% of ex-smokers, and 4.0% of never smokers. The prevalence of chronic cough among white women was 20.6% in smokers, 6.5% in ex-smokers, and 5.0% in never smokers. There was a smaller gradient in the prevalence of chronic cough by race (white>black). The prevalence of sputum production was similar to that of chronic cough in these groups.

Estimates based on the presence of airflow limitation. People may have respiratory symptoms such as cough and sputum production for many years before developing airflow limitation. Thus, COPD prevalence data based on the presence of airflow limitation provide a more accurate estimate of the burden of COPD that is, or probably soon will be, clinically significant. However, the use of different cut points to define airflow limitation makes comparing the results of different studies difficult.

In the NHANES 3 study, airflow limitation was defined as an

$FEV_1/FVC < 70\%$. The prevalence of airflow limitation was lower than the prevalence of respiratory symptoms found in the same study, but both sets of data reinforce the view that smoking is the most important determinant of COPD prevalence in developed countries. Among white males, airflow limitation was present in 4.2% of current smokers, 6.9% of ex-smokers, and 3.3% of never smokers. Among white females, the

prevalence of airflow limitation was 13.6% in smokers, 6.8% in ex-smokers, and 3.1% in never smokers. Airflow limitation was more common among white smokers than among black smokers.

Estimates based on physician diagnosis of COPD. COPD prevalence data based on physician diagnosis provide information about the prevalence of clinically significant COPD that is of sufficient severity to prompt a visit to a physician. Few population-based prevalence surveys have been published to provide this information, and available data are often confusing because asthma and COPD diagnoses are not separated, all age groups are considered together, or chronic bronchitis and emphysema are considered separately.

Global Burden of Disease Study used data from both published and unpublished studies to estimate the prevalence of various diseases in different countries and regions around the world. The study finds that asthma is the most common chronic respiratory disease worldwide, with twice the number of cases of COPD in 2015, but that deaths from COPD were eight times more common than deaths from asthma. Many cases of asthma and COPD can be treated or prevented with affordable interventions, but people are often left undiagnosed, misdiagnosed, or undertreated.

The prevalence of COPD is highest in countries where cigarette smoking has been, or still is, very common, while the prevalence is lowest in countries where smoking is less common, or total tobacco consumption per capita is still low. Disease burden due to COPD in 2015 was highest in Papua New Guinea, India, Lesotho, and Nepal, and burden of asthma was highest in Afghanistan, Central African Republic, Fiji, Kiribati, Lesotho, Papua New Guinea, and Swaziland. The lowest COPD disease burden was seen in some countries in high-income Asia Pacific, Central Europe, North Africa and the Middle East, the Caribbean, Western Europe, and Andean Latin America, and the lowest asthma disease burden was seen in countries in Eastern and Central Europe, plus China, Italy, and Japan.

The main risk factors for COPD were smoking and air pollution, followed by household air pollution, occupational risks (such as exposure to asbestos, diesel fumes, arsenic, and benzene), ozone, and secondhand smoke, leading the authors to call for public health interventions to reduce air pollution and further reduce global smoking rates.

Morbidity

Morbidity includes physician visits, emergency department visits, and hospitalizations. 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 women

In 2008, there were about 822,500 hospital stays for chronic obstructive pulmonary disease (COPD) among adults age 40 years and older. COPD stays that explicitly coded an acute exacerbation accounted for 514,000 (62.5 percent) of all COPD stays. The remaining COPD stays discharged with a principal diagnosis of COPD, but without explicitly noting “acute exacerbation,” accounted for 308,500 (37.5 percent) of COPD hospitalizations. Thus, nearly 1 out of every 5 patients 40 years or older in U.S. hospitals has a diagnosis of COPD. The mean length of hospitalizations (about 4.7 days) and average cost per stay ($7,500) were similar for acute exacerbation and other COPD hospitalizations. Hospitalization rates were also highest in the poorest communities (533 versus 312 stays per 100,000) and in rural areas (563 stays versus 305 stays per 100,000 in large metropolitan areas), where smoking rates tend to be higher.

Mortality

The WHO reported that 3 million people died of COPD in 2005. That represents 5 percent of all deaths worldwide. Ninety percent of those deaths take place in low or middle-income regions. It is the third leading cause of death in the United States. In 2010, COPD claimed 134,676 American lives.

According to the American Lung Association, smoking is linked to about 80 percent of all COPD deaths. In women, smokers are 13 times more likely to die from COPD than non-smoking women. For men, smokers are 12 times more likely to die from COPD than their non-smoking counterparts. The lowest death rate is among Hispanics. Almost 80 percent of COPD-related deaths are among non-Hispanic whites.

ECONOMIC AND SOCIAL BURDEN OF COPD

Because COPD is highly prevalent and can be severely disabling, direct medical expenditures and the indirect costs of morbidity and premature mortality from COPD can represent a substantial economic and social burden for societies and public and private insurance payers worldwide. Nevertheless, very little quantitative information concerning the economic and social burden of COPD is available in the literature today.

Cost of illness studies provide insight into the economic impact of a disease. Some countries attempt to separate economic burden into disease-attributable direct and indirect costs. The direct cost is the value of health care resources devoted to diagnosis and medical management of the disease. Indirect costs reflect the monetary consequences of disability, missed work and school, premature mortality, and caregiver or family costs resulting from the illness. Data on these topics from developing countries are not available, but data from the US and some European countries provide an understanding of the economic burden of COPD in developed countries.

***United States*.** The costs of chronic obstructive pulmonary disease (COPD) pose a major economic burden to the United States. Thirteen articles reporting comprehensive estimates of the direct costs of COPD (costs related to the provision of medical goods and services) were identified from searches of relevant primary literature published since 1995. The National Heart, Lung, and Blood Institute (NHLBI) provides the single current estimate of the total (direct plus indirect) annual cost of COPD to the U.S., $38.8 billion in 2005 dollars. More than half of this cost ($21.8 billion) was direct, aligning with the $20-26 billion range reported by two other recent analyses of large national datasets. For per-patient direct costs in 2005 studies yield attributable cost estimates in the range of $2,700-$5,900 annually, and excess cost estimates in the range of $6,100-$6,600 annually.

On average, COPD patients in the U.S. lose around $1,800 of their income each year as a direct result of their condition. This equates to a lifetime loss of nearly $20,000. Nearly 1 in 5 of 45-67 year olds with COPD are forced to retire prematurely due to their condition, thereby incurring increased healthcare utilization costs, reducing personal tax and pension contributions and increasing government disability costs. The impact of COPD on people’s earning power and overall income makes them concerned about its impact on their lives, and those of their families, and therefore their ability to maintain the same lifestyle as they had before.

Despite considerable advances in the management of COPD over recent years, there remain a number of outstanding issues. These include the fact that patients continue to endure disabling symptoms, which worsen as the disease progresses, and many patients still die directly or indirectly of COPD and its complications. The burden of the disease to society is high, and the societal costs of patients with severe COPD are 4 to 17 times

higher than those of patients with mild disease. Patients with comorbid conditions (accounting for 30–57% of patients in different countries) are also costly to society.

Although current drug therapy has not been shown to have any significant effect on the accelerated loss of lung function, it does produce significant improvements in symptoms and health status, and reduces the frequency of exacerbations. Reducing the burden of COPD requires better evaluation and diagnosis, as well as improved management of chronic symptoms. A high priority should be given to interventions aimed at delaying the progression of disease, preventing exacerbations, and reducing the risk of comorbidities, to alleviate the clinical and economic burden of COPD. The goal of modern COPD management is the development of therapies that affect the natural history of the disease and, in particular, reduce mortality.

Chapter 3: Risk Factors

KEY POINTS:

Figure 3-1. Risk Factors for COPD	
Host Factors	• Genes (e.g., alpha-1 antitrypsin deficiency) • Airway Hyperresponsiveness • Lung Growth
Exposures	• Tobacco Smoke • Occupational Dusts and Chemicals • Indoor and Outdoor Air Pollution • Infections • Socioeconomic Status

• Risk factors for COPD include both host factors and environmental exposures, and the disease usually arises from an interaction between these two types of factors.

• The host factor that is best documented is a rare hereditary deficiency of alpha-1 antitrypsin. Other genes involved in the pathogenesis of COPD have not yet been identified.

• The major environmental factors are tobacco smoke, occupational dusts and chemicals (vapors, irritants, fumes), and indoor/outdoor air pollution.

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 an important 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. Further studies of other risk factors could lead to similar powerful interventions.

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, none of them has monitored the progression of the disease through its entire course. Thus, current understanding of risk factors for COPD is in many respects incomplete.

The division into "Host Factors" and "Exposures" reflects the current understanding of COPD as resulting from an interaction between the two types of factors. 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; longer life expectancy will allow greater lifetime exposure to risk factors; etc. Understanding the relationships and interactions among risk factors is a crucial area of ongoing investigation.

The best-documented host factor is a severe hereditary deficiency of alpha-1 antitrypsin. The major environmental factors are tobacco smoke, occupational dusts and chemicals (vapors, irritants, fumes), and

indoor and outdoor air pollution. Since the original Gold report, it has been determined that the most prevalent environmental risk factor for COPD is cigarette smoking.

The role of gender as a risk factor for COPD remains unclear. In the past, most studies showed that COPD prevalence and mortality were greater among men than women. More recent studies from developed countries show that the prevalence of the disease is almost equal in men and women, which probably reflects changing patterns of tobacco smoking. Some studies have in fact suggested that women are *more* susceptible to the effects of tobacco smoke than men. This is an important question given the increasing rate of smoking among women in both developed and developing countries.

The role of nutritional status 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. The association of starvation and anabolic/catabolic status with the development of emphysema has been shown in experimental studies in animals.

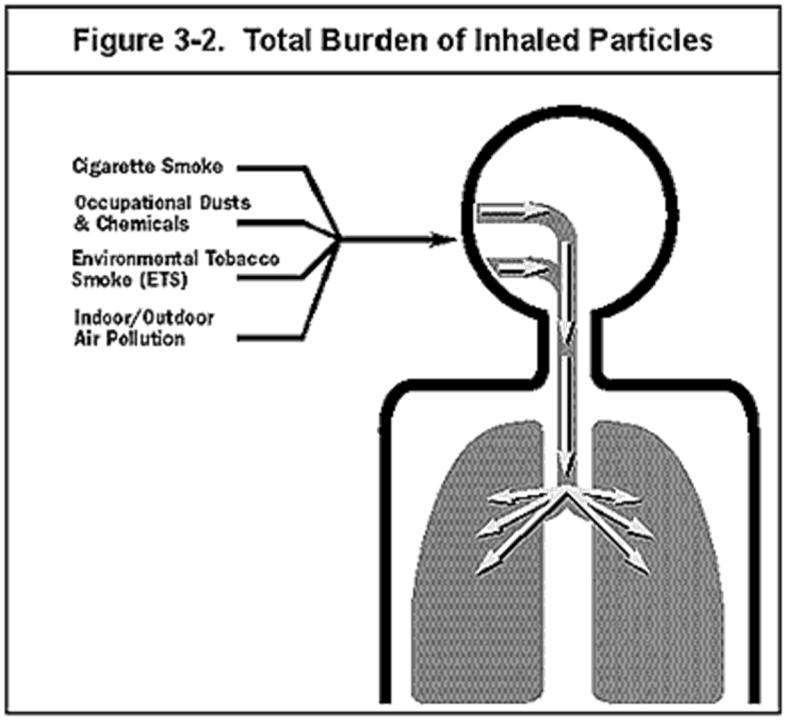
HOST FACTORS

Genes

It is believed that many genetic factors increase (or decrease) a person's risk of developing COPD. Studies have demonstrated an increased risk of COPD within families with COPD probands. Some of this risk may be due to shared environmental factors, but several studies in diverse populations also suggest a shared genetic risk.

The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin, a major circulating inhibitor of serine proteases. This rare hereditary deficiency is a recessive trait most commonly seen in individuals of Northern European origin. 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 host factors 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.

Exploratory studies have revealed a number of candidate genes that may influence a person's risk of COPD, including ABO secretor status, microsomal epoxide hydrolase, glutathione S-transferase, alpha-1 antichymotrypsin, the complement component GcG, cytokine TNF-α [1], and micro-satellite instability. However, when several studies of a given trait are available, the results are often inconsistent. Several of these genes are thought to be involved in inflammation, and therefore are related to potential pathogenic mechanisms of COPD.



Airway Hyperresponsiveness

Asthma and airway hyperresponsiveness (AHR), identified as risk factors that contribute to the development of COPD, are complex disorders related to a number of genetic and environmental factors. The relationship between asthma/airway hyperresponsiveness and increased risk of developing COPD was originally described by Orie and colleagues and termed the "Dutch hypothesis." AHR appears to be present in at least one out of two individuals with COPD.

Lung Growth

There is increasing evidence that chronic obstructive pulmonary disease (COPD) is not simply a disease of old age that is largely restricted to heavy smokers, but may be associated with insults to the developing lung as a fetus and during the first few years life, when lung growth and development are rapid. Reduced maximal attained lung function (as measured by spirometry) may identify individuals who are at increased risk for the development of COPD.

EXPOSURES

It may be helpful conceptually to think of a person's exposures in terms of his or her 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. Of the many inhalational exposures that people may encounter over a lifetime, only tobacco smoke and occupational dusts and chemicals (vapors, irritants, and fumes) are known to cause COPD on their own. Tobacco smoke and occupational exposures also appear to act additively to increase a person's risk of developing COPD.

Tobacco Smoke

Cigarette smoking is by far the most important risk factor for COPD and the most important way that tobacco contributes to the risk of 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. These differences between cigarette smokers and nonsmokers increase in direct proportion to the quantity of smoking. Pipe and cigar smokers have greater COPD morbidity and mortality rates than nonsmokers, although their rates are lower than those for cigarette smokers.

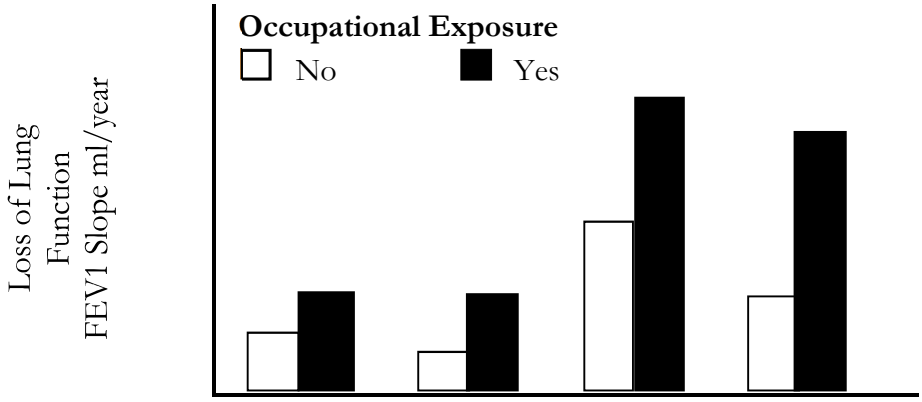
Other types of tobacco smoking popular in various countries are also risk factors for COPD, although their risk relative to cigarette smoking has not been reported.

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. Although it is unclear what percentage of smokers develop the disease, reputable sources state the numbers as between 8% and 30%. It is difficult to quantify because COPD is both under-diagnosed and under-appreciated.

Passive exposure to cigarette smoke (also known as environmental tobacco smoke or ETS) may also contribute to respiratory symptoms and COPD by increasing the lungs' total burden of inhaled particles and gases. 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.

Occupational Dusts and Chemicals

Figure 3.3 Interaction of Smoking and Occupational Exposures



Occupational dusts and chemicals (vapors, irritants, and fumes) can also cause COPD when the exposures are sufficiently intense or prolonged, such as those experienced by miners in many countries. These exposures can both cause COPD independently of cigarette smoking and increase the risk in the presence of concurrent cigarette smoking. Exposure to coal dust alone in sufficient doses can produce airflow limitation.

Exposure to particulate matter, irritants, organic dusts, and sensitizing agents can cause an increase in airway hyperresponsiveness, especially in airways already damaged by other occupational exposures, cigarette smoke, or asthma. There is some evidence from community studies that a combination of dust exposure and gas or fume exposure may have an additive effect on the risk of COPD.

Indoor and 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. The relative effect of short-term, high peak exposures and long-term, low-level exposures is a question yet to be resolved.

Over the past two decades, air pollution in most cities in developed countries has decreased appreciably. In contrast, air pollution has increased markedly in many cities in developing countries. Although it is not clear which specific elements of ambient air pollution are harmful, there is some evidence that particles found in polluted air will add to a person's total inhaled burden. Indoor air pollution from biomass fuel has been implicated as a risk factor for the development of COPD. This exposure is greatest in regions where biomass fuel is used for cooking and heating in poorly vented dwellings, leading to high levels of particulate matter in indoor air.

Infections

A history of severe childhood infection has been associated with reduced lung function and increased respiratory symptoms in adulthood. 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. 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-induced emphysema; HIV-induced pulmonary inflammation may play a role in this process.

Socioeconomic Status

There is evidence that the risk of developing COPD is inversely related to socioeconomic status. 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.

Chapter 4: Pathogenesis, Pathology, and Pathophysiology

KEY POINTS:

• Exposure to inhaled noxious particles and gases causes inflammation of the lungs that can lead to COPD if the normal protective and/or repair mechanisms are overwhelmed or defective.

• Exacerbations of COPD are associated with an increase in airway inflammation.

• Although inflammation is important in both diseases, the inflammatory response in COPD is markedly different from that in asthma.

• In addition to inflammation, two other processes thought to be important in the pathogenesis of COPD are an imbalance of proteinases and anti-proteinases in the lung, and oxidative stress.

• Pathological changes characteristic of COPD are found in the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature.

• The peripheral airways become the major site of airways obstruction in COPD. The structural changes in the airway wall are the most important cause of the increase in peripheral airways resistance in COPD. Inflammatory changes such as airway edema and mucus hypersecretion also contribute to airway narrowing.

• Most common in COPD patients is the centrilobular form of emphysema, which involves dilatation and destruction of the respiratory bronchioles.

• Physiological changes characteristic of the disease include mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and cor pulmonale, and they usually develop in this order over the course of the disease.

• The irreversible component of airflow limitation is primarily due to remodeling of the small airways. Parenchymal destruction (emphysema) also contributes but plays a smaller role.

• In advanced COPD, peripheral airways obstruction, parenchymal destruction, and pulmonary vascular abnormalities reduce the lung's capacity for gas exchange, producing hypoxemia and later on, hypercapnia. Inequality in the ventilation/perfusion ration (V_A/Q) is the major mechanism behind hypoxemia in COPD.

• Pulmonary hypertension develops late in the course of COPD. It is the major cardiovascular complication of COPD and is associated with a poor prognosis.

• COPD is associated with systemic inflammation and skeletal muscle dysfunction that may contribute to limitation of exercise capacity and decline of health status.

INTRODUCTION

Inhaled noxious particles and gases that lead to COPD cause lung inflammation, induce tissue destruction, impair the defense mechanisms that serve to limit the destruction, and disrupt the repair mechanisms that may be able to restore tissue structure in the face of some injuries. The results of lung tissue damage are mucus hypersecretion, airway narrowing and fibrosis, destruction of the parenchyma (emphysema), and vascular changes. In turn, these pathological changes lead to airflow limitation and the other physiological abnormalities characteristic of COPD.

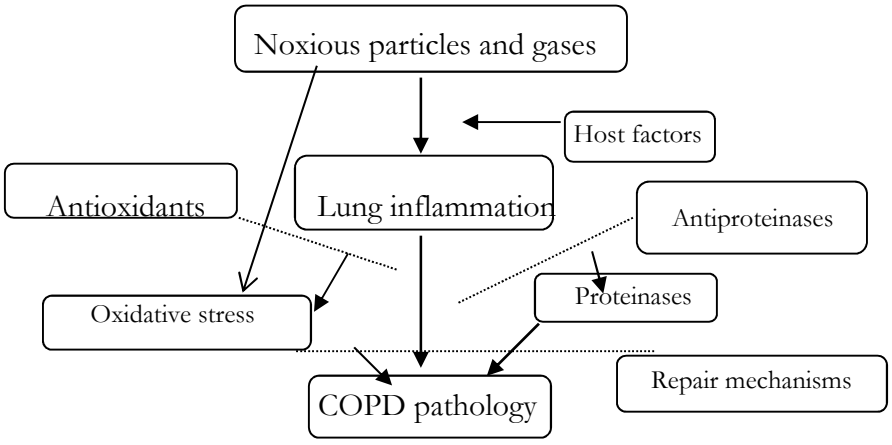
Much of the information concerning the pathogenesis of COPD comes from studies in experimental animals or *in vitro* systems. These experimental systems are limited as they differ from human disease in a number of respects. Studies in human subjects of the pathogenesis, pathology, and pathophysiology of COPD are often limited by patient selection, small numbers of subjects, and limited access to the relevant tissue. Therefore, an evidence-based perspective on these topics is in many respects incomplete.

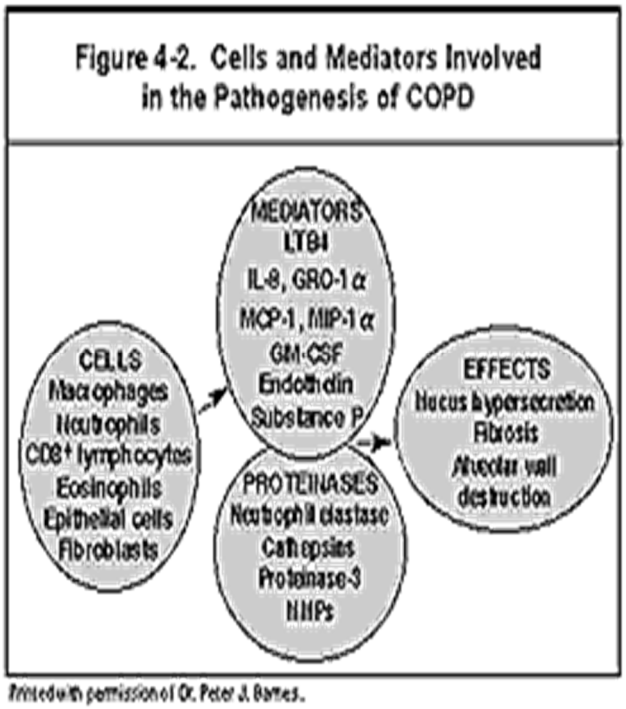
PATHOGENESIS

COPD is characterized by chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature. The intensity and cellular and molecular characteristics of the inflammation vary as the disease progresses. Over time, inflammation damages the lungs and leads to the pathologic changes characteristic of COPD.

In addition to inflammation, two other processes thought to be important in the pathogenesis of COPD are an imbalance of proteinases and anti-proteinases in the lung, and oxidative stress. These processes may themselves be consequences of inflammation, or they may arise from environmental (e.g., oxidant compounds in cigarette smoke) or genetic (e.g., alpha-1 antitrypsin deficiency) factors. **Figure 4-1** details the interactions between these mechanisms. The multiplicity of cells and mediators thought to be involved in the pathogenesis of COPD is presented schematically in **Figure 4-2.**

Figure 4. Pathogenesis of COPD





Inflammatory Cells

Figure 4.3 Sites of Inflammatory Cell Increases in COPD

Large Airways	• Macrophages • T lymphocytes (especially CD8+) • Neutrophils (severe disease only) • Eosinophils (in some patients)
Small Airways	• Macrophages • T lymphocytes (especially CD8+) • Eosinophils (in some patients)
Parenchyma	• Macrophages • T lymphocytes (especially CD8+) • Neutrophils (severe disease only)
Pulmonary Arteries	• T lymphocytes (especially CD8+) • Neutrophils (severe disease only)

COPD is characterized by an increase in neutrophils, macrophages, and T lymphocytes (especially $CD8^+$) in various parts of the lung (**Figure 4-3**). There may also be an increase in eosinophils in some patients, particularly during exacerbations. These increases are brought about by increases in inflammatory cell

recruitment, survival, and/or activation. Many studies reveal a correlation between the number of inflammatory cells of various types in the lung and the severity of COPD.

Neutrophils. Increased numbers of activated neutrophils are found in sputum and bronchoalveolar lavage (BAL) fluid of patients with COPD, although the role of neutrophils in COPD is not yet clear. Neutrophils are also increased in smokers without COPD. However, neutrophils are little increased in airway and parenchyma tissue sections, which may reflect their rapid transit through these parts of the lung. Induced sputum studies also show an increase in myeloperoxidase (MPO) and human neutrophil lipocalin, indicating neutrophil activation. Acute exacerbations of COPD are characterized by a marked increase in the number of neutrophils in BAL fluid. Neutrophils secrete several proteinases, including neutrophil elastase (NE), neutrophil cathepsin G, and neutrophil proteinase-3, which may contribute to parenchymal destruction and chronic mucus hypersecretion.

Macrophages. Increased numbers of macrophages are present in the large and small airways and lung parenchyma of patients with COPD, as reflected in histopathology, BAL, bronchial biopsy, and induced sputum studies. In patients with emphysema, macrophages are localized to sites of alveolar wall destruction. Macrophages likely play an orchestrating role in COPD inflammation by releasing mediators such as tumor necrosis factor-a (TNF-α), interleukin 8 (IL-8), and leukotriene B4 (LTB4), which promote neutrophilic inflammation.

T lymphocytes. Histopathology and bronchial biopsy studies show an increase in T lymphocytes, especially $CD8^+$ (cytotoxic) cells, throughout the lungs of patients with COPD. Their role in COPD inflammation is not yet fully understood, but one way that $CD8^+$ cells may contribute to COPD is by releasing perforin, granzyme-B, and TNF-a, which can cause the cytolysis and apoptosis of alveolar epithelial cells that may be responsible for the persistence of inflammation. An increased number of lymphocyte-like natural killer (NK) cells has also been reported in patients with severe COPD.

Eosinophils. The presence and role of eosinophils in COPD are uncertain. Some bronchial biopsy studies show eosinophils increased in the airways of some patients with stable COPD. However, some of these patients may have had coexisting asthma, as other studies report no increase in eosinophils in COPD patients. The levels of eosinophil cationic protein (ECP) and eosinophil peroxidase (EPO) in induced sputum are elevated in COPD, suggesting that eosinophils may be present but degranulated, and therefore no longer recognizable by light microscopy. The high levels of neutrophil elastase (NE) often found in COPD may be responsible for this degranulation. Most studies agree that airway eosinophils are increased during acute exacerbations of COPD.

Epithelial cells. Airway and alveolar epithelial cells are likely to be important sources of inflammatory mediators in COPD, though their role in inflammation in this disease has not yet been thoroughly studied. Exposure of nasal or bronchial epithelial cells from healthy volunteers to nitrogen dioxide (NO_2), ozone (O_3), and diesel exhaust particles results in significant synthesis and release of pro-inflammatory mediators, including eicosanoids, cytokines, and adhesion molecules. The adhesion molecule E-selectin, involved in recruitment and adhesion of neutrophils, is up-regulated on airway epithelial cells in COPD patients. Cultured human bronchial epithelial cells from COPD patients release lower levels of inflammatory mediators such as TNF-a and IL-8 than similar preparations from nonsmokers or smokers without COPD, suggesting that some form of down-regulation of inflammatory mediator release may occur in epithelial cells of individuals with COPD.

Inflammatory Mediators

Activated inflammatory cells in COPD release a variety of mediators, including a spectrum of potent proteinases, oxidants, and toxic peptides. Many of the mediators thought to be important in the disease — notably LTB4, IL-8, and TNF- α — are capable of damaging lung structures and/or sustaining neutrophilic inflammation. The damage induced by these moieties may further potentiate inflammation by releasing chemotactic peptides from the extracellular matrix. Little is yet known about the specific role of these inflammatory mediators in COPD. Studies of the therapeutic use of selective mediator antagonists should identify the molecules relevant in COPD.

Leukotriene B4 (LTB4). LTB4, a potent chemoattractant of neutrophils, is found at increased levels in the sputum of patients with COPD. It is probably derived from alveolar macrophages, which secrete more LTB4 in patients with COPD. Several potent LTB4 receptor antagonists have been developed for clinical studies and should elucidate further the role of this mediator in COPD. So far there is no evidence that cysteinyl leukotrienes (LTC4, LTD4, LTE4) are involved in COPD. Selective antagonists of the cysteinyl leukotriene 1 receptor ($CysLT_1$) have proven helpful in patients with asthma and studies of these drugs in COPD patients are now underway. The role of the cysteinyl leukotriene 2 receptor (CysLT2) in respiratory disease is as yet unknown.

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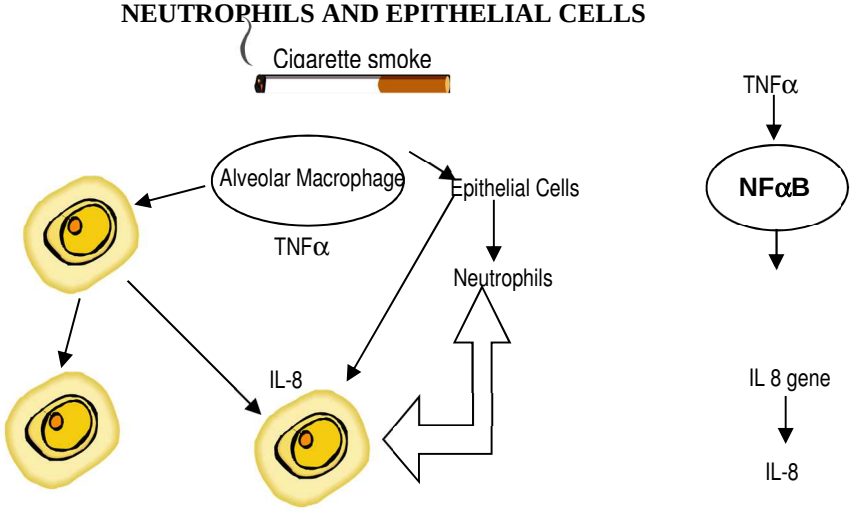
FIGURE 4.4 INTERACTION BETWEEN MACROPHAGES, NEUTROPHILS AND EPITHELIAL CELLS



Cigarette smoke activates macrophages and epithelial cells to produce tumor necrosis factor α (TNF-α), switching on the gene for interleukin 8 (IL-8), which recruits and activates neutrophils. This process occurs via activation of the transcription factor nuclear factor - κB (NF-κB).

Interleukin 8 (IL-8). IL-8, a selective chemoattractant of neutrophils that may be secreted by macrophages, neutrophils, and airway epithelial cells, is present at high concentrations in induced sputum and BAL fluid of patients with COPD. IL-8 may play a primary role in the activation of both neutrophils and eosinophils in the airways of COPD patients and may serve as a marker in evaluating the severity of airway inflammation.

Tumor necrosis factor- α (TNF- α). TNF-xx activates the transcription factor nuclear factor-kB (NF-kB), which in turn activates the IL-8 gene in epithelial cells and macrophages (**Figure 4-4**). TNF-a is present at high concentrations in sputum and is detectable in bronchial biopsies in patients with COPD. TNF- α serum levels

and production by peripheral blood monocytes are increased in weight-losing COPD patients, suggesting that this mediator may play a role in the cachexia of severe COPD.

Differences Between Inflammation in COPD and Asthma

Although inflammation is important in both diseases, the inflammatory response in COPD is markedly different from that in asthma, as summarized in **Figure 4-5**. However, some patients with COPD also have asthma, and the inflammation in their lungs may show characteristics of both diseases.

Figure 4.5 Characteristics of Inflammation in COPD and Asthma

	COPD	Asthma
Cells	• Neutrophils • Large increases in macrophages • Increase in CD8+ lymphocytes	• Eosinophils • Small increase in macrophages • Increase in CD4+ Th2 lymphocytes • Activation of mast cells
Mediators	• LTB4 • IL-8 • TNF-α	• LTD4 • IL-4, IL-5 • Plus many others
Consequences	• Squamous metaplasia of epithelium • Parenchymal destruction • Mucus metaplasia • Glandular enlargement	• Fragile epithelium • Thickening of basement membrane • Mucus metaplasia • Glandular enlargement
Response to treatment	• Corticosteroids have little or no effect	• Corticosteroids inhibit inflammation

Since inflammation is a feature of COPD, it follows that anti-inflammatory therapies may have clinical benefit in controlling symptoms, preventing exacerbations, and slowing the progression of the disease. However, the inflammatory response in COPD appears to be poorly responsive to the corticosteroids that are effective anti-inflammatory medications in asthma.

Inflammation and COPD Risk Factors

The connection between cigarette smoke and inflammation has been most extensively studied. Cigarette smoke activates macrophages and epithelial cells to produce TNF-$_{\alpha}$ and may also cause macrophages to release other inflammatory mediators, including IL-8 and LTB4.

Inflammation is present in the lungs of smokers without a diagnosis of COPD. This inflammation is similar to, but less intense than, the inflammation in the lungs of patients with COPD. For example, induced sputum studies show that smokers without COPD have a greater proportion of neutrophils in their lungs than age-matched nonsmokers, but a smaller proportion than COPD patients. Thus, the inflammation characteristic of COPD is thought to represent an exaggeration of a normal, protective response to inhalational exposures.

However, not all smokers develop COPD, and why the normal, protective inflammatory response becomes an exaggerated, harmful one in some smokers is poorly understood. Presumably the inflammation caused by cigarette smoking interacts with other host or environmental factors to produce the excess decline in lung function that results in COPD. Inflammatory changes are also present in bronchial biopsies in ex-smokers, suggesting that the inflammatory response in COPD may persist even in the absence of continuous exposure to risk factors.

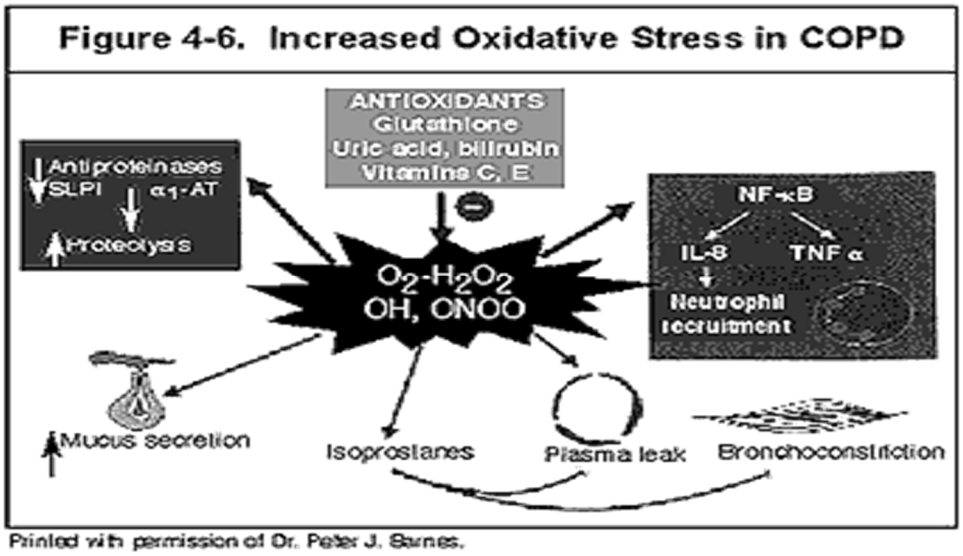
A number of studies have demonstrated that a variety of particulates (e.g., diesel exhaust, grain dust) can initiate respiratory tract inflammation. It is likely that indoor air pollution derived from the burning of biomass fuels will prove to have similar effects.

Proteinase-Antiproteinase Imbalance

The observation that α_1-antitrypsin-deficient individuals are at increased risk of developing emphysema has led to the theory that an imbalance between proteinases and antiproteinases leads to lung destruction. In COPD, there is either an increased production/activity of proteinases or a decreased production/activity of antiproteinases. The main proteinases, proteolytic enzymes such as neutrophil elastin are released by macrophages or neutrophils. The antiproteinases inhibit the damage caused by the proteolytic enzymes. The main antiproteinase is α_1-antitrypsin, also known as α_1-proteinase inhibitor. Cigarette smoke has been shown to inactivate this protein. Oxidative stress also decreases the activity of antiproteinases.

Oxidative Stress

There is increasing evidence that an oxidant/antioxidant imbalance, in favor of oxidants, occurs in COPD. (See Figure 4-6). Oxidative stress is now recognized as a major predisposing factor in the pathogenesis of COPD. Existing therapies for COPD are ineffective at halting disease progression, with bronchodilators being the mainstay of pharmacotherapy, providing symptomatic relief only. It is, therefore, important for a better understanding of the underlying mechanisms by which oxidative stress drives disease pathogenesis to develop more effective therapies. Antioxidant capacity in COPD is substantially reduced as a result of cigarette smoking and exacerbations, with oxidative stress persisting long after the cessation of cigarette smoking or exacerbation, due to the continued production of reactive oxygen species from endogenous sources.



Oxidative stress contributes to COPD in a variety of ways. Oxidants can react with, and damage, a variety of biological molecules, including proteins, lipids, and nucleic acids, and this can lead to cell dysfunction or death, as well as damage to the lung extracellular matrix. Oxidants also promote inflammation, for example by activating the transcription factor NF-$_k$B, which orchestrates the expression of multiple inflammatory genes thought to be important in COPD such as IL-8 and TNF-$_\alpha$. Finally, oxidative stress may contribute to reversible airway narrowing. Current antioxidant strategies have failed so far, but work in this area is ongoing.

PATHOLOGY

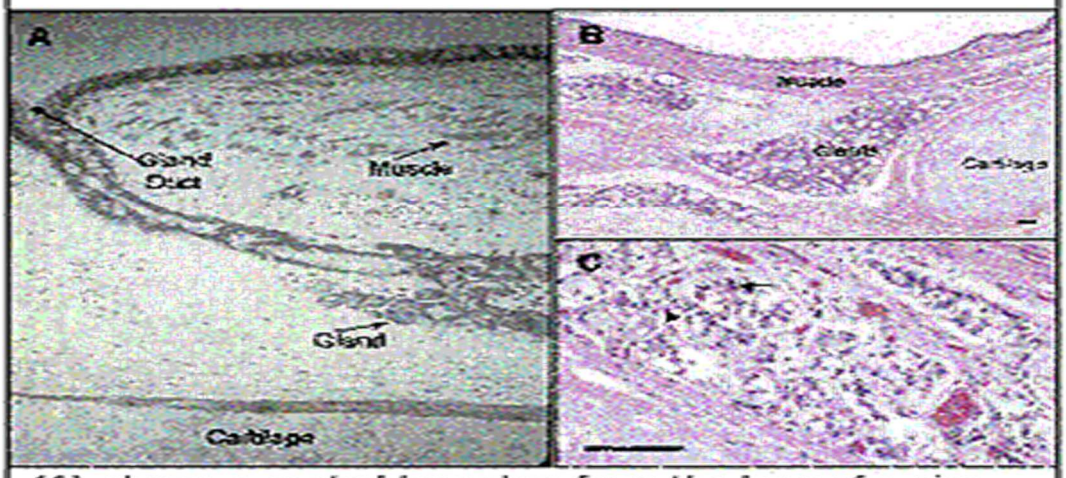
Pathological changes characteristic of COPD are found in the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature. The various lesions are a result of chronic inflammation in the lung, which in turn is initiated by the inhalation of noxious particles and gases such as those present in cigarette smoke. The lung has natural defense mechanisms and a considerable capacity to repair itself, but the working of these mechanisms may be affected by genetic traits (e.g., alpha-1 antitrypsin deficiency) or exposure to other environmental risk factors (e.g., infection, atmospheric pollution), as well as by the chronic nature of the inflammation and repeated nature of the injury.

Central Airways

The central airways include the trachea, bronchi, and bronchioles greater than 2-4 mm in internal diameter. In patients with chronic bronchitis, an inflammatory exudate of fluid and cells infiltrates the epithelium lining the central airways and associated glands and ducts. The predominant cells in this inflammatory exudate are

macrophages and CD8+T lymphocytes. Chronic inflammation in the central airways is also associated with an increase in the number (metaplasia) of epithelial goblet and squamous cells; dysfunction, damage, and/or loss of cilia; enlarged submucosal mucus-secreting glands; an increase in the amount of smooth muscle and connective tissue in the airway wall; degeneration of the airway cartilage; and mucus hypersecretion. The mechanisms of mucus gland hypertrophy and goblet cell metaplasia have not yet been identified, but animal studies show that irritants including cigarette smoke can produce these changes. The various pathological changes in the central airways are responsible for the symptoms of chronic cough and sputum production, which identify people at risk for COPD and may continue to be present throughout the course of the disease. Thus, these pathological changes may be present either on their own or in combination with the changes in the peripheral airways and lung parenchyma described below.

Figure 4-7. Pathological Changes of the Central Airways in COPD



(A) shows a central bronchus from the lung of a cigarette smoker with normal lung function. Only small amounts of muscle are present and the epithelial glands are small. This contrasts sharply with a diseased bronchus (B), where the muscle appears as a thick bundle and the glands are enlarged. (C) shows these enlarged glands at a higher magnification. There is evidence of a chronic inflammatory process involving polymorphonuclear (arrowhead) and mononuclear cells, including plasma cells (arrow).

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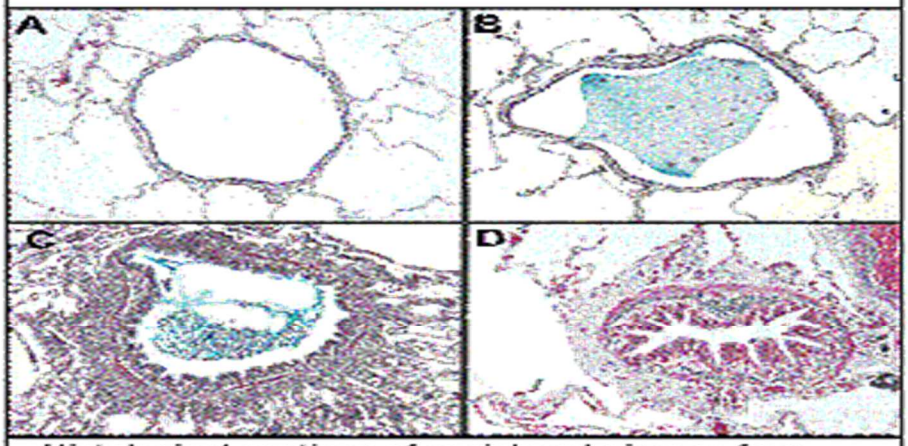
Peripheral Airways

The peripheral airways include small bronchi and bronchioles that have an internal diameter of less than 2 mm (**Figure 4-8**). The early decline in lung function in COPD is correlated with inflammatory changes in the peripheral

airways, similar to those that occur in the central airways: exudate of fluid and cells in the airway wall and lumen, goblet and squamous cell metaplasia of the epithelium, edema of the airway mucosa due to inflammation, and excess mucus in the airways due to goblet cell metaplasia.

Figure 4-8. Pathological Changes of the Peripheral Airways in COPD



Histological sections of peripheral airways from patients who are cigarette smokers. (A) is a nearly normal airway; (B) shows a plug of mucoid exudate in the lumen with little or no evidence of inflammation in the wall; (C) shows the presence of an inflammatory exudate in the wall and lumen of the airway; and (D) shows an airway with reduced lumen, structual reorganization of the airway wall, increased smooth muscle, and depostition of peri-bronchial connective tissue.

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However, the most characteristic change in the peripheral airways of patients with COPD is airway narrowing. Inflammation initiated by cigarette smoking and other risk factors leads to repeated cycles of injury and repair of the walls of the peripheral airways. Injury is caused either directly by inhaled toxic particles and gases such as those found in cigarette smoke, or indirectly by the action of inflammatory mediators; this injury then initiates repair processes. Although airway repair is only partly understood, it seems likely that disordered repair processes can lead to tissue remodeling with altered structure and function. Cigarette smoke may impair lung repair mechanisms, thereby further contributing to altered lung structure. Even normal lung repair mechanisms can lead to airway remodeling because tissue repair in the airways, as elsewhere in the body, may involve scar tissue formation. In any case, this injury-and-repair process results in a structural remodeling of the airway wall, with increasing collagen content and scar tissue formation, that narrows the lumen and produces fixed airways obstruction.

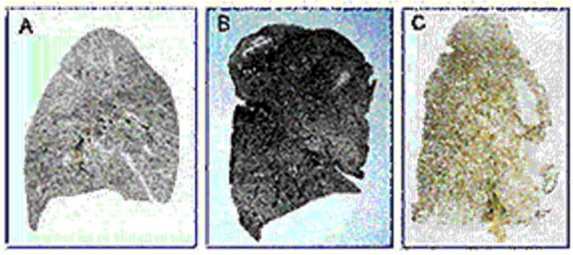
The peripheral airways become the major site of airways obstruction in COPD, and direct measurements of peripheral airways resistance show that the structural changes in the airway wall are the most important cause of the increase in peripheral airways resistance in COPD. Inflammatory changes such as airway edema and mucus hypersecretion also contribute to airway narrowing in COPD. So does loss of elastic recoil, but fibrosis of the small airways plays the largest role.

Fibrosis in the peripheral airways, as elsewhere in the body, is characterized by the accumulation of mesenchymal cells (fibroblasts and myofibroblasts) and extracellular connective tissue matrix. Several cell types including mononuclear phagocytes and epithelial cells may produce mediators that drive this process. The mediators that drive the accumulation of these cells and of the matrix are incompletely defined, but it is likely that several mediators including TGF-ß, ET-1, Insulin-like growth factor-1, fibronectin, platelet-derived growth factor (PDGF), and others are involved.

Lung Parenchyma

The lung parenchyma includes the gas exchanging surface of the lung (respiratory bronchioles and alveoli) and the pulmonary capillary system (**Figure 4-9**). The most common type of parenchymal destruction in COPD patients is the centrilobular form of emphysema which involves dilatation and destruction of the respiratory bronchioles. These lesions occur more frequently in the upper lung regions in milder cases, but in advanced disease they may appear diffusely throughout the entire lung and also involve destruction of the pulmonary capillary bed. Panacinar emphysema, which extends throughout the acinus, is the characteristic lesion seen in alpha-1 antitrypsin deficiency and involves dilatation and destruction of the alveolar ducts and sacs as well as the respiratory bronchioles. It tends to affect the lower more than upper lung regions. Because this process usually affects all of the acini in the secondary lobule, it is also referred to as panlobular emphysema. The primary mechanism of lung parenchyma destruction, in both smoking-related COPD and alpha-1 antitrypsin deficiency, is thought to be an imbalance of endogenous proteinases and antiproteinases in the lung. Oxidative stress, another consequence of inflammation, may also contribute.

Figure 4-9. Normal and Emphysematous Lungs



Photomicrographs of paper-mounted whole lung sections prepared from (A) a normal lung, (B) a lung with mild centrilobular emphysema, and (C) a lung with severe panacinar emphysema. Note that the centrilobular form affects mainly the upper lung regions whereas the panacinar form is more apparent in the lower lung regions.

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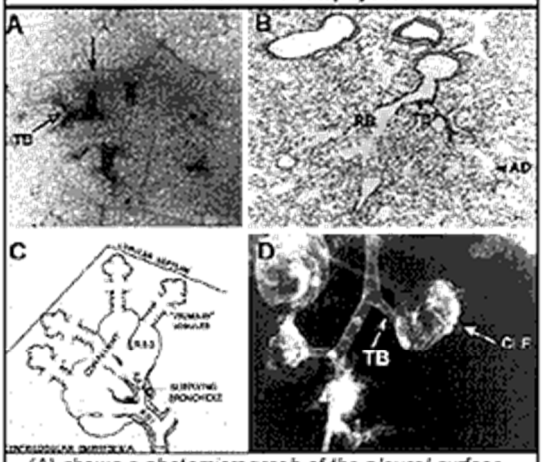
Figure 4-10. Normal Respiratory Bronchioles and Centrilobular Emphysema



(A) shows a photomicrograph of the pleural surface of a normal lung, with a secondary lobule defined by a connective tissue septum (solid arrow) and several terminal bronchioles (TB) filled with opaque material. (B) shows a low-power photomicograph of a normal terminal bronchiole (TB) branching into a respiratory bronchiole (RB), which eventually end in alveolar ducts (AD). (C) is a schematic diagram of centrilobular emphysema and (D) shows the bronchographic appearance of this lesion (TB=terminal bronchiole; CLE=centrilobular emphysema).

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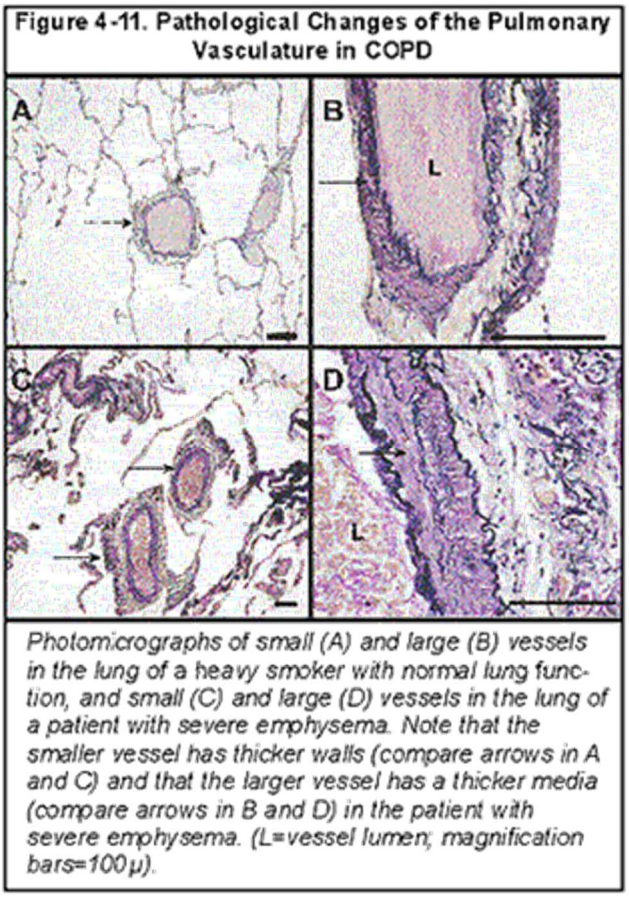


Pulmonary Vasculature

Pulmonary vascular changes in COPD (**Figure 4-11**) are characterized by a thickening of the vessel wall that begins early in the natural history of the disease, when lung function is reasonably well maintained and pulmonary vascular pressures are normal at rest. Endothelial dysfunction of the pulmonary arteries, which may be caused directly by cigarette smoke products or indirectly by inflammatory mediators, occurs early in COPD. Since endothelium plays an important role in regulating vascular tone and cell proliferation, it is likely that endothelial dysfunction might initiate the sequence of events that results ultimately in structural changes. Thickening of the intima is the first structural change, followed by an increase in vascular smooth muscle and the infiltration of the vessel wall by inflammatory cells, including macrophages and CD8+ T lymphocytes. These structural changes are correlated with an increase in pulmonary vascular pressure that develops first with exercise and then at rest. As COPD worsens, greater amounts of smooth muscle, proteoglycans, and collagen further thicken the vessel wall. In advanced disease, the changes in the muscular arteries may be associated with emphysematous destruction of the pulmonary capillary bed.

PATHOPHYSIOLOGY

Pathological changes in COPD lead to corresponding physiological abnormalities that usually become evident first on exercise and later also at rest. Physiological changes characteristic of the disease include mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and cor pulmonale, and they usually develop in this order over the course of the disease. In turn, various physiological abnormalities contribute to the characteristic symptoms of COPD — chronic cough and sputum production and dyspnea.

Mucus Hypersecretion and Ciliary Dysfunction

Mucus hypersecretion in COPD is caused by the stimulation of the enlarged mucus secreting glands and increased number of goblet cells by inflammatory mediators such as leukotrienes, proteinases, and neuropeptides. Ciliated epithelial cells undergo squamous metaplasia leading to impairment in mucociliary clearance mechanisms. These changes are usually the first physiological abnormalities to develop in COPD, and can be present for many years before any other physiological abnormalities develop.

Airflow Limitation and Pulmonary Hyperinflation

Expiratory airflow limitation is the hallmark physiological change of COPD. The airflow limitation characteristic of COPD is primarily irreversible, with a small reversible component. Several pathological characteristics contribute to airflow limitation and changes in pulmonary mechanics, as summarized in **Figure 4-12**. The irreversible component of airflow limitation is primarily due to remodeling — fibrosis and narrowing — of the small airways that produces fixed airways obstruction and a consequent increase in airways resistance. The sites of airflow limitation in COPD are the smaller conducting airways, including bronchi and bronchioles less than 2 mm in internal diameter. In the normal lung, resistance of these smaller airways makes up a small percentage of the total airways resistance. But in patients with COPD the total lower airways resistance approximately doubles, and most of the increase is due to a large increase in peripheral airways resistance. Although some have argued that a larger proportion of the total resistance should be attributed to peripheral airways in the normal lung, there is wide agreement that the peripheral airways become the major site of obstruction in COPD.

Figure 4.12 Causes of Airflow Limitation in COPD

Irreversible	• Fibrosis and narrowing of airways • Loss of elastic recoil due to alveolar destruction • Destruction of alveolar support that maintains patency of small airways
Reversible	• Accumulation of inflammatory cells, mucus, and plasma exudate in bronchi • Smooth muscle contraction in peripheral and central airways • Dynamic hyperinflation during exercise

Parenchymal destruction (emphysema) plays a smaller role in this irreversible component but contributes to expiratory airflow limitation and the increase in airways resistance in several ways. Destruction of alveolar attachments inhibits the ability of the small airways to maintain patency. Alveolar destruction is also associated with a loss of elastic recoil of the lung, which decreases the intra-alveolar pressure driving exhalation.

Although both the destruction of alveolar attachments to the outer wall of the peripheral airways and the loss of lung elastic recoil produced by emphysema have been implicated in the pathogenesis of peripheral airways obstruction, direct measurements of peripheral airways resistance show that the structural changes in the airway wall are the most important cause of the increase in peripheral airways resistance in COPD.

Airway smooth muscle contraction, ongoing airway inflammation, and intraluminal accumulation of mucus and plasma exudate may be responsible for the small part of airflow limitation that is reversible with treatment. Inflammation and accumulation of mucus and exudate may be particularly important during exacerbations.

Airflow limitation in COPD is best measured through spirometry, which is key to the diagnosis and management of the disease. The essential spirometric measurements for diagnosis and monitoring of COPD patients are the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). As COPD progresses, with increased thickness of the airway wall, loss of alveolar attachments, and loss of lung elastic recoil, FEV_1 and FVC decrease. A decrease in the ratio of FEV_1 to FVC is often the first sign of developing airflow limitation. FEV_1 declines naturally with age, but the rate of decline in COPD patients is generally greater than that in normal subjects.

With increasing severity of airflow limitation, expiration becomes flow-limited during tidal breathing. Initially, this occurs only during exercise, but later it is also seen at rest. In parallel with this, functional residual capacity (FRC) increases due to the combination of the decrease in the elastic properties of the lungs, premature airway closure, and a variable dynamic element reflecting the breathing pattern adopted to cope with impaired lung mechanics. As airflow limitation develops, the rate of lung emptying is slowed and the interval between inspiratory efforts does not allow expiration to the relaxation volume of the respiratory system; this leads to dynamic pulmonary hyperinflation. The increase in FRC can impair inspiratory muscle function and coordination, although the contractility of the

diaphragm, when normalized for lung volume, seems to be preserved. These changes occur as the disease advances but are almost always seen first during exercise, when the greater metabolic stimulus to ventilation stresses the ability of the ventilatory pump to maintain gas exchange.

Gas Exchange Abnormalities

In advanced COPD, peripheral airways obstruction, parenchymal destruction, and pulmonary vascular abnormalities reduce the lung's capacity for gas exchange, producing hypoxemia and, later on, hypercapnia. The correlation between routine lung function tests and arterial blood gases is poor, but significant hypoxemia or hypercapnia is rare when FEV_1 is greater than 1.00 L102. Hypoxemia is initially only present during exercise, but as the disease continues to progress it is also present at rest.

Inequality in the ventilation/perfusion ratio (V_A/Q) is the major mechanism behind hypoxemia in COPD, regardless of the stage of the disease. In the peripheral airways, injury of the airway wall is associated with VA/Q mismatching, as indicated by a significant correlation between bronchiolar inflammation and the distribution of ventilation. In the parenchyma, destruction of the lung surface area by emphysema reduces diffusing capacity and interferes with gas exchange. High V_A/Q units probably represent emphysematous regions with alveolar destruction and loss of pulmonary vasculature. The severity of pulmonary emphysema appears to be related to the overall inefficiency of the lung as a gas exchanger. This is reflected by the good correlation between the diffusing capacity of carbon monoxide per liter of alveolar volume ($DLco/V_A$) and the severity of macroscopic emphysema. Reduced ventilation due to loss of elastic recoil in the emphysematous lung, together with the loss of the capillary bed and the generalized inhomogeneity of ventilation due to the patchy nature of these changes, leads to areas of V_A/Q mismatching that result in arterial hypoxemia.

The relationship between pulmonary vascular abnormalities and V_A/Q relationships has been investigated in patients with mild COPD. The more severe the vessel wall damage is, the less the reversal of hypoxic vasoconstriction by oxygen. This suggests that pathology in the pulmonary artery wall, particularly when it affects the intimal layer, may play a key role in determining the loss of vascular response to hypoxia that contributes to V_A/Q mismatching. Chronic hypercapnia usually reflects inspiratory muscle dysfunction and alveolar hypoventilation.

Pulmonary Hypertension and Cor Pulmonale

Pulmonary hypertension develops late in the course of COPD (*Stage III*: Severe COPD and Stage IV: Very Severe COPD), usually after the development of severe hypoxemia (PaO_2 < 8.0 kPa or 60 mm Hg) and often hypercapnia as well. It is the major cardiovascular complication of COPD and is associated with the development of cor pulmonale and with a poor prognosis. However, even in patients with severe disease, pulmonary arterial pressure is

usually only modestly elevated at rest, though it may rise markedly with exercise. Pulmonary hypertension in COPD is believed to progress rather slowly even if left untreated. Further studies are required to firmly establish the natural history of pulmonary hypertension in COPD.

Factors that are known to contribute to the development of pulmonary hypertension in patients with COPD include vasoconstriction; remodeling of pulmonary arteries, which thickens the vessel walls and reduces the lumen; and destruction of the pulmonary capillary bed by emphysema, which further increases the pressure required to perfuse the pulmonary vascular bed. Vasoconstriction may itself have several causes, including hypoxia, which causes pulmonary vascular smooth muscle to contract; impaired mechanisms of endothelium-dependent vasodilation, such as reduced NO synthesis or release; and abnormal secretion of vasoconstrictor peptides (such as ET-1, which is produced by inflammatory cells). In advanced COPD, hypoxia plays the primary role in producing pulmonary hypertension, both by causing vasoconstriction of the pulmonary arteries and by promoting remodeling of the vessel wall (either by inducing the release of growth factors or as a consequence of the mechanical stress that results from hypoxic vasoconstriction).

Pulmonary hypertension is associated with the development of cor pulmonale, defined as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart, as in congenital heart disease." This is a pathological definition and the clinical diagnosis and assessment of right ventricular hypertrophy is difficult in life.

The prevalence and natural history of cor pulmonale in COPD are not yet clear. Pulmonary hypertension and reduction of the vascular bed due to emphysema can lead to right ventricular hypertrophy and right heart failure, but right ventricular function appears to be maintained in some patients despite the presence of pulmonary hypertension. Right heart failure is associated with venous stasis and thrombosis that may result in pulmonary embolism and further compromise the pulmonary circulation.

Systemic Effects

COPD is associated with systemic (i.e., extrapulmonary) effects, such as systemic inflammation and skeletal muscle dysfunction. Evidence of systemic inflammation includes the presence of systemic oxidative stress, abnormal concentrations of circulating cytokines, and activation of inflammatory cells. Evidence of skeletal muscle dysfunction includes the progressive loss of skeletal muscle mass and the presence of several bioenergetic abnormalities. These systemic effects have important clinical consequences, as they contribute to the limitation of patients' exercise capacity and thus the decline of health status in COPD. The presence of these systemic effects appears to worsen a patient's prognosis.

Pathophysiology and the Symptoms of COPD

Chronic cough and sputum production, sometimes labeled as chronic bronchitis, are a result of airway inflammation, which leads to mucus hypersecretion and dysfunction of the normal ciliary clearance mechanisms. Sputum is produced in COPD as a result of the inflammatory response, and contains plasma proteins exuded from the microvessels of the bronchial circulation, inflammatory cells, and small amounts of mucus from epithelial goblet cells. The volume of sputum produced overpowers clearance mechanisms, resulting in cough and expectoration. Some pathological abnormalities, such as inflammation of the submucosal glands and hyperplasia of goblet cells, may contribute to chronic sputum production, although these pathological abnormalities are not present in all patients with this symptom.

Dyspnea, an abnormal awareness of the act of breathing, usually reflects an imbalance between the neural drive to the respiratory muscles and the effectiveness of the resulting ventilation. Different individuals use different words to describe the feeling of breathlessness, which is also influenced by other factors such as mood. In COPD patients, dyspnea is mainly the result of impaired lung mechanics (increased airways resistance, decreased elastic recoil). It is only present on vigorous exercise in the early stages of disease but may be present at rest as the mechanical impairment becomes severe.

PATHOLOGY AND PATHOPHYSIOLOGY OF ACUTE EXACERBATIONS

The progressive course of COPD is complicated by acute exacerbations that have many causes and occur with increasing frequency as the disease progresses.

Pathology

Distinguishing the pathology of these acute events from that of the underlying disease is difficult because patients experiencing an exacerbation are usually too ill to study. The limited evidence available suggests that mild COPD exacerbations are associated with increases of both neutrophils and eosinophils in sputum and biopsies, while severe COPD exacerbations are associated with an increase in sputum neutrophils and eosinophils. At least in sputum, the changes in inflammatory cells during exacerbations of COPD are the same as those observed during exacerbations of asthma. So far no study has been conducted examining the pathological abnormalities associated with fatal exacerbations of COPD, which can be considered the extreme end of the spectrum of severity.

Pathophysiology

Expiratory airflow is almost unchanged during mild exacerbation, and only slightly reduced during severe exacerbations. Although the pathophysiology of acute exacerbations is not fully understood, the primary physiological change in severe acute exacerbations is a further worsening of gas exchange, primarily produced by

increased V_A/Q inequality. As VA/Q relationships worsen, increased work of the respiratory muscles results in greater oxygen consumption, decreased mixed venous oxygen tension, and further amplification of gas exchange abnormalities. Worsening of V_A/Q relationships has several causes in acute exacerbations. Airway inflammation and edema, mucus hypersecretion, and bronchoconstriction may contribute to changes in the distribution of ventilation, while hypoxic constriction of pulmonary arterioles may modify the distribution of perfusion. Additional contributors to worsening gas exchange in acute exacerbations include abnormal patterns of breathing and fatigue of the respiratory muscles. These can cause further deterioration in blood gases and worsening of respiratory acidosis, leading to severe respiratory failure and death. Alveolar hypoventilation also contributes to hypoxemia, hypercapnia, and respiratory acidosis. In turn, hypoxemia and respiratory acidosis promote pulmonary vasoconstriction, which increases pulmonary artery pressures and imposes an added load on the right ventricle.

Chapter 5: Management of COPD

INTRODUCTION

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 disease (*Stage III and Stage IV*) often requires 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.

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

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

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

These goals should be reached with minimal side effects from treatment, a particular challenge in COPD patients because they commonly have co-morbidities. 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. However, the benefits of community-based spirometric screening, of either the general population or smokers, are still unclear. Educating patients and physicians to recognize that cough, sputum production, and especially breathlessness are not trivial symptoms is an essential aspect of the public health care of this disease.

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

Important differences exist between countries in the approach to chronic illnesses such as COPD and in the acceptability 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:

- Diagnosis of COPD is based on a history of exposure to risk factors and the presence of airflow limitation that is not fully reversible, with or without the presence of symptoms. - Patients who have chronic cough and sputum production with a history of exposure to risk factors should be tested for airflow limitation, even if they do not have dyspnea.

- For the diagnosis and assessment of COPD, spirometry is the gold standard as it is the most reproducible, standardized, and objective way of measuring airflow limitation. $FEV_1/FVC < 70\%$ and a post-bronchodilator $FEV_1 < 80\%$ predicted confirms the presence of airflow limitation that is not fully reversible.

- Health care workers involved in the diagnosis and management of COPD patients should have access to spirometry.

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

INITIAL DIAGNOSIS

A diagnosis of COPD should be considered in any patient who has cough, sputum production, or dyspnea, and/or a history of exposure to risk factors for the disease (**Figure 5-1-1**). The diagnosis is confirmed by spirometry. The presence of a post-bronchodilator $FEV_1 < 80\%$ of the predicted value in combination with an $FEV_1/FVC < 70\%$ confirms the presence of airflow limitation that is not fully reversible. Where spirometry is unavailable, the diagnosis of COPD should be made using all available tools. Clinical symptoms and signs, such as abnormal shortness of breath and increased forced expiratory time, can be used to help with the diagnosis. A low peak flow is consistent with COPD, but has poor specificity since it can be caused by other lung diseases and by poor performance. In the interest of improving the diagnosis of COPD, every effort should be made to provide access to standardized spirometry.

Assessment of Symptoms

Although exceptions occur, the general patterns of symptom development in COPD are well established. The main symptoms among patients in *Stage 0: At Risk and 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. As airflow limitation develops in *Stage II: Moderate COPD,* patients often experience dyspnea, which may interfere with their daily activities. Typically, this is the stage at which they seek medical attention and are 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 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. *Stage IV: Very Severe*, is a newer classification. It indicates end stage COPD. With stage IV COPD, a person's quality of life will be profoundly impaired with symptoms ranging from serious to life-threatening. The risk of respiratory failure is high, and may lead to complications including a cor pulmonale.

Table 5.1.1 - Key Indicators for Considering a Diagnosis of COPD	
Chronic cough:	• Present intermittently or every day. Often present throughout the day; seldom only nocturnal.
Chronic sputum production:	• Any pattern of chronic sputum production may indicate COPD.
Dyspnea that is:	• Progressive (worsens over time). • Persistent (present every day). • Described by the patient as: "increased effort to breathe", "heaviness", "air hunger", or "gasping". • Worse on exercise. • Worse during respiratory infections.
History of exposure to risk factors, especially:	• Tobacco smoke • Occupational dusts and chemicals • Smoke from home cooking and heating fuels

Figure 5-1-2. Causes of Chronic Cough with a Normal Chest X-ray

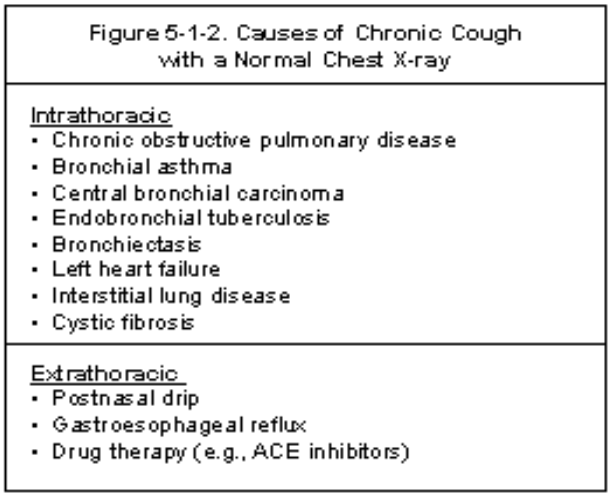


Figure 5-1-3. Questionaire for Assessing the Impact of Respiratory Symptoms[8]

WHEEZING

Does your chest ever sound wheezing or whistling?	Yes No
IF YOU ANSWERED "YES" TO THIS QUESTION: Do you get this on most days – or nights?	Yes No
Have you ever had attacks of shortness of breath with wheezing?	Yes No
IF YOU ANSWERED "YES" TO THIS QUESTION: Is/was your breathing absolutely normal between attacks?	Yes No

CHEST ILLNESSES

During the last three years have you had any chest illnesses which have kept you from your usual activities for as much as a week?	Yes No
IF YOU ANSWERED YES TO THIS QUESTION: Did you bring up phlegm more than usual during these illnesses?	Yes No
IF YOU ANSWERED YES TO THIS QUESTION: Have you had more than one illness like this in the past three years?	Yes No

BREATHLESSNESS

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 yards or after a few minutes on the level.

I am too breathless to leave the house or I am breathless when dressing or undressing.

Cough: Chronic cough, usually the first symptom of COPD to develop, 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, and is seldom entirely nocturnal. The chronic cough in COPD may be unproductive. In some cases, significant airflow limitation may develop without the presence of a cough. **Figure 5-1-2** lists some of the other causes of chronic cough in individuals with a normal chest X-ray.

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 is the epidemiological definition of chronic bronchitis, 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.

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. The terms used to describe dyspnea vary both by individual and by culture. 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 5-1-3**). This questionnaire relates well to other measures of health status.

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). Eventually, breathlessness is present during everyday activities (e.g., dressing, washing) or at rest, leaving the patient confined to the home.

Wheezing and chest tightness. Wheezing and chest tightness are relatively non-specific 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.* 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. *Stage IV* chest tightness impacts the ability to move normally or take care of daily needs. Such symptoms will likely lead to becoming housebound or chairbound during the end stage of this disease.

Additional symptoms in severe disease. Weight loss and anorexia are common problems in advanced COPD. Hemoptysis can occur during respiratory tract infections in COPD patients. However, this can 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. Psychiatric morbidity, especially symptoms of depression and/or anxiety, is common in advanced COPD. Ankle swelling can be the only symptomatic pointer to the development of cor pulmonale.

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 acute exacerbations of COPD.

• *Presence of co-morbidities:* such as heart disease and rheumatic disease, which may also contribute to restriction of activity.

• *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, 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, reduced cardiac dullness, and widening xiphisternal angle.

• Resting respiratory rate is often increased to more than 20 breaths per minute and breathing can be relatively shallow.

• Patients commonly show pursed-lip breathing, which may serve to slow expiratory flow and permit more efficient lung emptying.

• COPD patients often have resting muscle activation while lying supine. Use of the scalene and sternocleidomastoid 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.

• The presence of wheezing during quiet breathing is a useful pointer to airflow limitation. However, wheezing heard only after forced expiration is of no diagnostic value.

• 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)

Measurement of Airflow Limitation (Spirometry)

Spirometry measurements should be undertaken for any patient who may have COPD. To help identify individuals earlier in the course of the disease, spirometry should be performed for patients who have chronic cough and sputum production even if they do not have dyspnea. 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. Health care workers who care for COPD patients should have access to spirometry, which is useful in both diagnosis and periodic monitoring. **Figure 5-1-4** summarizes some considerations that are crucial to achieving consistently accurate test results.

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.
- 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

- Spirometry should be performed using techniques that meet published standards[iii].
- 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 12 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.

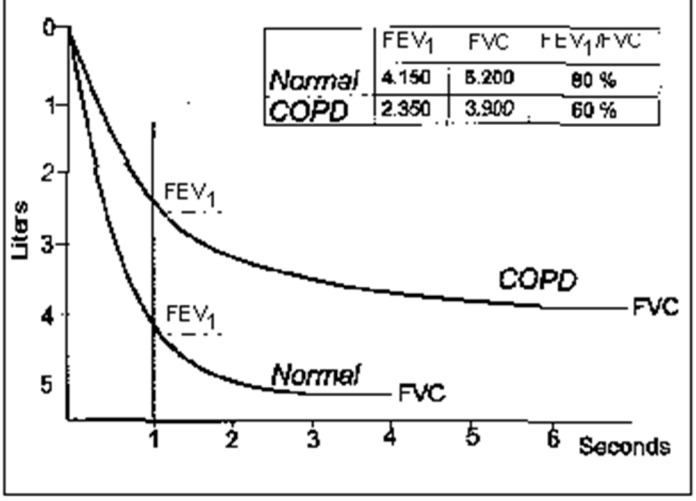
Evaluation

- Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race (e.g., see reference 14).
- The presence of a postbronchodilator $FEV_1 < 80\%$ predicted together with an $FEV_1/FVC < 70\%$ confirms the presence of airflow limitation that is not fully reversible.
- In patients with $FEV_1 \geq 80\%$ predicted, $FEV_1/FVC < 70\%$ may be an early indicator of developing airflow limitation.

Spirometry should measure the maximal 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 based on age, height, sex, and race (use appropriate reference values, e.g., see reference 14).

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 a post-bronchodilator FEV_1 < 80% of the predicted value in combination with an FEV_1/FVC < 70% confirms the presence of airflow limitation that is not fully reversible. The FEV_1/FVC on its own is a more sensitive measure of airflow limitation, and an FEV_1/FVC < 70% is considered an early sign of airflow limitation in patients whose FEV_1 remains normal (≥ 80% predicted). This approach to defining airflow limitation is a pragmatic one in view of the fact that universally applicable reference values for FEV_1 and FVC are not available.

Figure 5-1-5. Normal Spirogram and Spirogram Typical of Patients with Mild to Moderate COPD



Peak expiratory flow (PEF) is sometimes used as a measure of airflow limitation, but in COPD the relationship between PEF and FEV_1 is poor. PEF may underestimate the degree of airways obstruction in these patients. If spirometry is unavailable, prolongation of the forced expiratory time beyond 6 seconds is a crude, but useful, guide to the presence of an FEV_1/FVC ratio < 50%.

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. However, there are no data to indicate that screening spirometry is effective in directing management decisions or in improving COPD outcomes.

Assessment of Severity

Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality, and the presence of complications such as respiratory failure and right heart failure (**Figure 1-2**). The use of specific spirometric cut-points (e.g., $FEV_1 \geq$ 80% predicted) to define different stages of COPD is for purposes of simplicity; these cut-points have not been clinically validated and may underestimate the prevalence of COPD in some groups, such as the elderly.

Although the presence of airflow limitation is key to the current understanding of COPD, it may be valuable from a public health perspective to identify individuals at risk for the disease before significant airflow limitation develops (*Stage 0, At Risk*). 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. 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, 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 minor respiratory symptoms may be markers of future ill health.

The severity of a patient's breathlessness is important and can be gauged by the MRC scale (**Figure 5-1-3**). Arterial blood gases should be measured in all patients who have $FEV_1 < 40\%$ predicted or clinical signs of respiratory failure or right heart failure.

Additional Investigations

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

Bronchodilator reversibility testing. Generally performed only once, at the time of diagnosis, this test is useful for several reasons:

• *To help rule out a diagnosis of asthma.* If FEV_1 returns to the predicted normal range after administration of a bronchodilator, the patient's airflow limitation is likely due to asthma.

• *To establish a patient's best attainable lung function at that point in time.*

• *To gauge a patient's prognosis.* Some studies show that the post-bronchodilator FEV_1 is a more reliable prognostic marker than pre-bronchodilator FEV_1. In addition, the Intermittent Positive Pressure Breathing (IPPB) Study, a multicenter clinical trial, suggested that the degree of bronchodilator response is inversely related to the rate of FEV_1 decline in COPD patients.

• *To assess potential response to treatment.* Patients who show significant improvement in FEV_1 after administration of a bronchodilator are more likely to benefit from treatment with bronchodilators and have a positive response to corticosteroids. However, individual responses to bronchodilator tests are influenced by many factors, and failure of FEV_1 to change by an arbitrary amount on one day does not preclude a response on another. Moreover, even patients who do not show a significant FEV_1 response to a short-acting bronchodilator test may benefit symptomatically from long-term bronchodilator therapy.

Between-day reproducibility of spirometry in the same individual is approximately 178 ml. Thus, an acute change that exceeds both 200 ml and 12% of the base line measurement is unlikely to have arisen by chance. A protocol for bronchodilator reversibility testing is listed in **Figure 5-1-6.**

Figure 5-1-6. Bronchodilator Reversibility Testing

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 β_2 agonists in the previous 12 hours, or sustained-release theophyllines 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.
- Suitable dosage protocols are 400 mg β_2-agonist, 80 mg anticholinergic, or the two combined. FEV_1 should be measured again 30-45 minutes after the bronchodilator is given.

Results

- An increase in FEV_1 that is both greater than 200 ml and 12% above the pre-bronchodilator FEV_1 is considered significant.

Glucocorticosteroid reversibility testing. Long-term glucocorticosteroid treatment in COPD can at present only be justified in patients with a consistent, significant FEV_1 response to corticosteroids, or in those with repeated exacerbations. The simplest, and potentially safest, way to identify these patients is by a treatment trial with inhaled corticosteroids for 6 weeks to 3 months, using as criteria for glucocorticosteroid reversibility an FEV_1 increase of 200 ml and 15% above baseline. The response to corticosteroids should be evaluated with respect to the *post*-bronchodilator FEV_1 (i.e., the effect of treatment with inhaled glucocortico-steroids should be in addition to that of regular treatment with a bronchodilator). Where treatment with corticosteroids is restricted for economic reasons to patients with a substantial spirometric response, a trial of oral glucocorticosteroid therapy may help select those with the largest response. However, prolonged oral glucocorticosteroid treatment beyond 2 weeks is NOT recommended in clinically stable patients.

Chest X-ray. A chest X-ray is seldom diagnostic in COPD unless obvious bullous disease is present, but it is valuable in excluding alternative diagnoses. 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) might help in the differential diagnosis. In addition, if a surgical procedure such as bullectomy or lung volume reduction is contemplated, chest CT is helpful.

Arterial blood gas measurement. In advanced COPD measurement of arterial blood gases is important. This test should be performed in patients with FEV_1 < 40% predicted or with clinical signs suggestive of respiratory failure or right heart failure.

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

A major differential diagnosis is asthma. In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques, 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.

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) co-morbidities. 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 same questions at each visit.

Figure 5-1-8. Suggested Questions for Follow-Up Visits*

Monitor exposure to risk factors:

- Have you continued to stay off cigarettes?
- If not, how many cigarettes per day are you smoking?
- 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 dyspnea worsened, improved, or stayed the same since your last visit?
- Have you had to reduce your activities because of dyspnea or other symptoms?
- 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 due to dyspnea or other symptoms?
- Since your last visit, have you missed any work because of your symptoms?

Monitor pharmacotherapy and other medical treatment:

- What medications are you taking?
- How often do you take each medication?
- How much do you take each time?
- Have you missed or stopped taking any regular doses of your medications 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 medication been effective in controlling your symptoms?
- Has your medication 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. 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 (DLCO) measurements, 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. Measurement of arterial blood gas tensions should be performed in all patients with FEV_1 < 40% predicted or when clinical signs of respiratory failure or right heart failure are present. Respiratory failure is indicated by a PaO_2 < 8.0 kPa (60 mm Hg) with or without $PaCO_2$ > 6.0 kPa (45 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% may be a useful way of selecting patients for arterial blood gas measurement. However, pulse oximetry gives no information about CO_2 tensions.

Several considerations are important to ensure accurate test results. Oxygen pressure in the inspired air (FiO_2) should be measured, taking note 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.

Adequate pressure must be applied at the puncture site for at least one minute; failure to do so can lead to painful bruising.

Clinical signs of respiratory failure or right heart failure include central cyanosis, ankle swelling, and an increase in the jugular venous pressure. Clinical signs of hypercapnia are extremely nonspecific outside of acute exacerbations.

Assessment of pulmonary hemodynamics. Pulmonary hypertension 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. Polycythemia can be identified by hematocrit > 55%.

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 expiratory 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).

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, 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 corticosteroids 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 Co-morbidities

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

Component 2: Reduce Risk Factors

KEY POINTS:

- Reduction of total personal exposure to tobacco smoke, occupational dusts and chemicals, and indoor and outdoor air pollutants are important goals to prevent the onset and progression of COPD.

- Smoking cessation is the single most effective - and cost effective - way in most people to reduce the risk of developing COPD and stop its progression **(Evidence A)**.

- Brief tobacco dependence counseling is effective **(Evidence A)** and every tobacco user should be offered at least this treatment at every visit to a health care provider.

- Three types of counseling are especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment **(Evidence A)**.

- Several effective pharmacotherapies for tobacco dependence are available **(Evidence A)**, and at least one of these medications should be added to counseling if necessary and in the absence of contraindications **(Evidence A)**.

- Progression of many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases **(Evidence B)**.

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 major risk factor for COPD worldwide, 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 dust, 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, schools, and radio, television, and print media. National and local campaigns should be undertaken to reduce exposure to tobacco smoke in public forums. Legislation to establish smoke-free schools, public facilities, and work environments should be encouraged by government officials, public health workers, and the public. Smoking prevention programs should target all ages, including young children, adolescents, young adults, and pregnant women. Physicians and public health officials should encourage smoke-free homes.

The first exposure to cigarette smoke may begin *in utero* when the fetus is exposed to blood-borne metabolites from the mother. Neonates and infants may 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.

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. A statement by the WHO (**Figure 5-2-1**) emphasizes the health and economic benefits to be gained from

smoking cessation. 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.

Figure 5-2-1. World Health Organization Statement on Smoking Cessation[6]

Smoking cessation is a critical step toward substantially reducing the health risks run by current smokers, thereby improving world health. Tobacco has been shown to cause about twenty-five life-threatening diseases, or groups of diseases, many of which can be prevented, delayed, or mitigated by smoking cessation. As life expectancy increases in developing countries, the morbidity and mortality burden of chronic diseases will increase still further. This projected concentration of tobacco-related disease burden can be lightened by intensive efforts at smoking cessation. Studies have shown that 75-80% of smokers want to quit, while one-third have made at least three serious cessation attempts. Cessation efforts cannot be ignored in favor of primary prevention; rather, both efforts must be made in conjunction with one another. If only small portions of today's 1.1 billion smokers were able to stop, the long-term health and economic benefits would be immense. Governments, communities, organizations, schools, families and individuals are called upon to help current smokers stop their addictive and damaging habit.

Smoking cessation interventions are effective in both genders, 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 costs per life year gained.* Interventions that have been investigated include nicotine replacement with transdermal patch, counseling from physicians and other health professionals (with and without nicotine patch), self-help and group programs, and community-based stop-smoking contests. In the U.S., the 2008 estimate for the cost per life-year saved of tobacco dependence treatment was $3,539. A review of data from a number of countries estimated the median societal cost of various smoking cessation interventions at $990 to $13,000 per life year gained. 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.

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. 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 or evidence of airflow limitation.

Guidelines for smoking cessation entitled *Treating Tobacco Use and Dependence: A Clinical Practice Guideline* were published by the US Public Health Service. The major conclusions are summarized in **Figure 5-2-2.**

Figure 5-2-2. Public Health Service Report: *Treating Tobacco Use and Dependence: A Clinical Practice Guideline* - Major Findings and Recommendations[10]

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 tobacco dependence treatment is effective and every tobacco user should be offered at least brief treatment.
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. The guidelines emphasize that tobacco dependence is a chronic disease (**Figure 5-2-4**) and urge clinicians to recognize that relapse is common and reflects the chronic nature of dependence, not failure on the part of the clinician or the patient.

Figure 5-2-3. Brief Strategies to Help the Patient Willing to Quit[10-13]

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.

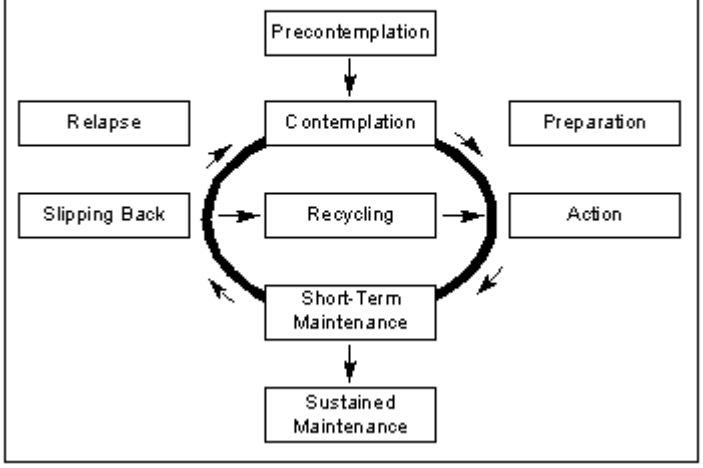
5. ARRANGE: Schedule follow-up contact.
Schedule follow-up contact, either in person or via telephone.

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 this is a chronic condition comparable to diabetes, hypertension, or hyperlipidemia requiring simple counseling advice, support, and appropriate pharmacotherapy.
- Relapse is common, which is the nature of dependence and not the failure of the clinician or the patient.

Most individuals go through several stages before they stop smoking (**Figure 5-2-5**). 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 5-2-5. Stages of Change Model



Counseling. Counseling delivered by physicians and other health professionals significantly increases quit rates over self-initiated strategies. Even a brief (3-minute) period of counseling to urge a smoker to quit results

in smoking cessation rates of 5-10%. At the very least, this should be done for every smoker at every health care provider visit. In the U.S., Smoking cessation is cost effective, and Medicare now allows reimbursement for smoking cessation counseling.

However, there is a strong dose-response relationship between counseling intensity and cessation success. Ways to make the treatment more intense include increasing the length of the treatment session, the number of treatment sessions, and the number of weeks over which the treatment is delivered. Counseling sessions of 3 to 10 minutes result in cessation rates of around 12%. With more complex interventions (for example, controlled clinical trials that include skills training, problem solving, and psychosocial support), quit rates can reach 20-30%. In one multicenter controlled clinical trial, a combination of physician advice, group support, skills training, and nicotine replacement therapy achieved a quit rate of 35% at one year and a sustained quit rate of 22% at 5 years.

Studies show that any contact time significantly increased abstinence rates over those produced by no contact. However, there is a clear trend for abstinence rates to increase across contact/counsiling time, up to the 90-minute mark. There was no evidence that more than 90 minutes of total contact time substantially increases abstinence rates.

Both individual and group counseling are effective formats for smoking cessation. 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**. The common subjects covered in successful problem solving/skills training programs include:

Figure 5-2-6. Patient Support in Smoking Cessation Programs[9-10]

- **Encourage the patient in the quit attempt.** Indicate that effective cessation treatments are now available and, in fact, half of all people who smoked have now quit. Communicate your confidence in the patient's ability to quit.
- **Communicate care and concern.** Ask how the patient feels about smoking and whether he/she wants to quit, expressing concern along with the ability and willingness to help. Be open to the patient's fears of quitting.
- **Encourage the patient to talk about the quitting process.** Talk to the patient about the reasons he/she wants to quit, difficulty encountered while quitting, success the patient has achieved, and concerns and worries about quitting.
- **Provide basic information about smoking, the risks of continuing, the benefits of quitting, and the techniques that optimize success.** Outline the nature, symptoms, and time course of withdrawal and techniques for dealing with withdrawal.

• Recognition of danger signals likely to be associated with the risk of relapse, such as being around other smokers, 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 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.

Pharmacotherapy. Numerous effective pharmacotherapies for smoking cessation now exist **(Evidence A)**, 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. According to smokefree.gov, cessation programs that include medications are twice as likely to help a person stop smoking.

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. Nicotine replacement therapy is more effective when combined with counseling and behavior therapy, 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. Long-term use of nicotine gum has not been found to be harmful.

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. There are now nicotine lozenges, nasal sprays, and inhalers available.

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, 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 temporo-mandibular joint symptoms, and unpleasant taste have been noted. In highly dependent smokers, the 4 mg gum is more effective than the 2 mg gum.

Lozenges may cause an upset stomach, hiccups, heartburn, headache, or excessive gas. Those who use inhalers might have a scratchy throat, cough, or upset stomach. Inhalers are not always the best choice for those with

respiratory problems. Nicotine nasal spray can be used, but side effects include hot, peppery feeling in the back of the nose or throat, runny nose, throat irritation, watering eyes, sneezing, and coughing.

Other pharmacotherapy. Bupropion hydrochloride is a medicine for depression, but it also helps people quit smoking. Brand names include Zyban®, Wellbutrin®, Wellbutrin SR® and Wellbutrin XL® but this medication is also available as a generic. Varenicline is a relatively new medicine that may help smokers quit. It is currently available under the brand name Chantix®. Both medicines work by blocking the flow of chemicals in the brain that make a person want to smoke. They both come in as pills, starting with a low dose and gradually increasing up to the full dose. They begin to work about one week after starting, so they should be started before a person stops smoking. Nortriptyline is another antidepressant, but it needs to be started 10 to 28 days before quitting. Clonidine is normally used to treat high blood pressure, but it may help when it is started before quitting. This drug comes in oral form, or as a patch.

According to a study done in 2000, study participants who reported using varenicline, bupropion, or the nicotine patch were more likely to maintain six-month continuous abstinence from smoking compared to those who attempted to quit without medication. Consistent with evidence from randomized controlled trials, smokers in the UK, Canada, Australia, and the US are more likely to succeed in quit attempts if they use varenicline, bupropion or nicotine patch.

OCCUPATIONAL EXPOSURES

Although it is not known how many individuals are at risk of developing respiratory disease from occupational exposures in either developing or developed countries, many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases:

• Implement 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 workers and policy-makers 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.

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. Although outdoor and indoor air pollution are generally thought of separately, the concept of total personal exposure may be more relevant for COPD. Reducing the risk from indoor and outdoor air pollution requires a combination of public policy and protective steps taken by individual patients.

Regulation of Air Quality

At the national level, achieving a set level of air quality 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.

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.

Patient-Oriented Control

The health care provider should consider susceptibility (including family history and exposure to indoor/outdoor pollution) for each individual patient.

• Patients should be counseled concerning the nature and degree of their susceptibility. Those who are at high risk should avoid vigorous exercise outdoors during pollution episodes.

• If various solid fuels are used for cooking and heating, adequate ventilation should be encouraged.

• Persons with severe COPD should monitor public announcements of air quality and should stay indoors when air quality is poor.

• The use of medication should follow the usual clinical indications; therapeutic regimes should not be adjusted because of the occurrence of a pollution episode without evidence of worsening of symptoms or function.

• Respiratory protective equipment has been developed for use in the workplace in order to minimize exposure to toxic gases and particles. However, under most circumstances, health care providers should not suggest respiratory protection as a method for reducing the risks of ambient air pollution.

• Air cleaners have not been shown to have health benefits, whether directed at pollutants generated by indoor sources or at those brought in with outdoor air.

Component 3: Manage Stable COPD

KEY POINTS:

- The overall approach to managing stable COPD should be characterized by a stepwise increase in treatment, depending on the severity of the disease.

- For patients with COPD, health education can play a role in improving skills, ability to cope with illness, and health status. It is effective in accomplishing certain goals, including smoking cessation **(Evidence A)**.

- None of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this disease **(Evidence A)**. Therefore, pharmacotherapy for COPD is used to decrease symptoms and/or complications.

- Bronchodilator medications are central to the symptomatic management of COPD **(Evidence A)**. They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms.

- The principal bronchodilator treatments are $ß_2$-agonists, anticholinergics, theophylline, and a combination of these drugs **(Evidence A)**.

- Regular treatment with inhaled corticosteroids should only be prescribed for symptomatic COPD patients with a documented spirometric response to corticosteroids or in those with an $FEV_1 < 50\%$ predicted and repeated exacerbations requiring treatment with antibiotics or oral corticosteroids **(Evidence B)**.

- Chronic treatment with systemic corticosteroids should be avoided because of an unfavorable benefit-to-risk ratio **(Evidence A)**.

- All COPD patients benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue **(Evidence A)**.

- The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival **(Evidence A)**.

INTRODUCTION

The overall approach to managing stable COPD should be characterized by a stepwise increase in treatment, depending on the severity of the disease. The 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 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.

The classification of severity **(Figure 1-2)** of stable COPD incorporates an individualized assessment of disease severity and therapeutic response into the management strategy. This classification is a guide that should help health care workers make decisions about the management of COPD in individual patients. Treatment depends on the patient's educational level and willingness to apply the recommended management, on cultural and local conditions, and on the availability of medications.

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

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 **(Evidence B)**, but it can play a role in improving skills, ability to cope with illness, and health status. 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 **(Evidence A)**. Education also improves patient response to acute exacerbations **(Evidence B)**. Prospective end-of-life discussions can lead to understanding of advance directives and effective therapeutic decisions at the end of life **(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 non-pharmacologic treatments - e.g., maintaining an exercise program 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

Stage 0: At Risk • Information and advice about reducing risk factors
Stage I: Mild COPD to Stage II: Moderate COPD Above Topic plus: • Information about the nature of COPD • Instruction on how to use inhalers and other treatments • Recognition and treatment of acute exacerbations • Strategies for minimizing dyspnea
Stage III: Severe COPD to Stage IV: Very Severe COPD Above Topic plus: • Information about complications • Information about oxygen treatment • Pulmonary rehabiliation programs
Stage IV: Very Severe COPD Above Topic plus: • Information about surgery including lung volume reduction and transplant • Advance directives and end-of-life decisión

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, peak flow monitoring).

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 **(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, 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.

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 has been shown to modify the long-term decline in lung function that is the hallmark of this disease **(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:

• There should be a stepwise increase in treatment, depending on the severity of the disease. (The step-down approach used in the chronic treatment of asthma is not applicable to COPD.)

• Regular treatment needs to be maintained at the same level for long periods of time unless significant side effects occur or the disease worsens.

• Treatment response of an individual patient is variable and should be monitored closely and adjusted frequently.

The medications are presented in the order in which they would normally be introduced in patient care, based on the level of disease severity. 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, co-morbidities (cardiovascular disease, sleep-related disorders, etc.), and general health status.

Bronchodilators

Medications that increase the FEV_1 or change other spirometric variables, usually by altering airway smooth muscle tone, are termed bronchodilators, 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, and improve exercise performance. The extent of these changes, especially in moderate to severe disease, is not easily predictable from the improvement in FEV. Regular bronchodilation with drugs that act primarily on airway smooth muscle does not modify the decline of function in mild COPD and, by inference, the prognosis of the disease **(Evidence B)**.

Bronchodilator medications are central to the symptomatic management of COPD **(Evidence A)**. 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 co-morbidities, so their risk of developing side effects is greater. A summary of bronchodilator therapy in COPD is provided in **Figure 5-3-4**.

Figure 5-3-4. Bronchodilators in Stable COPD

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

When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential. 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 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.

Wet nebulizers are not recommended for regular treatment because they are more expensive and require appropriate maintenance. A list of currently available inhaler devices is provided at http://www.goldcopd.com/inhalers/. The choice will depend on availability, cost, the prescribing physician, and the skills and ability of the patient.

Figure 5-3-6

Medications Commonly Used for Treating COPD: Dosage, Cost, and Adverse Effects (2017)

Medication	Dosage	Cost per month*	Serious adverse effects†	Common adverse effects†	Comment
Anticholinergics (inhaled)					
Ipratropium (Atrovent)	2 or 3 puffs three or four times daily	$77 (for 14 g; 200 inhalations)	Anaphylaxis, angioedema, bronchospasm (paradoxical), glaucoma (narrow-angle), hypersensitivity reaction, laryngospasm	COPD exacerbation, cough, dizziness, dry mouth, GI upset, headache, nausea, nervousness, oral irritation, rash, urticaria	Improves symptoms and quality of life and decreases exacerbations, hospitalizations, and deaths
Tiotropium (Spiriva)	1 cap daily	140	Angioedema, bronchospasm (paradoxical), glaucoma, hypersensitivity reaction	Abdominal pain, blurred vision, candidiasis, chest pain, constipation, dry mouth, dyspepsia, edema, epistaxis, infection, myalgia, pharyngitis, rash, rhinitis, tachycardia, URTI symptoms, urinary hesitancy or retention, UTI, vomiting	Improves quality of life and sleep and decreases rescue inhaler use and office visits Higher cost
$Beta_2$ agonists (inhaled)					

Medication	Dosage	Cost per month*	Serious adverse effects†	Common adverse effects†	Comment
Albuterol (Ventolin HFA)	2 to 4 puffs every 6 hours as needed	36 (for 18 g; around 200 inhalations)	Angina, angioedema, arrhythmias, bronchospasm (paradoxical), hypertension, hypokalemia, QT-interval prolongation, seizures, urticaria	Bad taste in the mouth, cough, throat irritation, tremor, URTI symptoms	Improves breathlessness but not other patient-oriented outcomes
Salmeterol (Serevent)	1 inhalation every 12 hours	131	Anaphylaxis, angioedema, arrhythmias, asthma exacerbation, bronchospasm (paradoxical), death (asthma-related), hypertension, laryngospasm	Bronchitis, headache, nasal congestion, nervousness, palpitations, pharyngitis, rash, rhinitis, tachycardia, throat irritation, tracheitis, tremor, urticaria	Does not improve breathlessness but may decrease exacerbations (single study)
Corticosteroids (inhaled)					
Fluticasone (Flovent HFA; 44 to 220 mcg per puff)	88 to 440 mcg two times daily	90 (for 10.6 g; around 120 inhalations)	Adrenal suppression, anaphylactoid reactions, angioedema, behavioral disturbances (children), bronchospasm, cataracts, Churg-Strauss syndrome, Cushingoid features, eosinophilia, glaucoma, growth suppression (children), hyperglycemia, osteoporosis, vasculitis	Candidiasis (oral), cough, dysphonia, headache, hoarseness, pharyngitis, sinusitis, throat irritation, URTI	Decrease exacerbations in patients with moderate to severe disease[13]
Budesonide (Pulmicort; 90 to 180 mcg per puff)	180 to 360 mcg two times daily	177 (200 inhalations)			Maintain lowest effective dose
Triamcinolone (Azmacort;100 mcg per puff)	2 puffs three or four times daily	134 (for 20 g; around 240 inhalations)			

Medication	Dosage	Cost per month*	Serious adverse effects†	Common adverse effects†	Comment
Combinations					
Inhaled anticholinergic/short-agonist (albuterol/acting beta$_2$ ipratropium [Combivent])	1 or 2 puffs four times daily as needed	100 (for 14.7 g; around 200 inhalations)	Anaphylaxis, angioedema, arrhythmias, bronchospasm (paradoxical), glaucoma (narrow-angle)	Bronchitis, cough, dyspnea, headache, nausea, pain, URTI	Use in patients requiring more than one bronchodilator
Inhaled corticosteroid/long-acting agonist (fluticasone/beta$_2$ salmeterol inhaled [Advair Diskus]: 100/50, 250/50, or 500/50 mcg per puff)	1 inhalation twice daily	210	Adrenal suppression, angioedema, arrhythmia (ventricular), asthma exacerbation, bronchospasm (paradoxical), cataracts, Churg-Strauss syndrome, cushingoid features, death (asthma-related), glaucoma, growth suppression (children), hypokalemia (severe), laryngospasm	Bronchitis, candidiasis (oral), cough, dermatitis, diarrhea, dizziness, dyspepsia, dysphonia, headache, hoarseness, hypokalemia, nausea or vomiting, palpitations, pharyngitis, sinusitis, taste changes, throat irritation, tremor, URI	Improves lung function and quality of life and decreases exacerbations in patients with moderate to severe disease[14]
Mucolytics					
N-acetylcysteine (Mucomyst‡)	600 mg orally two times daily	328 (4 mL 20% solution)	Anaphylaxis, bro		

ß$_2$-agonists. The principal action of ß$_2$-agonists is to relax airway smooth muscle by stimulating ß$_2$-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 **(Evidence A)**.

Adverse effects. Stimulation of ß$_2$-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 ß$_2$-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, and oxygen consumption can be increased under resting conditions, these metabolic effects show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO_2 occur after administration of both short- and long-acting ß$_2$-agonists, but the clinical significance of these changes is doubtful. Despite the concerns raised some years ago, further detailed study has found no association between ß$_2$-agonist use and an accelerated loss of lung function or increased mortality in COPD.

Anticholinergics. The most important effect of anticholinergic medications in COPD patients appears to be blockage of acetylcholine's effect on M3 receptors. Inhaled short- and long-acting anticholinergics improve symptoms and quality of life in patients with COPD. Recent studies show is a slightly greater benefit from the longer-acting agent tiotropium (Spiriva). Ipratropium (Atrovent) use has shown improved patient-oriented outcomes such as exercise tolerance and sleep quality. Ipratropium also has been shown to improve pulmonary function as demonstrated by a greater forced expiratory volume in one second (FEV_1) and forced vital capacity, especially in patients with a history of tobacco use. Studies of tiotropium have shown that it improves symptom control and reduces exacerbations, rescue inhaler use, and hospitalizations.

The bronchodilating effect of short-acting inhaled anticholinergics lasts longer than that of short-acting ß$_2$-agonists, with some bronchodilator effect generally apparent up to 8 hours after administration **(Evidence A)**.

Adverse effects. The most common adverse effect is dry mouth. This side effect typically resolves during the course of therapy. Additional side effects included constipation, blurred vision, glaucoma, increased heart rate, and urinary retention. The modest comparative benefits of the longer-acting agent must be balanced against its higher cost. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe overall.

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. Data on duration of action for conventional, or even slow-release, xanthine preparations are lacking in COPD. Treatment with theophylline may cause a small improvement in FEV_1; however, it is poorly tolerated, requires monitoring, and does not improve patient-oriented outcomes such as breathlessness. A systematic review of 20 RCTs ranging from one week to three months in duration found no difference in symptoms with theophylline. Changes in inspiratory muscle function have been reported in patients treated with theophylline, 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 **(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 5-3-7.**

Figure 5-3-7. Drugs and Physiological Variables that Affect Theophylline Metabolism in COPD

Increased	Decreased
▪ Tobacco smoking ▪ Anticonvulsant drugs ▪ Rifampicin ▪ Alcohol	▪ 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 therapy. Combining drugs with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects. A combination of a short-acting ß$_2$-agonist and the anticholinergic drug ipratropium in stable COPD 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 **(Evidence A)**. The combination of inhaled steroids and long-acting beta$_2$ agonists reduces exacerbations, improves quality of life, and improves lung function in patients with moderate to severe COPD. In a systematic review of six RCTs, combination therapy was demonstrated to reduce exacerbations and improve quality of life compared with placebo and with beta$_2$ agonists alone, but was no more effective than steroids alone.

Bronchodilator therapy by disease severity. **Figure 5-3-8** provides a summary of bronchodilator and other treatment at each stage of COPD. Bronchodilators remain the cornerstone of COPD treatment, especially inhaled β2-adrenergic receptor agonists and inhaled anticholinergics. Long-acting bronchodilators are considered more effective and convenient than short-acting bronchodilators for the maintenance treatment in patients with moderate to very severe COPD. For patients with few or intermittent symptoms (*Stage I: Mild COPD*), short-acting inhaled therapy as needed to control dyspnea or coughing spasms is sufficient. If inhaled bronchodilators are not available, regular treatment with slow-release theophylline should be considered. ß$_2$-agonists and anticholinergics taken by inhalation are generally equipotent, with some studies suggesting that the latter are more likely to be effective in a given clinical setting **(Evidence A)**. Consideration of costs and possible side effects will determine the choice of drug for monotherapy, but for patients with *Stage I: Mild COPD* or *Stage II: Moderate COPD* as-needed treatment with either is a reasonable first step. Failure of one of these bronchodilator classes to control symptoms should prompt a trial of the other class, and if symptoms are still troublesome, regular treatment with a combination of drugs is appropriate. One post-hoc review has

suggested that hospitalization days are reduced in patients whose treatment regimens contain an inhaled anticholinergic (**Evidence C**), but this issue requires prospective study as it would be of considerable economic importance if confirmed. One-time, objective changes in spirometry are a poor guide to the long-term, subjective benefit of bronchodilator treatment. Empirical treatment trials, rather than a laboratory assessment of bronchodilator response, should be used to determine whether treatment should continue.

Corticosteroids

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

Oral corticosteroids - short-term. The recommendations regarding the use of systemic steroids in COPD differ substantially depending on the phase of the disease. In moderate and severe acute exacerbations oral steroids are advocated based on the findings of several placebo-controlled trials that have been performed in secondary-care settings: these studies showed that systemic steroids improve lung function, dyspnoea and gas exchange. In addition, steroid use resulted in fewer treatment failures, a lower relapse rate and shorter hospital stays

In Stage III or Stage IV COPD, inhaled steroids can be tried if the patient has repeated exacerbation of his/her COPD or if, in the past, steroids have been shown to be beneficial.

Oral corticosteroids - long-term. . No study has shown a significant long-term benefit of systemic corticosteroids in stable COPD. In fact, there is a suggestion that the use of systemic steroids in patients over the age of 65 with stable COPD may increase mortality. Additionally, chronic use of systemic corticosteroids is associated with significant toxicity, including hyperglycemia, myopathy, hypertension, and osteoporosis. In view of the well-known toxicity of long-term treatment with oral corticosteroids, and the large body of evidence on side effects, long-term treatment with oral corticosteroids is not recommended in COPD **(Evidence A)**.

Inhaled corticosteroids. Recent guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD)1 and the American College of Physicians (ACP) have addressed the management of acute exacerbations. GOLD recommends long-and short-acting bronchodilators for day-to-day symptom control, with the addition of an inhaled corticosteroid for symptomatic patients with a forced expiratory volume in one second (FEV_1) less than 50 percent of predicted volume. Two large studies in 2008 showed no slowing in the rate of decline in lung function over the study period, however there was an initial significant improvement in FEV_1 and a slowing of the progression of disease over the initial six months of the study when compared with placebo. Overall, the risk-benefit ratio appears to favor inhaled corticosteroid treatment in patients with moderate to severe COPD.

Other Pharmacologic Treatments

Vaccines. The GOLD guidelines recommend that all patients with COPD receive an annual influenza vaccination. The influenza vaccine has been shown to reduce serious illness for patients with COPD by as much as 50%.**(Evidence A).** Pneumococcal vaccine is also recommended for patients >65years old and has been shown to reduce pneumococcal pneumonia in patients with COPD, and community acquired pneumonia in general in patients <65years old with severe airway obstruction (i.e. FEV1<40% of predicted).

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. Severe deficiency of alpha-1 antitrypsin (AAT) is associated with early onset pulmonary emphysema, as well as several forms of liver disease, including cirrhosis, neonatal hepatitis, and hepatocellular carcinoma. The discovery of the structure and function of the AAT protein, and its subsequent isolation and purification, have allowed augmentation therapy (so-called because of less than total replacement) aimed at preventing progression of emphysema.

Antibiotics. In several large-scale controlled studies, prophylactic, continuous use of antibiotics was shown to have no effect on the frequency of acute exacerbations in COPD. Most respiratory infections are caused by viruses, which will not improve with antibiotic treatment. Tthe use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is not recommended. **(Evidence A)**.

Mucolytic (mucokinetic, mucoregulator) agents (ambroxol, erdosteine, carbocysteine, iodinated glycerol). Mucolytic agents, through their actions on inflammatory and oxidative pathways, have potential benefits in COPD. The effect of Mucolytic use appears to be of a similar magnitude to the reduction in exacerbations seen with tiotropium and inhaled corticosteroids. Mucolytics do not affect the rate of lung function decline, but they also do not have any significant adverse effects. Mucolytic treatment should be considered in: patients with more severe COPD who have frequent or prolonged exacerbations; those who are repeatedly admitted to hospital; or in those patients with frequent exacerbations who are unable to take tiotropium or ICS. Mucolytics represent a safe way to further reduce exacerbations among patients with COPD (**Evidence A**).

Antioxidant agents. The International Journal of Pulmonary Disease published a study that showed targeting oxidative stress with antioxidants or boosting the endogenous levels of antioxidants is likely to be beneficial in the treatment of COPD. Since a variety of oxidants, free radicals, and aldehydes are implicated in the pathogenesis of COPD, it is possible that therapeutic administration of multiple antioxidants will be effective in the treatment of COPD. **(Evidence B)**. Ongoing trials should be carefully watched in this exciting area of study.

Immunoregulators (immunostimulators, immunomodulators). . Based on a study done in 2016, the blockade of CD39 pathways may be a novel approach to the control of AECOPD (acute exacerbations of chronic obstructive pulmonary disease), reducing the dependency on antibiotics. The Gold report advises further studies in this promising are .**(Evidence B)**.

Antitussives. Cough, although sometimes a troublesome symptom in COPD, has a significant protective role. Thus the regular use of antitussives is contraindicated 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. Therefore, based on the available evidence, nitric oxide is contraindicated in stable COPD.

Respiratory stimulants. Almitrine bismesylate, a relatively specific peripheral chemoreceptor stimulant that increases ventilation at any level of CO_2 under hypoxemic conditions, has been studied in both stable respiratory failure and acute exacerbations. It improves ventilation-perfusion relationships by modifying the hypoxic vasoconstrictor response. Oral almitrine has been shown to improve oxygenation, but to a lesser degree than low doses of inspired O_2. There is no evidence that almitrine improves survival or quality of life,

and in large clinical trials it was associated with a number of significant side effects, particularly peripheral neuropathy. Therefore, on the present evidence almitrine is not recommended for regular use in stable COPD patients **(Evidence B)**. The use of doxapram, a non-specific but relatively safe respiratory stimulant available as an intravenous formulation, is not recommended in stable COPD (**Evidence D**).

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

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

Figure 5.3.8 Therapy at Each Stage of COPD

Patients must be taught how and when to use their treatments and treatments being prescribed for other conditions should be reviewed. Beta-blocking agents (including eye drop formulations) should be avoided.

Stage	Characteristics	Recommended treatment
ALL		• Avoidance of risk factor(s) • Influenza vaccination
0: At Risk	• Chronic symptoms (cough, sputum) • Exposure to risk factor(s) • Normal spirometry	

I: Mild COPD	• $FEV_1/FVC<70\%$ • $FEV_1 \geq 80\%$ predicted • With or without symptoms	Short-acting bronchodilator when needed	
II: Moderate COPD	• $FEV_1/FVC<70\%$ • 50% $FEV_1<80\%$ predicted • with or without symptoms	• Regular treatment with one or more bronchodilators • Rehabilitation	Inhaled corticosteroids if significant symptoms and lung function response
III: SEVERE COPD	• $FEV_1/FVC<70\%$ • 30% $FEV_1<50\%$ predicted • with or without symptoms	• Regular treatment with one or more bronchodilator • Rehabilitation	Inhaled corticosteroids if significant symptoms and lung function response or if repeated exacerbations
IV: Very Severe COPD	• $FEV_1/FVC<70\%$ • $FEV_1<30\%$ predicted or presence of respiratory failure or right heart failure	• Regular treatment with one or more bronchodilators • Inhaled corticosteroids if significant symptoms and lung function response or if repeated exacerbations • Treatment of complications • Rehabilitation • Long-term oxygen therapy if respiratory failure • Consider surgical treatments	

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.

For patients who remain highly symptomatic, the addition of oral slow-release theophylline can be tried, but it should be titrated against directly measured plasma theophylline levels to reduce the risk of serious side effects and obtain maximum benefit. Theophylline increases exercise tolerance in patients with COPD and reduces air trapping. In high doses (with plasma concentration 10–20 mg/L) it is a useful additional bronchodilator in patients with severe COPD and has an added effect to a LABA. Low-dose theophylline reduces exacerbations in patients with COPD by approximately 50% when used as single therapy over 1 year 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 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. In general, nebulized therapy for a stable patient is not appropriate unless it has been shown to be better than conventional dose therapy.

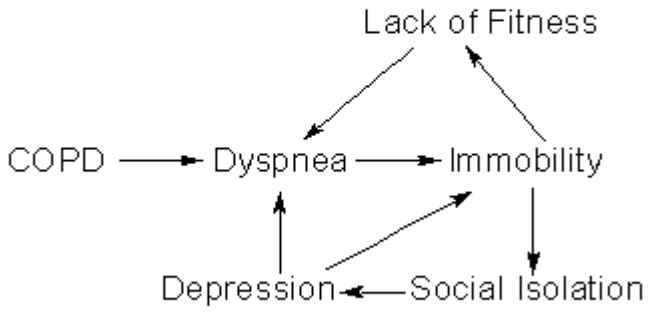
NON-PHARMACOLOGIC TREATMENT

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 inter-linked processes can interrupt the "vicious circle" in COPD so that positive gains occur in all aspects of the illness (**Figure 5-3-9**).

Figure 5-3-9. The Cycle of Physical, Social, and Psychosocial Consequences of COPD



Pulmonary rehabilitation has been carefully evaluated in a large number of clinical trials; the various benefits are summarized in **Figure 5-3-10**.

Figure 5-3-10. Benefits of Pulmonary Rehabilitation in COPD

- Improves exercise capacity (**Evidence A**).
- Reduces the perceived intensity of breathlessness (**Evidence A**).
- Can improve 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**).

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 **(Evidence A)**. Data suggest that these benefits can be sustained even after a single pulmonary rehabilitation program. 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. 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 **(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 (**Evidence B**).

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

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 **(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.

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. The optimum length for an exercise program has not been investigated in randomized, controlled trials. Thus, 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.

Participants are often encouraged to achieve a predetermined target heart rate, 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. 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 co-morbidities that restrict other forms of exercise. 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.

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. 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. A reduction in body mass index is an independent risk factor for mortality in COPD patients (**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 co-morbidities (pulmonary sepsis, lung tumors, etc.) should be managed appropriately.

Improving the nutritional state of weight-losing COPD patients can lead to improved respiratory muscle strength. However, controversy remains as to whether this additional effort is cost effective. 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. This approach has not been formally tested in large numbers of subjects.

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, St. George Respiratory Questionnaire, 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 to enable comparison of quality of life in different diseases.

Economic cost of rehabilitation programs: A study from the UK provided evidence that an intensive (6-week, 18-visit) multidisciplinary rehabilitation program was effective in decreasing use of health services (**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 non-pharmacologic treatments for patients with *Stage III or Stage IV COPD* 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. It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state. Continuous oxygen therapy decreased resting pulmonary artery pressure in one study but not in another study. Several controlled prospective studies have shown that the primary hemodynamic effect of oxygen therapy is preventing the progression of pulmonary hypertension. 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.

Long-term oxygen therapy is generally introduced in *Stage III: Severe COPD and 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 A**); or

• PaO_2 between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg), or SaO2 of 89%, 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.

Oxygen therapy given during exercise increases walking distance and endurance, optimizing oxygen delivery to tissues and utilization by muscles. However, there are no data to suggest that long-term oxygen therapy changes exercise capacity per se. Where available, this treatment is usually restricted to patients who meet the criteria for continuous oxygen therapy, or experience significant oxygen desaturation during exercise (**Evidence C**).

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. Often the patient keeps a cylinder of oxygen at home to use as needed. Whether this is of physiological, psychological, or any benefit at all is not known (**Evidence C**).

Cost considerations. Supplemental home oxygen is usually the most costly component of outpatient therapy for adults with COPD who require this therapy. 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.

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. 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 cannula or 31% by Venturi face mask. 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, 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 traveling 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.

Ventilatory Support

Although both noninvasive ventilation (using either negative or positive pressure devices) and invasive (conventional) mechanical ventilation are essentially designed to manage and treat acute episodes of COPD, for years noninvasive ventilation has been applied in patients with *Stage III: Severe COPD* and *Stage IV: Very Severe COPD* and chronic respiratory failure. This has followed the successful use of noninvasive ventilation in other forms of chronic respiratory failure due to chest wall deformities and/or neuromuscular disorders. Several scientific studies have examined the use of ventilatory support and there is no convincing evidence that this therapy has a role in the management of stable COPD. It is possible that some patients with chronic hypercapnia may benefit from this form of treatment, but no randomized controlled study has yet been reported.

Noninvasive mechanical ventilation. This modality of ventilatory support is applied when endotracheal and nasotracheal ventilation are not needed, using either negative pressure ventilation (nPV) or noninvasive intermittent positive pressure ventilation (NIPPV).

Noninvasive negative pressure ventilation (nPV). The use of tank respirators, cuirass, or poncho ventilation is largely of historical interest in COPD. Problems with patient comfort and limited access restrict future use of nPV. When this treatment is used in chronic respiratory failure, some patients develop upper airway obstruction during sleep. A comparison of domiciliary active and sham nPV in patients with chronic respiratory failure due to COPD showed no differences in shortness of breath, exercise tolerance, arterial blood gases, respiratory muscle strength, or quality of life between the two treatments.

Noninvasive intermittent positive pressure ventilation (NIPPV). The role of NIPPV in chronic respiratory failure remains unsettled, although this is now the standard means of providing noninvasive ventilatory support in other instances of chronic respiratory failure not directly related to COPD. NIPPV can be delivered by different types of ventilators: volume-controlled, pressure-controlled, bi-level positive airway pressure, or continuous positive airway pressure. New devices with lower cost, greater ease of operation, and greater portability are constantly being developed. Recent technical improvements have facilitated the use of NIPPV while reducing the possibility of air leaking through face or nasal masks.

A study of NIPPV compared to conventional therapy in a population with end-stage COPD using a randomized, crossover design for a 3-month period found that the noninvasive approach is not well tolerated and is associated with marginal clinical and functional improvements (**Evidence B**). The use of NIPPV together with long-term oxygen therapy in a randomized crossover study in a small subset of patients produced a significant improvement in daytime arterial blood gases, total sleep time, sleep efficiency, quality of life, and overnight $PaCO_2$ compared with oxygen therapy alone, indicating that NIPPV may be a useful addition to long-term oxygen therapy (**Evidence B**). However, a similar approach in a larger series of patients concluded

that NIPPV plus long-term oxygen therapy does not improve long-term survival. In this study, however, intensive care admissions were reduced and exercise capacity was improved (**Evidence C**).

Given this conflicting evidence, long-term NIPPV cannot be recommended for the routine treatment of patients with chronic respiratory failure due to COPD. Nonetheless, 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.

Invasive (conventional) mechanical ventilation. The appropriateness of using invasive (conventional) ventilation in end-stage COPD continues to be debated. There are no guidelines to define which patients will benefit.

Surgical Treatments

Bullectomy. Bullectomy is an older surgical procedure for bullous emphysema. By removing a large bulla that does not contribute to gas exchange, the adjacent lung parenchyma is decompressed. Bullectomy can be performed thoracoscopically. In carefully selected patients, this procedure is effective in reducing dyspnea and improving lung function (**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 non-bullous 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. 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.

Lung volume reduction surgery (LVRS). LVRS is a surgical procedure in which parts of the lung are resected to reduce hyperinflation, 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). In addition, LVRS increases the elastic recoil pressure of the lung and thus improves expiratory flow rates.

In some centers with adequate experience, perioperative mortality of LVRS has been reported to be less than 5%. Results have been reported following bilateral (upper parts) resection using median sternotomy or video-assisted thoracoscopy (VATS). Most studies select patients with FEV_1 < 35% predicted, PaCO2 < 6.0 kPa (45 mm Hg), predominant upper lobe emphysema on CT scan, and a residual volume of > 200% predicted. The average increase in FEV_1 following LVRS has ranged from 32% to 93%, and the decrease in TLC from 15% to 20%. LVRS appears to improve exercise capacity as well as quality of life in some patients. There are reports of these effects lasting more than one year.

One observation of the Gold Report is that LVRS is quite costly when compared to healthcare programs that do not include surgery.

Lung transplantation. In appropriately selected patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity (**Evidence C**), 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. 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.

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, Carini*) or bacterial (*Pseudomonas, Staphylococcus species*) infections, lymphoproliferative disease, and lymphomas.

Another limitation of lung transplantation is its cost. The typical cost of transplant in the United States is **$500,000-$800,000,** depending on whether the procedure involves one or both lungs. A 2011 report on the cost of organ and tissue transplants in the United States found the total cost of a single lung transplant to be **$561,200,** which includes **$10,300** for a month's worth of care leading up to the transplant; **$73,100** for the procurement of the organ; **$302,900** for hospital transplant admission; **$33,500** for the surgeon; and **$23,700** for immunosuppressants and other prescription drugs. The report estimates the total cost for a double transplant to be **$797,300.**

Component 4: Manage Exacerbations

KEY POINTS:

- Exacerbations of respiratory symptoms requiring medical intervention are important clinical events in COPD.

- The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified (**Evidence B**).

- Inhaled bronchodilators (particularly inhaled ß$_2$-agonists and/or anticholinergics), theophylline, and systemic, preferably oral, corticosteroids are effective treatments for acute exacerbations of COPD (**Evidence A**).

- Patients experiencing COPD exacerbations with clinical signs of airway infection (e.g., increased volume and change of color of sputum, and/or fever) may benefit from antibiotic treatment (**Evidence B**).

- Noninvasive intermittent positive pressure ventilation (NIPPV) in acute exacerbations improves blood gases and pH, reduces in-hospital mortality, decreases the need for invasive mechanical ventilation and intubation, and decreases the length of hospital stay (**Evidence A**).

INTRODUCTION

COPD is often associated with acute exacerbations of symptoms. In patients with *Stage I: Mild COPD to Stage II: Moderate COPD,* an exacerbation is associated with increased breathlessness, often accompanied by increased cough and sputum production, and may require medical attention outside of the hospital. The need for medical intervention intensifies as the airflow limitation worsens. Exacerbations in *Stage III: Severe COPD* and *Stage IV: Very Severe COPD* are associated with acute respiratory failure, representing a significant burden on the health care system. Hospital mortality of patients admitted for an acute exacerbation of COPD is approximately 10%, and the long-term outcome is poor. Mortality reaches 40% in one year, and is even higher (up to 59%) for patients older than 65 years. These figures vary from country to country depending on the health care system and the availability of intensive care unit (ICU) beds.

The most common causes of an exacerbation (Figure 5-4-1) are infection of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified. The role of bacterial infections, once believed to be the main cause of COPD exacerbations, is controversial. Conditions that may mimic an acute exacerbation include pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, and arrhythmia.

Figure 5-4-1. Common Causes of Acute Exacerbations of COPD	
Primary	▪ Tracheobronchial infection. ▪ Air pollution.
Secondary	▪ Pneumonia. ▪ Pulmonary embolism. ▪ Pneumothorax. ▪ Rib fractures/chest trauma. ▪ Inappropriate use of sedatives, narcotics, beta-blocking agents. ▪ Right and/or left heart failure or arrhythmias.

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 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.

Assessment of Severity

Assessment of the severity of an acute exacerbation is based on the patient's medical history before the exacerbation, symptoms, physical examination, lung function tests, arterial blood gas measurements, and other laboratory tests (**Figure 5-4-2**). 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 tests of lung function and arterial blood gases are extremely useful for comparison with those made during the acute episode, as an acute change in these tests is more important than their absolute values. 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 very severe COPD, the most important sign of a severe exacerbation is a change in the alertness of the patient and this signals a need for immediate evaluation in the hospital.

Figure 5-4-2. Medical History and Signs of Severity of Acute Exacerbations of COPD

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

Lung function tests. Even simple lung function tests can be difficult for a sick patient to perform properly. In general, a PEF < 100 L/min or an FEV_1 < 1.00 L indicates a severe exacerbation, except in patients with chronically severe airflow limitation. For instance, an FEV_1 of 0.75 L, or a PaO_2/FiO_2 (FiO_2 = fractional concentration of oxygen in dry inspired gas) of 33 kPa (24.5 mm Hg) may be well tolerated by a subject with severe COPD who copes with these values in stable conditions, whereas they may reflect a severe exacerbation for a subject with slightly higher values, e.g., an FEV_1 of 0.90 L or a PaO_2/FiO_2 of 38 kPa (28.2 mm Hg) in stable conditions.

Arterial blood gases. In the hospital, measurement of arterial blood gases is essential to assess the severity of an exacerbation. A PaO_2 < 8.0 kPa (60 mm Hg) and/or SaO_2 < 90% when breathing room air indicate respiratory failure. In addition, a PaO_2 < 6.7 kPa (50 mm Hg), $PaCO_2$ > 9.3 kPa (70 mm Hg), and pH < 7.30 point toward a life-threatening episode that needs ICU management.

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 acute exacerbation, especially in severe COPD, because right ventricular hypertrophy and large pulmonary arteries lead to confusing ECG and radiographic results. Spiral CT scanning and angiography, and perhaps specific D-dimer assays, are the best tools presently available for the diagnosis of pulmonary embolism in patients with COPD, but ventilation-perfusion scanning is of no value. A low systolic blood pressure and an inability to increase the PaO_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. Streptococcus pneumoniae, Hemophiles 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

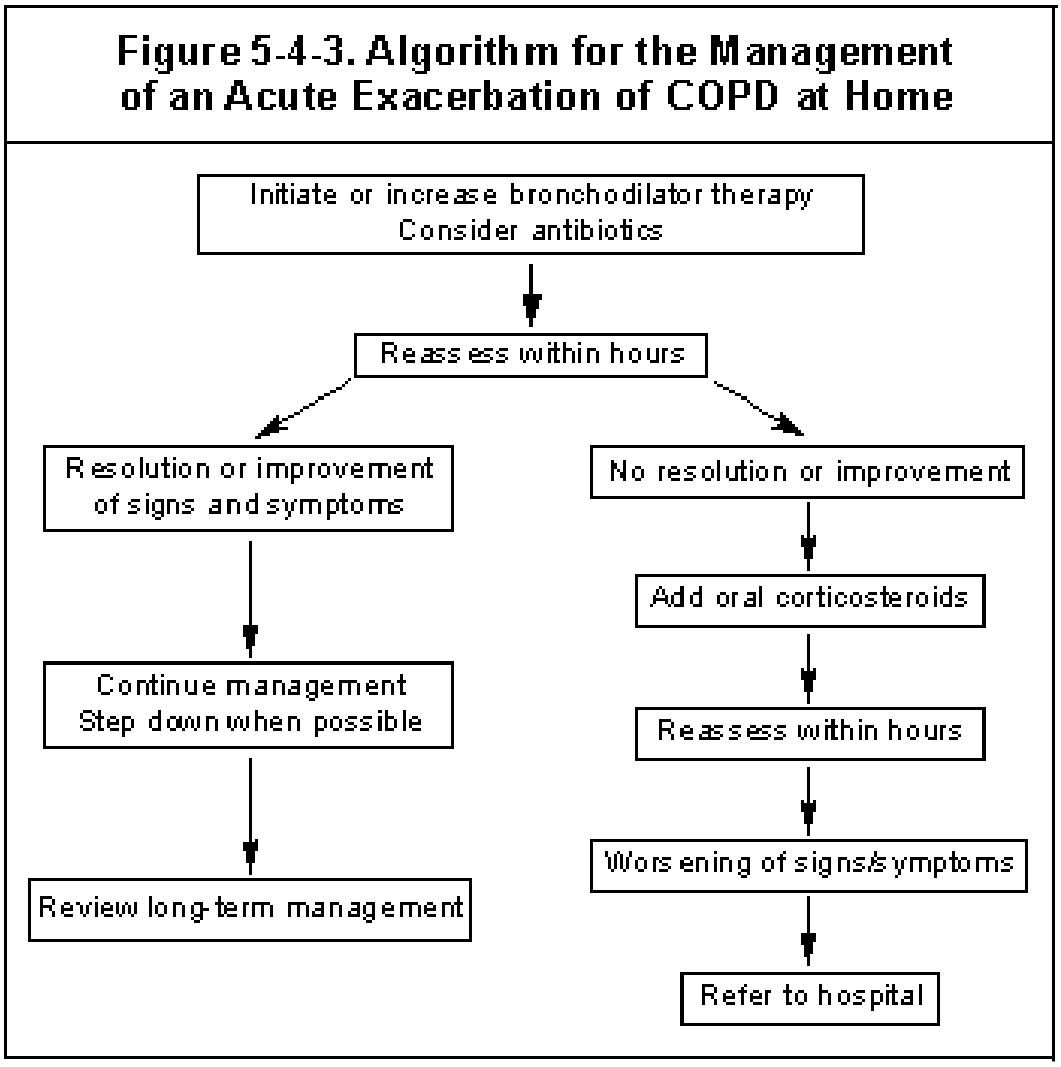
treatment, a sputum culture and an antibiogram should be performed. Biochemical tests can reveal whether the cause of the exacerbation is an electrolyte disturbance(s) (hyponatremia, hypokalemia, etc.), a diabetic crisis, or poor nutrition (low proteins), and may suggest a metabolic acid-base disorder.

HOME MANAGEMENT

There is increasing interest in home care for end-stage COPD patients, although economic studies of home-care services have yielded mixed results. One study found that quality of life improved and hospital days per admission fell after a home-care program was instituted, but a randomized controlled trial found that substituting home care for inpatient hospital care produced no better health outcomes while increasing costs. A major outstanding issue is when to treat an exacerbation at home and when to hospitalize the patient.

The algorithm reported in **Figure 5-4-3** may assist in the management of an acute exacerbation at home; a stepwise therapeutic approach is recommended.

Figure 5-4-3. Algorithm for the Management of an Acute Exacerbation of COPD at Home



Bronchodilator Therapy

Home management of COPD exacerbations involves increasing the dose and/or frequency of existing bronchodilator therapy (**Evidence A**). If not already used, an anticholinergic can be added until the symptoms

improve. In more severe cases, high-dose nebulizer therapy can be given on an as-needed basis for several days and if a suitable nebulizer is available. However, long-term use of nebulizer therapy after an acute episode is not routinely recommended.

Corticosteroids

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

Antibiotics

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

HOSPITAL MANAGEMENT

The risk of dying from an acute exacerbation of COPD is closely related to the development of respiratory acidosis, the presence of significant co-morbidities, and the need for ventilatory support. 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, 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. Several randomized controlled trials have confirmed that this is a safe alternative to hospitalization, although it probably only applies to about 25% of COPD admissions. Savings on inpatient expenditures offset the additional costs of maintaining a community-based COPD nursing team. However, detailed cost-benefit analyses of these approaches are awaited.

Hospital assessment/admission should be considered for all patients who fit the criteria shown in **Figure 5-4-4.** Some patients need immediate admission to an intensive care unit (ICU). 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 5-4-4. Indications for Hospital Assessment or Admission for Acute Exacerbations of COPD*

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

Figure 5-4-5. Indications for ICU Admission of Patients with Acute Exacerbations of COPD*

- Severe dyspnea that responds inadequately to initial emergency therapy.
- Confusion, lethargy, coma.
- Persistent or worsening hypoxemia (PaO_2 < 6.7 kPa, 50 mm Hg), and/or severe/worsening hypercapnia ($PaCO_2$ > 9.3 kPa, 70 mm Hg), and/or severe/worsening respiratory acidosis (pH < 7.30) des[ote si[[;e,emta; pxugem amd NIPPV.

Local resources need to be considered.

Emergency Department or Hospital

The first actions when a patient reaches the emergency department are to provide controlled oxygen therapy and to determine whether the exacerbation is life threatening. If so, the patient should be admitted to the ICU immediately. Otherwise, the patient may be managed in the emergency department or hospital as detailed in **Figure 5-4-6.**

Figure 5-4-6. Management of Severe but Not Life-Threatening Exacerbations of COPD in the Emergency Department or the Hospital*

- Assess severity of symptoms, blood gases, chest X-ray.
- Administer controlled oxygen therapy and repeat arterial blood gas measurement after 30 minutes.
- Bronchodilators
  - Increase doses or frequency.
  - Combine $ß_2$-agonists and anticholinergics.
  - Use spacers or air-driven nebulizers.
  - Consider adding intra-venous aminophylline, if needed.
- Add oral or intravenous glucocorticosteroids.
- Consider antibiotics:
  - When signs of bacterial infection, oral or occasionally intravenous.
- Consider noninvasive mechanical ventilation.
- At all times:
  - Monitor fluid balance and nutrition.
  - Consider subcutaneousheparin.
  - Identify and treat associated conditions (e.g., heart failure, arrhythmias).
  - Closely monitor conditionof the patient.

**Local resources need to be considered.*

Controlled oxygen therapy. Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. 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 blood gases should be checked 30 minutes later to ensure satisfactory oxygenation without CO_2retention or acidosis. Venturi masks are more accurate sources of controlled oxygen than are nasal prongs but are more likely to be removed by the patient.

Bronchodilator therapy. Short-acting inhaled $ß_2$-agonists are usually the preferred bronchodilators for treatment of acute exacerbations of COPD (**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 rather controversial. Despite its widespread clinical use, aminophylline's role in the treatment of exacerbations of COPD remains controversial. Most studies of aminophylline have demonstrated minor improvements in lung volumes but also worsening of gas exchange and hypoxemia. In more severe exacerbations, addition of an oral or intravenous methylxanthine to the treatment can be considered. However, close monitoring of serum theophylline is recommended to avoid the side effects of these drugs.

Corticosteroids. Oral or intravenous corticosteroids are recommended as an addition to bronchodilator therapy (plus eventually antibiotics and oxygen therapy) in the hospital management of acute exacerbations of COPD (**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 10 to 14 days is a reasonable compromise between efficacy and safety (**Evidence D**). Prolonged treatment does not result in greater efficacy and increases the risk of side effects.

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

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

Noninvasive mechanical ventilation. Noninvasive intermittent positive pressure ventilation (NIPPV) has been studied in many uncontrolled and five randomized controlled trials in acute respiratory failure. The studies show consistently positive results with success rates of 80-85%. Taken together they provide evidence that NIPPV increases pH, reduces $PaCO_2$, reduces the severity of breathlessness in the first 4 hours of treatment, and decreases the length of hospital stay (**Evidence A**). More importantly, mortality - or its surrogate, intubation rate - is reduced by this intervention. However, NIPPV is not appropriate for all patients, as summarized in **Figure 5-4-7.**

Figure 5-4-7. Selection and Exclusion Criteria for NIPPV

Selection criteria (at least 2 should be present)

- Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion.
- Moderate to severe acidosis (pH 7.30-7.35) and hypercapnia ($PaCO_2$ > 6.0-8.0 kPa, 45-60 mm Hg).
- Respiratory frequency 25 breaths per minute.

Exclusion criteria (any may be present)

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

Invasive (conventional) mechanical ventilation. During exacerbations of COPD the events occurring within the lungs include bronchoconstriction, airway inflammation, increased mucous secretions, 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. As a result of these processes, an elastic threshold load, referred to as intrinsic or auto-positive end-expiratory pressure (PEEPi), is imposed on the inspiratory muscles at the beginning of inspiration and increases the work of breathing. For these reasons, patients who show impending acute respiratory failure and those with life-threatening acid-base status abnormalities and/or altered mental status despite aggressive pharmacologic therapy are likely to be the best candidates for invasive (conventional) mechanical ventilation. The indications for initiating mechanical ventilation during exacerbations of COPD are shown in **Figure 5-4-8,** the first being the commonest and most important reason. **Figure 5-4-9** details the factors determining benefit from invasive ventilation. The three ventilatory modes most widely used are assisted-control ventilation, and pressure support ventilation alone or in combination with intermittent mandatory ventilation.

Figure 5-4-8. Indications for Invasive Mechanical Ventilation

- Severe dyspnea with use of accessory muscles and paradoxical abdominal motion.
- Respiratory frequency > 35 breaths per minute.
- Life-threatening hypoxemia (PaO_2 < 5.3 kPa, 40 mm Hg or PaO_2/FiO_2 < 200 mm Hg).
- Severe acidosis (pH < 7.25) and hypercapnia ($PaCO_2$ > 8.0 kPa, 60 mm Hg).
- Respiratory arrest.
- Somnolence, impaired mental status.
- Cardiovascular complications (hypotension, shock, heart failure).
- Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion).
- NIPPV failure (or exclusion criteria, see Figure 5-4-7).

FiO_2: Fractional concentration of oxygen in dry inspired gas.

Figure 5-4-9. Factors Determining Benefit from Invasive 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.

The use of invasive ventilation in end-stage COPD patients is influenced by the likely reversibility of the precipitation event, the patient's wishes, and the availability of intensive care facilities. 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, mortality among COPD patients with respiratory failure is no greater than mortality among patients ventilated for non-COPD causes.

A review of a large number of North American COPD patients ventilated for respiratory failure indicated an in-hospital mortality of 17-30%. Further attrition over the next 12 months was particularly high 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 underlying disease, 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. When possible, a clear statement of the patient's own treatment wishes - an advance directive or "living will" - makes these difficult decisions much easier to resolve.

Weaning or discontinuation from mechanical ventilation can be particularly difficult and hazardous in patients with COPD. 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. By contrast, pulmonary gas exchange by itself is not a major difficulty in patients with COPD. Weaning patients from the ventilator can be a very difficult and prolonged process and the best method remains a matter of debate. Whether pressure support or a T-piece trial is used, weaning is shortened when a clinical protocol is adopted (**Evidence A**). Non-invasive ventilation has been applied to facilitate the weaning process in COPD patients with acute or chronic respiratory failure. Compared with invasive pressure support ventilation, noninvasive intermittent positive pressure ventilation (NIPPV) during weaning shortened weaning time, reduced the stay in the intensive care unit, decreased the incidence of nosocomial pneumonia, and improved 60-day survival rates. Similar findings have been reported when NIPPV is used after extubation for hypercapnic respiratory failure (**Evidence C**).

Other measures. Further treatments that can be used in the hospital include: fluid administration (accurate monitoring of fluid balance is essential); nutrition (supplementary when the patient is too dyspneic to eat); low molecular heparin 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.

Hospital Discharge and Follow-Up

Insufficient clinical data exist to establish the optimal duration of hospitalization in individual patients developing an exacerbation of COPD. Consensus and limited data support the discharge criteria listed in **Figure 5-4-10. Figure 5-4-11** 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.

Figure 5-4-10. Discharge Criteria for Patients with Acute 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.

Figure 5-4-11. Follow-Up Assessment 4-6 Weeks After Discharge from Hospital for Acute 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 severe COPD).

If hypoxemia developed during the exacerbation, arterial blood gases should be rechecked at discharge and at the follow-up visit. If the patient remains hypoxemic, long-term oxygen therapy should be instituted. Decisions about suitability for continuous domiciliary oxygen based on the severity of the acute hypoxemia during an exacerbation are frequently misleading.

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

Chapter 6: Future Research

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

Some research recommendations and future program goals are provided to stimulate the efforts of investigators around the world. There are many additional avenues to explore.

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

- The stages and natural history of COPD vary from one patient to another. The clinical utility of the four-stage classification of severity used in the GOLD Report needs to be evaluated.

- Surrogate markers of inflammation, possibly derived from the analysis of sputum (cells, mediators, enzymes) or exhaled condensates (lipid mediators, reactive oxygen species, cytokines), that may predict the clinical usefulness of new management and prevention strategies for COPD need to be developed.

- Information is needed about the cellular and molecular mechanisms involved in inflammation in stable COPD and exacerbations. Inflammatory responses in nonsmokers, ex-smokers, and smokers with and without COPD should be compared. The mechanisms responsible for the persistence of the inflammatory response in COPD should be investigated. Why inflammation in COPD is poorly responsive to corticosteroids and what treatments other than corticosteroids are effective in suppressing inflammation in COPD are research topics that could lead to new treatment modalities.

- Standardized methods for tracking trends in COPD prevalence, morbidity, and mortality over time need to be developed so that countries can plan for future increases in the need for health care services in view of predicted increases in COPD. This need is especially urgent in developing countries with limited health care resources.

- Longitudinal studies demonstrating the course of COPD are needed in a variety of populations exposed to various risk factors. Such studies would provide insight into the pathogenesis of COPD, identify additional genetic bases for COPD, and identify how genetic risk factors interact with environmental risk factors in specific patient populations. Factors that determine why some, but not all, smokers develop COPD need to be identified.

- Data are needed on the use, cost, and relative distribution of medical and non-medical resources for COPD, especially in countries where smoking and other risk factors are prevalent. These data are likely to have some impact on health policy and resource allocation decisions. As options for treating COPD grow, more research will be needed to help guide health care workers and health budget managers regarding the most efficient and effective ways of managing this disease. Methods and strategies for implementation of COPD management programs in developing countries will require special attention.

- While spirometry is recommended to assess and monitor COPD, other measures need to be developed and evaluated in clinical practice. Reproducible and inexpensive exercise-testing methodologies (e.g., stair-climbing tests) suitable for use in developing countries need to be evaluated and their use encouraged. Spirometers need to be developed that can ensure economical and accurate performance when a relatively untrained operator administers the test.

- Since COPD is not fully reversible (with current therapies) and slowly progressive, it will become ever more important to identify early cases as more effective therapies emerge. Consensus on standard methods for detection and definition of early disease need to be developed. Data to show whether or not screening is effective in directing management decisions in COPD outcomes are required.

- Primary prevention of COPD is one of the major objectives of GOLD. Investigations into the most cost-effective ways to reduce the prevalence of tobacco smoking in the general population and more specifically in young people are very much needed. Strategies to prevent people from starting to smoke and methods for smoking cessation require constant evaluation and improvement. Research is required to gauge the impact and reduce the risk from increasing air pollution, urbanization, recurrent childhood infections, occupational exposures, and use of local cigarette equivalents. Programs designed to reduce exposure to biomass fuel in countries where this is used for cooking and domestic heating should be explored in an effort to reduce exposure and improve ventilation in homes.

- The specific components of effective education for COPD patients need to be determined. It is not known, for example, whether COPD patients should be given an individual management plan, or whether these plans are effective in reducing health care costs or improving the outcomes of exacerbations. Developing and evaluating effective tools for physician education concerning prevention, diagnosis, and management of COPD will be important in view of the increasing public health problem presented by COPD.

- Studies are needed to determine whether education is an essential component of pulmonary rehabilitation. The cost effectiveness of rehabilitation programs has not been assessed and there is a need to assess the feasibility, resource utilization, and health outcomes of rehabilitation programs that are delivered outside the major teaching hospital setting. Criteria for selecting individuals for rehabilitation should be evaluated, along with methods to modify programs to suit the needs of individual patients.

- Collecting and evaluating data to classify COPD exacerbations by severity would stimulate standardization of this outcome measure that is so frequently used in clinical trials. Further exploration of the ethical principles of life support and greater insight into the behavioral influences that inhibit discussion of such intangible issues are needed, along with studies to define the needs of end-stage COPD patients.

- There is a pressing need to develop drugs that control symptoms and prevent the progression of COPD. Some progress has been made and there are several classes of drugs that are now in preclinical and clinical development for use in COPD patients.

Mediator antagonists: Attention has largely focused on mediators involved in recruitment and activation of neutrophils, and reactive oxygen species. In this category are the LTB4 antagonists, lipoxygenase inhibitors, chemokine inhibitors, and TNF-α inhibitors.

Antioxidants: Oxidative stress is increased in patients with COPD, particularly during exacerbations. Oxidants are present in cigarette smoke and are produced endogenously by activated inflammatory cells, including neutrophils and alveolar macrophages, suggesting that antioxidants may be of use in therapy for COPD.

Anti-inflammatory drugs: The limited value of corticosteroids in reducing inflammation in COPD suggests that novel types of nonsteroidal anti-inflammatory treatment may be needed. There are several new approaches to anti-inflammatory treatment in COPD including, for example, phosphodiesterase inhibitors, transcription factor NF-$_{kB}$ inhibitors, and adhesion molecule blockers.

Proteinase inhibitors: There is compelling evidence that an imbalance between proteinases that digest elastin (and other structural proteins) and antiproteinases that protect against this digestion exists in COPD. Considerable progress has been made in identifying the enzymes involved in elastolytic activity in emphysema and in characterizing the endogenous antiproteinases that counteract this activity, including neutrophil elastase

inhibitors, cathepsin G and proteinase 3 inhibitors, and matrix metalloproteinase inhibitors. Other serine proteinase inhibitors (serpins), such as elafin, may also be important in counteracting elastolytic activity in the lung.

Mucoregulators: It may be important to develop drugs that inhibit the hypersecretion of mucus, without suppressing the normal secretion of mucus or impairing mucociliary clearance. There are several types of mucoregulatory drugs in development including tachykinin antagonists, sensory neuropeptide inhibitors, mediator and enzyme inhibitors, mucin gene suppressors, mucolytic agents, macrolide antibiotics, and purinoceptor blockers.

Alveolar repair: A major mechanism of airway obstruction in COPD is loss of elastic recoil due to proteolytic destruction of the lung parenchyma. Thus, it seems unlikely that this obstruction can be reversed by drug therapy, although it might be possible to reduce the rate of progression by preventing the inflammatory and enzymatic disease processes. It is even possible that drugs might be developed to stimulate regrowth of alveoli. Studies are actively on-going, and, the goal of regenerating diseased lungs and curing destructive pulmonary diseases such as COPD seems to be closer to a reality. Although there are numerous obstacles to be overcome, lung regeneration therapy is expected to be translated safely and effectively from the laboratory to the bedside.

Route of delivery: Many inhalers that deliver bronchodilators have been optimized to deliver drugs to the respiratory tract in asthma. Methods to quickly and safely deliver medications to target sites of inflammation and tissue destruction in COPD need to be evaluated.

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COPD: The Gold Report Exam

Select the ***best*** answer to each of the following items. Mark your responses on the Answer form.

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

a. AMA
b. AARC
c. ANA
d. GOLD Report

2. Airflow limitation is measured by _____, as this is the most widely available, reproducible test of lung function.

a. blow-bottle tests
b. spirometry
c. reading broncho-grams
d. blood pressure reading after treadmill exercise

3. COPD is currently the _____ leading cause of death in the US and worldwide

a. first
b. fourth
c. tenth
d. fifteenth

4. According to the GOLD report, some physicians have adopted a *nihilistic* attitude towards COPD because the prevailing notion that COPD is_____.

a. curable
b. incurable
c. a medical mystery
d. largely a self-inflicted disease

5. A characteristic symptom of COPD is _____.

a. cough
b. sputum production
c. dyspnea upon exertion
d. all the above

6. COPD has a natural history, _____.

a. but researchers have yet to discover what it is
b. and all patients with the disorder follow the same course
c. but not all individuals follow the same course
d. and the prognosis is almost always a good one if discovered early

7. The management of COPD _____.

a. the same for all patients
b. depends on the age of the patient
c. is largely symptom driven
d. depends on the family history of breathing issues

8. COPD may be diagnosed _____.

a. only at the onset of its presence
b. only after the patient has been afflicted for at least 3 months
c. only after the patient has been afflicted for over a year
d. at any stage of the illness

9. The common statement that only 15-20% of smokers develop clinically significant COPD

a. has been confirmed by the Gold report
b. has been increased to about 30% by the Gold report
c. has been increased to about 75% by the Gold report
d. is misleading

10. According to the Gold report, the population surveys necessary to develop accurate estimates of COPD are costly to do _____.

a. and have not yet begun except in the United States
b. but have been completed in nearly every country
c. and therefore have not been conducted in many countries
d. and therefore should be abandoned

11. The prevalence of COPD is highest in countries where _____ have (has) been, or still is, very common, while the prevalence is lowest in countries where it is less common.

a. air pollution
b. industrialization
c. tuberculosis
d. cigarette smoking

12. The Gold study finds that asthma is the most common chronic respiratory disease worldwide, with twice the number of cases of COPD in 2015, but that deaths from COPD were eight times more common than deaths from asthma.

a. True
b. False

13. The best-documented host factor in cases of COPD is a severe hereditary deficiency of _____.

a. alpha-1 antitrypsin
b. iron
c. calcium
d. surfactant

14. Most common in COPD patients is the _____ form of emphysema, which involves dilatation and destruction of the respiratory bronchioles.

a. chronic
b. centrilobular
c. acute
d. linear

15. Pulmonary hypertension develops in the _____ stage(s) of COPD.

a. 0
b. I
c. II
d. III and IV

16. Health care workers involved in the diagnosis and management of COPD patients should have access to _____.

a. sphygmometers
b. blow-bottles
c. spirometry
d. the patient's medical history

17. Measurement of _____ should be considered in all patients with FEV_1 < 40% predicted or clinical signs suggestive of respiratory failure or right heart failure.

a. flow-volumes
b. expiratory volumes
c. inspiratory volumes
d. arterial blood gas tensions

18. _____ is usually the first symptom of COPD to develop.

a. Chronic cough
b. Mucus production
c. Dyspnea
d. Wheezing

19. In treating patients with COPD, it is important to consider the presence of concomitant conditions such as _____.

a. bronchial carcinoma
b. tuberculosis
c. sleep apnea
d. all of the above
e. none of the above

20. _____ is the single most effective - and cost effective - way to reduce exposure to COPD risk factors.

a. A health diet
b. Avoiding occupational dust
c. Smoking cessation
d. Daily exercise

21. Counseling delivered by _____ significantly increases quit rates over self-initiated strategies.

a. former smokers
b. family members
c. anti-tobacco advertisements
d. health care professionals

22. _____ medications are central to the symptomatic management of COPD.

a. Corticosteroid
b. Bronchodilator
c. Mucokenic
d. Allergy

23. Chronic treatment of COPD patients with _____ should be avoided because of an unfavorable benefit-to-risk ratio.

a. bronchodilators
b. nicotine patches
c. systemic glucocorticosteroids
d. oxygen therapy

24. According to the Gold report, COPD patient education is most effective when it _____.

a. relies heavily on printed materials
b. utilizes audio/video materials
c. is presented one-one-one
d. it is interactive and conducted in small workshops

25. Of the existing medications for COPD, _____ has been shown to modify the long-term decline in lung function that is the hallmark of this disease.

a. corticosteroids
b. bronchodilators
c. systemic glucocorticosteroids
d. none

26. Ideally, educational messages should be incorporated into the following aspect of care for COPD: _____.

a. consultations with physicians or other health care workers
b. home-care or outreach programs
c. comprehensive pulmonary rehabilitation programs
d. all the above

27. Because none of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this disease,

a. the focus of medications for COPD is to decrease symptoms and/or complications.
b. reverse damage from smoking and air pollution
c. increase expected life span by 2-5 years
d. eliminate the need to change a patients lifestyle

28. According to the Gold report, based on the lack of evidence of benefit, and the large body of evidence on side effects, long-term treatment with _____ is not recommended in COPD.

a. inhaled B2 agonists
b. slow-release theophylline
c. anticholinergics
d. oral corticosteroids

29. The long-term administration of _____ (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival.

a. bronchodilators
b. oxygen
c. systemic glucocorticosteroids
d. inhaled corticosteroids

30. The step-down approach used in the chronic treatment of _____ is not applicable to COPD since COPD is usually stable and very often progressive.

a. asthma
b. bronchitis
c. lung cancers
d. emphysema

31. The role of gender as a risk factor for COPD _____.

a. has long been recognized
b. has never been investigated
c. remains unclear
d. has recently become very clear

32. The presence and role of eosinophils in COPD _____.

a. are significant
b. seem to be slight
c. are uncertain
d. have only just recently been discovered

33. Inflammation is present in the lungs of smokers with no diagnosis of lung disease.

a. True
b. False

34. There is increasing evidence that an oxidant/antioxidant _____ occurs in COPD.

a. imbalance in favor of oxidants
b. imbalance in favor of antioxidants
c. implosion
d. balance

35. _____ characteristic of COPD are found in the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature.

a. Enzymes
b. Mucous
c. anaerobes
d. Pathological changes

36. As COPD worsens, greater amounts of smooth muscle, proteoglycans, and collagen _____.

a. act to combat the condition
b. further thicken the vessel walls
c. act to make the vessel walls thinner
d. cause vessels to break open

37. Airflow limitation in COPD is best measured through _____, which is key to the diagnosis and management of the disease.

a. spirometry
b. spectroscopy
c. bronchoscopy
d. the flow-bottle test

38. Diagnosis of COPD is based on a history of exposure to risk factors and the presence of _____ that is not fully reversible, with or without the presence of symptoms

a. lung scarring seen on radiographs
b. blood vessel thinning
c. blood vessel thickening
d. airflow limitation

39. Patients with COPD often have _____, but this finding is not sufficiently characteristic to make the diagnosis.

a. increased breath sounds
b. reduced breath sounds
c. increased lung size
d. reduced lung size

40. A chest X-ray is seldom diagnostic in COPD unless _____, but it is valuable in excluding alternative diagnoses.

a. lung size appears as increased
b. lung size appears as decreased
c. obvious bullous disease is present
d. it is accompanied by similar ultrasound findings

41. The first exposure to cigarette smoke may begin _____.

a. prior to conception through the mother's predisposition to smoking
b. in utero
c. in the baby's first year of life if exposed to second-hand smoke
d. as a teen or pre-teen

42. All forms of nicotine replacement therapy are _____ placebos.

a. really nothing more than
b. often not as effective as
c. about as effective as
d. significantly more effective than

43. COPD patients may have more problems in effective coordination and find it harder to use a simple _____ than do healthy volunteers or younger asthmatics.

a. spirometer
b. blow-bottle
c. metered dose inhaler
d. oxygen tank

44. _____, although sometimes a troublesome symptom in COPD, have (has) a significant protective role. Thus the regular use of antitussives is contraindicated in stable COPD (**Evidence D**).

a. Sneezes
b. Cough
c. Sleep apnea
d. Wheezing sounds

45. _____ is (are) usually the most costly component of outpatient therapy for adults with COPD who require this therapy.

a. Humidifiers
b. Corticosteroids
c. Metered Dose Inhalers
d. Supplemental home oxygen

46. _____ can be very difficult to distinguish from an acute exacerbation, especially in severe COPD, because right ventricular hypertrophy and large pulmonary arteries lead to confusing ECG and radiographic results

a. Pulmonary embolism
b. Myocardial infarction
c. An acute asthma attack
d. Pulmonary thrombosis

47. Home management of COPD exacerbations involves increasing the dose and/or frequency of existing bronchodilator therapy (**Evidence A**). If not already used, a (an) _____ can be added until the symptoms improve.

a. corticosteroid
b. anticholinergic
c. mucolytic
d. dose of nitric oxide

48. The most common causes of an exacerbation are _____, but the cause of about one-third of severe exacerbations cannot be identified.

a. allergies
b. lack of exercise
c. infection of the tracheobronchial tree and air pollution
d. stress

49. The prevalence and natural history of cor pulmonale in COPD _____.

a. have never really been investigated
b. have been well documented in most medical journals
c. only recently becoming clear through new mega-analysis methods
d. are not yet clear

50. Regular bronchodilation with drugs that act primarily on _____ does not modify the decline of function in mild COPD and, by inference, the prognosis of the disease **(Evidence B)**.

a. airway smooth muscle
b. the cilia
c. airway blood vessels
d. respiratory rate