Global Initiative for Chronic Obstructive Lung Disease

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

UPDATED 2007

EXECUTIVE SUMMARY

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

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PREFACE

Chronic Obstructive Pulmonary Disease (COPD) remains a major public health problem. It is the fourth leading cause of chronic morbidity and mortality in the United States[1], and is projected to rank fifth in 2020 in burden of disease caused worldwide, according to a study published by the World Bank/World Health Organization[2]. Yet, COPD remains relatively unknown or ignored by the public as well as public health and government officials.

In 1998, in an effort to bring more attention to COPD, its management, and its prevention, a committed group of scientists encouraged the US National Heart, Lung, and Blood Institute and the World Health Organization to form the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Among the important objectives of GOLD are to increase awareness of COPD and to help the millions of people who suffer from this disease and die prematurely from it or its complications.

The first step in the GOLD program was to prepare a consensus report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*, published in 2001. The present, newly revised document follows the same format as the original consensus report, but has been updated to reflect the many publications on COPD that have appeared.

A network of international experts, GOLD National Leaders have initiated investigations of the causes and prevalence of COPD in their countries, and developed innovative approaches for the dissemination and implementation of COPD management guidelines. We appreciate the enormous amount of work the GOLD National Leaders have done on behalf of their patients with COPD.

In spite of the achievements in the five years since the GOLD report was originally published, considerable additional work is ahead of all of us if we are to control this major public health problem. The GOLD initiative will continue to bring COPD to the attention of governments, public health officials, health care workers, and the general public, but a concerted effort by all involved in health care will be necessary. We look forward to our continued work with interested organizations and the GOLD National Leaders to meet the goals of this initiative.

We are most appreciative of the unrestricted educational grants from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Dey, GlaxoSmithKline, Mitsubishi Tanabe Pharma, Novartis, Nycomed, Pfizer, and Schering-Plough that enabled development of this report.

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years and die prematurely from it or its complications. The goals of the **G**lobal Initiative for Chronic **O**bstructive **L**ung **D**isease (**GOLD**) are to improve prevention and management of COPD through a concerted worldwide effort of people involved in all facets of health care and health care policy, and to encourage an expanded level of research interest in this highly prevalent disease.

One strategy to help achieve the objectives of GOLD is to provide health care workers, health care authorities, and the general public with state-of-the-art information about COPD and specific recommendations on the most appropriate management and prevention strategies. The GOLD report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*, is based on the best-validated current concepts of COPD pathogenesis and the available evidence on the most appropriate management and prevention strategies. A major part of the GOLD report is devoted to the clinical *Management of COPD* and presents a management plan with four components: (1) *Assess and Monitor Disease*; (2) *Reduce Risk Factors*; (3) *Manage Stable COPD*; (4) *Manage Exacerbations.* A new chapter at the end of the document will assist readers in *Translating Guideline Recommendations to the Context of (Primary) Care.*

GOLD is a partner organization in a program launched in March 2006 by the World Health Organization, the Global Alliance Against Chronic Respiratory Diseases (GARD). Through the work of the GOLD committees, and in cooperation with GARD initiatives, progress toward better care for all patients with COPD should be substantial in the next decade.

METHODOLOGY AND SUMMARY OF NEW RECOMMENDATIONS

Following the release of the 2001 GOLD report, a Science Committee was formed and charged with keeping the GOLD documents up-to-date by reviewing published research, evaluating the impact of this research on the management recommendations in the GOLD documents, and posting yearly updates of these documents on the GOLD Website (www.goldcopd.org). The methodology is described in each update (see e.g., 2005 update[3]).

In January 2005, the GOLD Science Committee initiated preparation of this revised 2006 document based on the most current scientific literature. Multiple meetings were held including several with GOLD National Leaders to discuss concepts and new recommendations. Prior to its publications, several reviewers were invited to submit comments.

A summary of the issues presented in this report include:

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

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

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

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

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

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

7. Chapter 4, Translating Guideline Recommendations to the Context of (Primary) Care, continues with the theme that inhaled cigarette smoke and other noxious particles cause lung inflammation, a normal response which appears to be amplified in patients who develop COPD. The chapter has been considerably updated and revised.

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

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

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

LEVELS OF EVIDENCE

Levels of evidence are assigned to management recommendations where appropriate in Chapter 3, Management of COPD with the system used in previous GOLD reports (**Figure 1**). Evidence levels are indicated in boldface type enclosed in parentheses after the relevant statement, e.g., (**Evidence A**).

Figure 1. Description of Levels of Evidence

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

1. DEFINITION, CLASSIFICATION OF SEVERITY, AND MECHANISMS OF COPD

DEFINITION

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

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Airflow limitation is best measured by spirometry, as this is the most widely available, reproducible test of lung function.

Because COPD often develops in long-time smokers in middle age, patients often have a variety of other diseases related to either smoking or aging[4]. COPD itself also has significant extrapulmonary (systemic) effects that lead to comorbid conditions[5]. Thus, COPD should be managed with careful attention also paid to comorbidities and their effect on the patient's quality of life. A careful differential diagnosis and comprehensive assessment of severity of comorbid conditions should be performed in every patient with chronic airflow limitation.

SPIROMETRIC CLASSIFICATION OF SEVERITY AND STAGES OF COPD

For educational reasons, a simple spirometric classification of disease severity into four stages is recommended (**Figure 2**). Spirometry is essential for diagnosis and provides a useful description of the severity of pathological changes in COPD. Specific spirometric cut-points (e.g., post-bronchodilator FEV_1/FVC ratio < 0.70 or FEV_1 < 80, 50, or 30% predicted) are used for purposes of simplicity: these cut-points have not been clinically validated.
A study in a random population sample found that the post-bronchodilator FEV_1/FVC exceeded 0.70 in all age groups, supporting the use of this fixed ratio[6]. However, because the process of aging does affect lung volumes, the use of this fixed ratio may result in overdiagnosis of COPD in the elderly, especially of mild disease.

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

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

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

The characteristic symptoms of COPD are chronic and progressive dyspnea, cough, and sputum production. Chronic cough and sputum production may precede the development of airflow limitation by many years. This pattern offers a unique opportunity to identify smokers and others at risk for COPD, and intervene when the disease is not yet a major health problem. Conversely, significant airflow limitation may develop without chronic cough and sputum production.

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

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

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

Stage IV: Very Severe COPD - Characterized by severe airflow limitation ($FEV_1/FVC < 0.70$; $FEV_1 < 30\%$ predicted *or* $FEV_1 < 50\%$ predicted plus the presence of chronic

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

While asthma can usually be distinguished from COPD, in some individuals with chronic respiratory symptoms and fixed airflow limitation it remains difficult to differentiate the two diseases. In many developing countries both pulmonary tuberculosis and COPD are common[7]. In countries where tuberculosis is very common, respiratory abnormalities may be too readily attributed to this disease[8]. Conversely, where the rate of tuberculosis is greatly diminished, the possible diagnosis of this disease is sometimes overlooked. Therefore, in all subjects with symptoms of COPD, a possible diagnosis of tuberculosis should be considered, especially in areas where this disease is known to be prevalent[9].

PATHOLOGY, PATHOGENESIS AND PATHOPHYSIOLOGY

Pathological changes characteristic of COPD are found in the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature[10]. The pathological changes include chronic inflammation, with increased numbers of specific inflammatory cell types in different parts of the lung, and structural changes resulting from repeated injury and repair. In general, the inflammatory and structural changes in the airways increase with disease severity and persist on smoking cessation.

The inflammation in the respiratory tract of COPD patients appears to be an amplification of the normal inflammatory response of the respiratory tract to chronic irritants such as cigarette smoke. The mechanisms for this amplification are not yet understood but may be genetically determined. Some patients develop COPD without smoking, but the nature of the inflammatory response in these patients is unknown[11]. Lung inflammation is further amplified by oxidative stress and an excess of proteinases in the lung. Together, these mechanisms lead to the characteristic pathological changes in COPD.

There is now a good understanding of how the underlying disease process in COPD leads to the characteristic physiologic abnormalities and symptoms. For example, decreased FEV_1 primarily results from inflammation and narrowing of peripheral airways, while decreased gas transfer arises from the parenchymal destruction of emphysema. The extent of inflammation, fibrosis, and luminal exudates in small airways is correlated with the reduction in FEV_1 and FEV_1/FVC ratio, and probably with the accelerated decline in FEV_1 characteristic of COPD[4]. Gas exchange abnormalities result in hypoxemia and hypercapnia, and have several mechanisms in COPD. In general, gas transfer worsens as the disease progresses. Mild to moderate pulmonary hypertension may develop late in the course of COPD and is due to hypoxic vasoconstriction of small pulmonary arteries. It is increasingly recognized that COPD involves several systemic features, particularly in patients with severe disease, and that these have a major impact on survival and comorbid diseases[12,13].

2. BURDEN OF COPD

COPD prevalence, morbidity, and mortality vary across countries and across different groups within countries but, in general, are directly related to the prevalence of tobacco smoking although in many countries, air pollution resulting from the burning of wood and other biomass fuels has also been identified as a COPD risk factor. The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the changing age structure of the world's population.

EPIDEMIOLOGY

In the past, imprecise and variable definitions of COPD have made it difficult to quantify prevalence, morbidity and mortality. Furthermore, the underrecognition and underdiagnosis of COPD lead to significant underreporting. The extent of the underreporting varies across countries and depends on the level of awareness and understanding of COPD among health professionals, the organization of health care services to cope with chronic diseases, and the availability of medications for the treatment of COPD[14].

Prevalence: Many sources of variation can affect estimates of COPD prevalence, including sampling methods, response rates, quality control of spirometry, and whether spirometry is performed pre- or post-bronchodilator. Despite these complexities, data are emerging that enable some conclusions to be drawn regarding COPD prevalence. A systematic review and meta-analysis of studies carried out in 28 countries

between 1990 and 2004[15], and an additional study from Japan[16], provide evidence that the prevalence of COPD (*Stage I: Mild COPD* and higher) is appreciably higher in smokers and ex-smokers than in nonsmokers, in those over 40 years than those under 40, and in men than in women.

Morbidity: Morbidity measures traditionally include physician visits, emergency department visits, and hospitalizations. Although COPD databases for these outcome parameters are less readily available and usually less reliable than mortality databases, the limited data available indicate that morbidity due to COPD increases with age and is greater in men than in women[17-19]. COPD in its early stages (*Stage I: Mild COPD* and *Stage 2: Moderate COPD*) is usually not recognized, diagnosed, or treated, and therefore may not be included as a diagnosis in a patient's medical record.

Morbidity from COPD may be affected by other comorbid chronic conditions[20] (e.g., musculoskeletal disease, diabetes mellitus) that are not directly related to COPD but nevertheless may have an impact on the patient's health status, or may negatively interfere with COPD management. In patients with more advanced disease (*Stage III: Severe COPD* and *Stage IV: Very Severe COPD*), morbidity from COPD may be misattributed to another comorbid condition.

Mortality: COPD is one of the most important causes of death in most countries. The Global Burden of Disease Study[2,21,22] has projected that COPD, which ranked sixth as the cause of death in 1990, will become the third leading cause of death worldwide by 2020. This increased mortality is driven by the expanding epidemic of smoking and the changing demographics in most countries, with more of the population living longer.

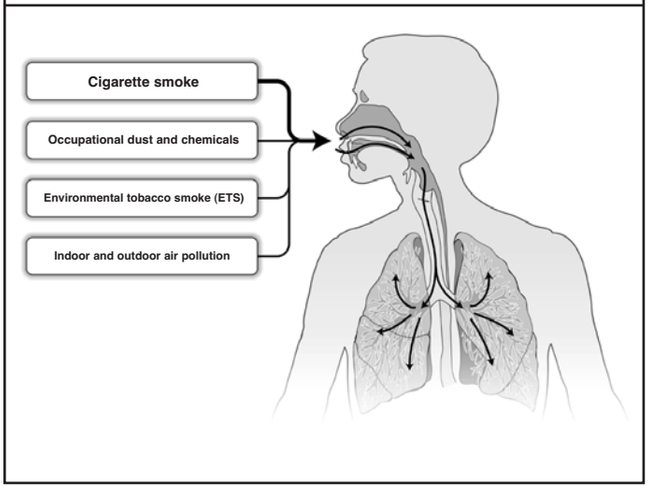
ECONOMIC AND SOCIAL BURDEN OF COPD

COPD is a costly disease. In developed countries, exacerbations of COPD account for the greatest burden on the health care system. In the European Union, the total *direct* costs of respiratory disease are estimated to be about 6% of the total health care budget, with COPD accounting for 56% (38.6 billion Euros) of this[23]. In the United States in 2002, the direct costs of COPD were $18 billion and the indirect costs totaled $14.1 billion[1]. Costs per patient will vary across countries since these costs depend on how health care is provided and paid[24]. Not surprisingly, there is a striking direct relationship between the severity of COPD and the cost of care[25], and the distribution of costs changes as the disease progresses.

RISK FACTORS

Identification of cigarette smoking as the most commonly encountered risk factor for COPD has led to the incorporation of smoking cessation programs as a key element of COPD prevention, as well as an important intervention for patients who already have the disease. However, although smoking is the best-studied COPD risk factor, it is not the only one and there is consistent evidence from epidemiologic studies that nonsmokers may develop chronic airflow obstruction[26,27] (**Figure 3**).

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



Genes: As the understanding of the importance of risk factors for COPD has grown, so has the recognition that essentially all risk for COPD results from a gene-environment interaction. The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin[28], a major circulating inhibitor of serine proteases. This rare recessive trait is most commonly seen in individuals of Northern European origin[29]. Genetic association studies have implicated a variety of genes in COPD pathogenesis. However, the results of these genetic association studies have been largely inconsistent, and functional genetic variants influencing the development of COPD (other than alpha-1 antitrypsin deficiency) have not been definitively identified[30].

Inhalational Exposures

Tobacco Smoke: Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV_1, and a greater COPD mortality rate than nonsmokers. Pipe and cigar smokers have greater COPD morbidity

and mortality rates than nonsmokers, although their rates are lower than those for cigarette smokers[31]. Other types of tobacco smoking popular in various countries are also risk factors for COPD[32,33]. Not all smokers develop clinically significant COPD, which suggests that genetic factors must modify each individual's risk[34]. Passive exposure to cigarette smoke may also contribute to respiratory symptoms[35] and COPD[36] by increasing the lungs' total burden of inhaled particles and gases[37,38]. 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[39,40].

Occupational Dusts and Chemicals: Occupational exposures include organic and inorganic dusts and chemical agents and fumes. A statement published by the American Thoracic Society concluded that occupational exposures account for 10-20% of either symptoms or functional impairment consistent with COPD[41].

Indoor and Outdoor Air Pollution: The evidence that indoor pollution from biomass cooking and heating in poorly ventilated dwellings is an important risk factor for COPD (especially among women in developing countries) continues to grow[42-48], with case-control studies[47,48] and other robustly designed studies now available. High levels of urban air pollution are harmful to individuals with existing heart or lung disease but the role of outdoor air pollution in causing COPD is unclear.

Gender: Studies from developed countries[1,49] show that the prevalence of the disease is now almost equal in men and women, probably reflecting the changing patterns of tobacco smoking. Some studies have suggested that women are more susceptible to the effects of tobacco smoke than men[50-52].

Infection: A history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood[53-55]. However, susceptibility to viral infections may be related to another factor, such as birth weight, that itself is related to COPD.

Socioeconomic Status: There is evidence that the risk of developing COPD is inversely related to socioeconomic status[56]. 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[57,58].

3. THE FOUR COMPONENTS OF COPD MANAGEMENT

INTRODUCTION

An effective COPD management plan includes four components: (1) Assess and Monitor Disease; (2) Reduce Risk Factors; (3) Manage Stable COPD; and (4) Manage Exacerbations. While disease prevention is the ultimate goal, once COPD has been diagnosed, effective management should be aimed at the following goals:

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

These goals should be reached with minimal side effects from treatment, a particular challenge in COPD patients because they commonly have comorbidities. The extent to which these goals can be realized varies with each individual, and some treatments will produce benefits in more than one area. In selecting a treatment plan, the benefits and risks to the individual, and the costs, direct and indirect, to the individual, his or her family, and the community must be considered.

Patients should be identified as early in the course of the disease as possible, and certainly before the end stage of the illness when disability is substantial. Access to spirometry is key to the diagnosis of COPD and should be available to health care workers who care for COPD patients. However, the benefits of community-based spirometric screening, of either the general population or smokers, are still unclear. Educating patients, physicians, and the public to recognize that cough, sputum production, and especially breathlessness are not trivial symptoms is an essential aspect of the public health care of this disease.

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

COMPONENT 1: ASSESS AND MONITOR DISEASE

KEY POINTS

- A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease. The diagnosis should be confirmed by spirometry.
- For the diagnosis and assessment of COPD, spirometry is the gold standard as it is the most reproducible, standardized, and objective way of measuring airflow limitation. A post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of airflow limitation that is not fully reversible.
- Health care workers involved in the diagnosis and management of COPD patients should have access to spirometry.
- Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality, and the presence of complications.
- Measurement of arterial blood gas tensions should be considered in all patients with $FEV_1 < 50\%$ predicted or clinical signs suggestive of respiratory failure or right heart failure.
- COPD is usually a progressive disease and lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy and to identify any complications that may develop.
- Comorbidities are common in COPD and should be actively identified. Comorbidities often complicate the management of COPD, and vice versa.

INITIAL DIAGNOSIS

A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease (**Figure 4**). The diagnosis should be confirmed by spirometry.

Assessment of Symptoms: 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. As lung function deteriorates, breathlessness becomes more intrusive. Chronic cough, often the first symptom of COPD to develop[59], may be intermittent, but later is present every day, often throughout the day. In some cases, significant airflow limitation may develop without the presence of a cough. COPD patients commonly raise small quantities of tenacious sputum after coughing bouts. Wheezing and chest tightness are nonspecific symptoms that may vary between days, and over the course of a single day. An absence of wheezing or chest tightness does not exclude a diagnosis of COPD. Weight loss, anorexia and psychiatric morbidity, especially symptoms of depression and/or anxiety are common problems in advanced COPD[60,61].

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

- Exposure to risk factors
- Past medical history, including asthma, allergy, sinusitis, or nasal polyps; respiratory infections in childhood; other respiratory diseases
- Family history of COPD or other chronic respiratory disease
- Pattern of symptom development

Figure 4. Key Indicators for Considering a Diagnosis of COPD

Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is needed to establish a diagnosis of COPD.

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

- History of exacerbations or previous hospitalizations for respiratory disorder
- Presence of comorbidities such as heart disease, malignancies, osteoporosis, and muscloskeletal disorders, which may also contribute to restriction of activity[62]
- Appropriateness of current medical treatments
- Impact of disease on patient's life, including limitation of activity, missed work and economic impact, effect on family routines, 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[63,64], and their detection has a relatively low sensitivity and specificity.

Measurement of Airflow Limitation (Spirometry): Spirometry should be undertaken in all patients who may have COPD. Spirometry should measure the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC) and the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second, FEV_1), and the ratio of these two measurements (FEV_1/FVC) should be calculated. Spirometry measurements are evaluated by comparison with reference values[65] based on age, height, sex, and race (use appropriate reference values, e.g., see reference 65). Patients with COPD typically show a decrease in both FEV_1 and FVC. The presence of airflow limitation is defined by a postbronchodilator $FEV_1/FVC < 0.70$. This approach is a pragmatic one in view of the fact that universally applicable reference values for FEV_1 and FVC are not available. Where possible, values should be compared to age-related normal values to avoid over-diagnosis of COPD in the elderly[66]. Using the fixed ratio (FEV_1/FVC) is particularly problematic in milder patients who are elderly as the normal process of aging affects lung volumes.

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

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

Bronchodilator reversibility testing: Despite earlier hopes, neither bronchodilator nor oral glucocorticosteroid reversibility testing predicts disease progression, whether judged by decline in FEV_1, deterioration of health status, or frequency of exacerbations[67,68] in patients with a clinical diagnosis of COPD and abnormal spirometry[68]. In some cases (e.g., a patient with an atypical history such as asthma in childhood and regular night waking with cough or wheeze) a clinician may wish to perform a bronchodilator and/or glucocorticosteroid reversibility test.

Chest X-ray. An abnormal chest X-ray is seldom diagnostic in COPD unless obvious bullous disease is present, but it is valuable in excluding alternative diagnoses and establishing the presence of significant comorbidities such as cardiac failure. Computed tomography (CT) of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD, high resolution CT (HRCT) scanning might help in the differential diagnosis. In addition, if a surgical procedure such as lung volume reduction is contemplated, a chest CT scan is necessary since the distribution of emphysema is one of the most important determinants of surgical suitability[69].

Arterial blood gas measurement. In advanced COPD, measurement of arterial blood gases while the patient is breathing air is important. This test should be performed in stable patients with $FEV_1 < 50\%$ predicted or with clinical signs suggestive of respiratory failure or right heart failure.

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

Differential Diagnosis: In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques, and it is assumed that asthma and COPD coexist in these patients. In these cases, current management is similar to that of asthma. Other potential diagnoses are usually easier to distinguish from COPD (**Figure 5**).

Figure 5. Differential Diagnosis of COPD

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

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

ONGOING MONITORING AND ASSESSMENT

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.

Follow-up visits should include a physical examination and discussion of symptoms, particularly any new or worsening symptoms. Spirometry should be performed if there is a substantial increase in symptoms or a complication. The development of respiratory failure is indicated by a PaO_2 < 8.0 kPa (60 mm Hg) with or without $PaCO_2$ > 6.7 kPa (50 mm Hg) in arterial blood gas measurements made while breathing air at sea level. Measurement of pulmonary arterial pressure is not recommended in clinical practice as it does not add practical information beyond that obtained from a knowledge of PaO_2.

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

Monitor Exacerbation History: Frequency, severity, likely causes of exacerbations and psychological well-being[268] should be evaluated. Increased sputum volume, acutely worsening dyspnea, and the presence of purulent sputum should be noted. Severity can be estimated by the increased need for bronchodilator medication or glucocorticosteroids and by the need for antibiotic treatment. Hospitalizations should be documented, including the facility, duration of stay, and any use of critical care or intubation.

Monitor Comorbidities: Comorbidities are common in COPD and may become harder to manage when COPD is present, either because COPD adds to the total level of disability or because COPD therapy adversely affects the comorbid disorder. Until more integrated guidance about disease management for specific comorbid problems becomes available, the focus should be on identification and management of these individual problems in line with local treatment guidance.

COMPONENT 2: REDUCE RISK FACTORS

KEY POINTS

- Reduction of total personal exposure to tobacco smoke, occupational dusts and chemicals, and indoor and outdoor air pollutants are important goals to prevent the onset and progression of COPD.
- Smoking cessation is the single most effective—and cost effective—intervention in most people to reduce the risk of developing COPD and stop its progression (**Evidence A**).
- Comprehensive tobacco control policies and programs with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel.
- Efforts to reduce smoking through public health initiatives should also focus on passive smoking to minimize risks for nonsmokers.
- Many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases.
- Reducing the risk from indoor and outdoor air pollution is feasible and requires a combination of public policy and protective steps taken by individual patients.

SMOKING PREVENTION AND CESSATION

Comprehensive tobacco control policies and programs with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel, including health care providers, community activities, schools, and radio, television, and print media. Legislation to establish smoke-free schools, public facilities, and work environments should be developed and implemented by government officials and public health workers, and encouraged by the public.

Smoking Cessation Intervention Process: Smoking cessation is the single most effective—and cost effective—way to reduce exposure to COPD risk factors. 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. Even a brief (3-minute) period of counseling to urge a smoker to quit results in smoking cessation rates of 5-10%[70]. At the very least, this should be done for every smoker at every health care provider visit[70,71].

Guidelines for smoking cessation entitled *Treating Tobacco Use and Dependence: A Clinical Practice Guideline* were published by the US Public Health Service[72] and recommend a five-step program for intervention (**Figure 6**), which provides a strategic framework helpful to health care providers interested in helping their patients stop smoking[72-75].

Figure 6. Brief Strategies to Help the Patient Willing to Quit[72-75]

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

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

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

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

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

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

Pharmacotherapy: Numerous effective pharmacotherapies for smoking cessation now exist[72,73,76] (**Evidence A**), and pharmacotherapy is recommended when counseling is not sufficient to help patients quit smoking. Numerous studies indicate that nicotine replacement therapy in any form (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge) reliably increases long-term smoking abstinence rates[72,77,269]. The antidepressants bupropion[78] and nortriptyline have also been shown to increase long-term quit rates[76,77,79], but should always be used as one element in a supportive intervention program rather than on their own. The effectiveness of the antihypertensive drug clonidine is limited by side effects[77]. Varenicline, a nicotinic acetylcholine receptor partial agonist that aids smoking cessation by relieving nicotine withdrawal symptoms and reducing the rewarding

properties of nicotine, has been demonstrated to be safe and efficacious[80-82]. Special consideration should be given before using pharmacotherapy in selected populations: people with medical contraindications, light smokers (fewer than 10 cigarettes/day), and pregnant and adolescent smokers.

OCCUPATIONAL EXPOSURES

Although it is not known how many individuals are at risk of developing respiratory disease from occupational exposures in either developing or developed countries, many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases[83-85]. 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.

INDOOR AND OUTDOOR AIR POLLUTION

Individuals experience diverse indoor and outdoor environments throughout the day, each of which has its own unique set of air contaminants and particulates that cause adverse effects on lung function[86]. Although outdoor and indoor air pollution are generally considered separately, the concept of total personal exposure may be more relevant for COPD. Reducing the risk from indoor and outdoor air pollution is feasible and requires a combination of public policy and protective steps taken by individual patients. At the national level, achieving a set level of air quality standards should be a high priority; this goal will normally require legislative action. Reduction of exposure to smoke from biomass fuel, particularly among women and children, is a crucial goal to reduce the prevalence of COPD worldwide. Although efficient non-polluting cooking stoves have been developed, their adoption has been slow due to social customs and cost.

The health care provider should consider COPD risk factors including smoking history, family history, exposure to indoor/outdoor pollution) and socioeconomic status for each individual patient. Those who are at high risk should avoid vigorous exercise outdoors during pollution episodes. Persons with advanced COPD should monitor public announcements of air quality and be aware that staying indoors when air quality is poor may help reduce their symptoms. If various solid fuels are used for cooking and heating, adequate ventilation should be encouraged. Under most circumstances, vigorous attempts should be made to reduce exposure through reducing workplace emissions and improving ventilation measures, rather than simply by using respiratory protection to reduce the risks of ambient air pollution. Air cleaners have not been shown to have health benefits, whether directed at pollutants generated by indoor sources or at those brought in with outdoor air.

COMPONENT 3: MANAGE STABLE COPD

KEY POINTS

- The overall approach to managing stable COPD should be individualized to address symptoms and improve quality of life.
- For patients with COPD, health education plays an important role in smoking cessation (**Evidence A**) and can also play a role in improving skills, ability to cope with illness and health status.
- None of the existing medications for COPD have been shown to modify the long-term decline in lung function that is the hallmark of this disease (**Evidence A**). Therefore, pharmacotherapy for COPD is used to decrease symptoms and/or complications.
- Bronchodilator medications are central to the symptomatic management of COPD (**Evidence A**). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations.
- The principal bronchodilator treatments are β_2-agonists, anticholinergics, and methylxanthines used singly or in combination (**Evidence A**).
- Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators (**Evidence A**).
- The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic COPD patients with an $FEV_1 < 50\%$ predicted (*Stage III: Severe COPD* and *Stage IV: Very Severe COPD*) and repeated exacerbations (**Evidence A**).

- Chronic treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio (**Evidence A**).
- In COPD patients, influenza vaccines can reduce serious illness (**Evidence A**). Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older and for COPD patients younger than age 65 with an FEV_1 < 40% predicted (**Evidence B**).
- All COPD patients benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue (**Evidence A**).
- The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival (**Evidence A**).

INTRODUCTION

The overall approach to managing stable COPD should be characterized by an increase in treatment, depending on the severity of the disease and the clinical status of the patient. Management of COPD is based on an individualized assessment of disease severity and response to various therapies. The classification of severity of stable COPD incorporates an individualized assessment of disease severity and therapeutic response into the management strategy. The severity of airflow limitation provides a general guide to the use of some treatments, but the selection of therapy is predominantly determined by the patient's symptoms and clinical presentation. Treatment also depends on the patient's educational level and willingness to apply the recommended management, on cultural and local conditions, and on the availability of medications.

EDUCATION

Although patient education is generally regarded as an essential component of care for any chronic disease, 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. Patient education alone does not improve exercise performance or lung function[87-90] (**Evidence B**), but it can play a role in improving skills, ability to cope with illness, and health status[91]. Patient education regarding smoking cessation has the greatest capacity to influence the natural history of COPD (**Evidence A**). Education also improves patient response to exacerbations[92,93] (**Evidence B**). Prospective end-of-life discussions can lead to understanding of advance directives and effective therapeutic decisions at the end of life[94] (**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. 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. 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.

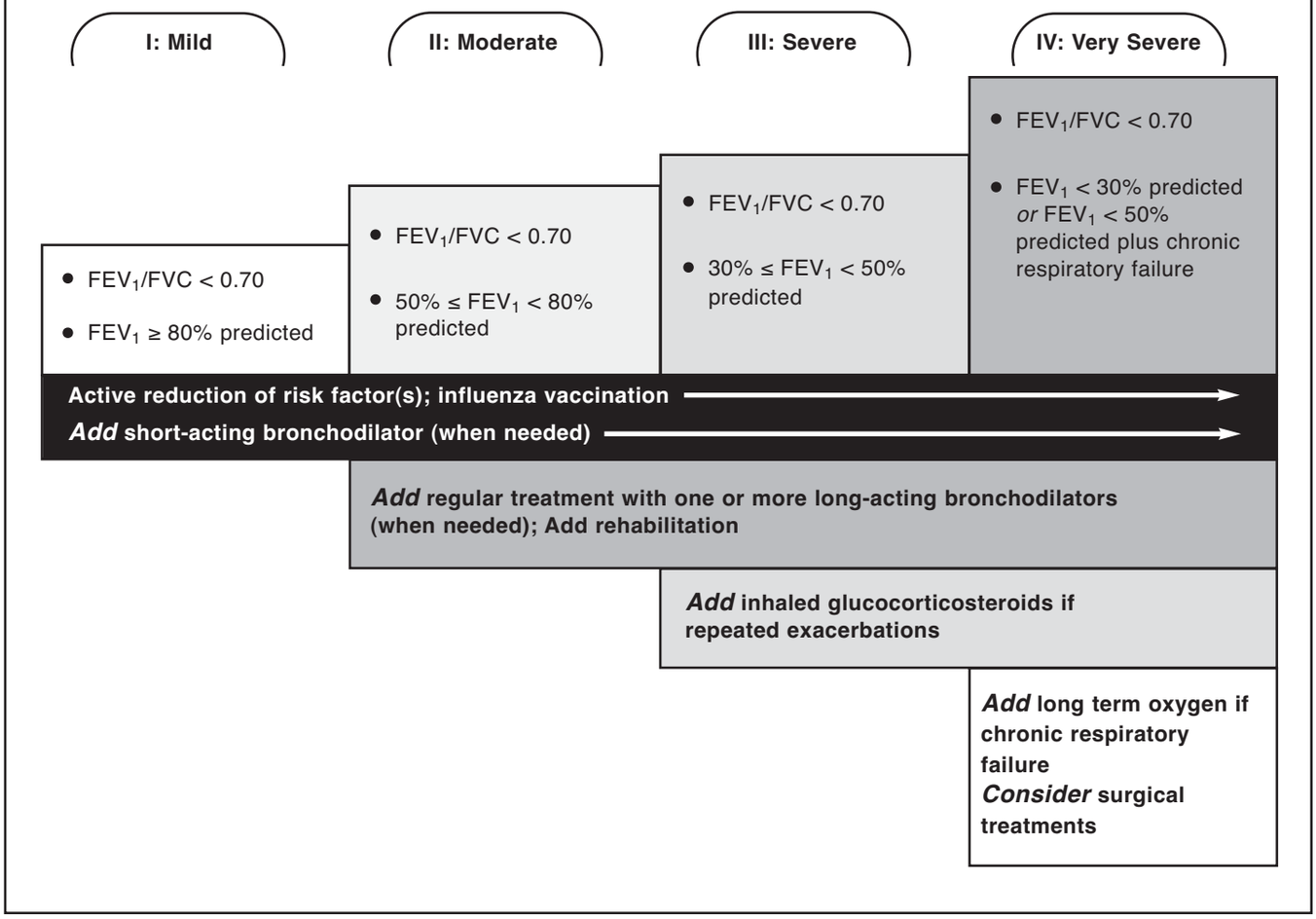
PHARMACOLOGIC TREATMENTS

Pharmacologic therapy is used to prevent and control symptoms (**Figure 7**), reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. None of the existing medications (**Figure 8**) for COPD have been shown to modify the long-term decline in lung function that is the hallmark of this disease[51,95-97] (**Evidence A**). However, this should not preclude efforts to use medications to control symptoms.

Bronchodilators: Bronchodilator medications are central to the symptomatic management of COPD[98-101] (**Evidence A**) (**Figure 9**). They are given either on an as-needed basis for relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms. 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. When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential.

Figure 7. Therapy at Each Stage of COPD

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



Bronchodilator drugs commonly used in treating COPD include β_2-agonists, anticholinergics, and methylxanthines. The choice depends on the availability of the medications and the patient's response. All categories of bronchodilators have been shown to increase exercise capacity in COPD, without necessarily producing significant changes in FEV_1[102-105] (**Evidence A**).

Low dose theophylline reduces exacerbations in patients with COPD but does not increase post-bronchodilator lung function[270] (**Evidence B**). Higher doses of theophylline are effective bronchodilators in COPD but, due to the potential for toxicity, inhaled bronchodilators are preferred.

All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations.

Although monotherapy with long-acting β_2-agonists appears to be safe[271,272], combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects. For example, a combination of a short-acting β_2-agonist and an anticholinergic produces greater and more sustained improvements in FEV_1 than either drug alone and does not produce evidence of tachyphylaxis over 90 days of treatment[112-114] (**Evidence A**).

The combination of a β_2-agonist, an anticholinergic, and/or theophylline may produce additional improvements in lung function[112-118] and health status[112,119]. Increasing the number of drugs usually increases costs, and an equivalent benefit may occur by increasing the dose of one bronchodilator when side effects are not a limiting

Figure 8. Commonly Used Formulations of Drugs used in COPD

Medication	Inhaler (μg)	Solution for Nebulizer (mg/ml)	Oral	Vials for Injection (mg)	Duration of Action (hours)
β_2-agonists					
Short-acting					
Fenoterol	100-200 (MDI)	1	0.5% (Syrup)		4-6
Levalbuterol		0.63, 1.25			4-6
Salbutamol (albuterol)	100, 200 (MDI & DPI)	5	5mg (Pill) 0.24% (Syrup)	0.1, 0.5	4-6
Terbutaline	400, 500 (DPI)	–		0.2, 0.25	4-6
Long-acting					
Formoterol	4.5–12 (MDI & DPI)				12+
Salmeterol	25-50 (MDI & DPI)				12+
Anticholinergics					
Short-acting					
Ipratropium bromide	20, 40 (MDI)	0.25-0.5			6-8
Oxitropium bromide	100 (MDI)	1.5			7-9
Long-acting					
Tiotropium	18 (DPI)				24+
Combination short-acting β_2-agonists plus anticholinergic in one inhaler					
Fenoterol/Ipratropium	200/80 (MDI)	1.25/0.5			6-8
Salbutamol/Ipratropium	75/15 (MDI)	0.75/4.5			6-8
Methylxanthines					
Aminophylline			200-600 mg (Pill)	240	Variable, up to 24
Theophylline (SR)			100-600 mg (Pill)		Variable, up to 24
Inhaled glucocorticosteroids					
Beclomethasone	50-400 (MDI & DPI)	0.2-0.4			
Budesonide	100, 200, 400 (DPI)	0.20, 0.25, 0.5			
Fluticasone	50-500 (MDI & DPI)				
Triamcinolone	100 (MDI)	40		40	
Combination long-acting β_2-agonists plus glucocorticosteroids in one inhaler					
Formoterol/Budesonide	4.5/160, 9/320 (DPI)				
Salmeterol/Fluticasone	50/100, 250, 500 (DPI) 25/50, 125, 250 (MDI)				
Systemic glucocorticosteroids					
Prednisone			5-60 mg (Pill)		
Methyl-prednisolone			4, 8, 16 mg (Pill)		

factor. Detailed assessments of this approach have not been carried out.

Dose-response relationships using the FEV_1 as the outcome are relatively flat with all classes of broncho-dilators[98-101]. Toxicity is also dose related. Increasing the dose of either a β_2-agonist or an anticholinergic by an order of magnitude, especially when given by a wet nebulizer, appears to provide subjective benefit in acute episodes[120] (**Evidence B**) but is not necessarily helpful in stable disease[121] (**Evidence C**).

When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential. The choice of inhaler device will depend on availability, cost, the prescribing physician, and the skills

and ability of the patient. COPD patients may have more problems in effective coordination and find it harder to use a simple metered-dose inhaler (MDI) than do healthy volunteers or younger asthmatics. It is essential to ensure that inhaler technique is correct and to re-check this at each visit.

Figure 9. Bronchodilators in Stable COPD

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

Regular treatment with inhaled glucocorticosteroids does not modify the long-term decline of FEV_1 in patients with COPD[95-97,122]. However, regular treatment with inhaled glucocorticosteriods has been shown to reduce the frequency of exacerbations and thus improve health status[140] for symptomatic COPD patients with an FEV_1 < 50% predicted (*Stage III: Severe COPD* and *Stage IV: Very Severe COPD*) and repeated exacerbations (for example, 3 in the last 3 years)[122-128] (**Evidence A**) and withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients[128]. Treatment with inhaled glucocorticosteriods increases the likelihood of pneumonia and does not reduce overall mortality[271].

An inhaled glucocorticosteroid combined with a long-acting β_2-agonist is more effective than the individual components in reducing exacerbations and improving lung function and health status[123,125,126,130,131,271,272] (**Evidence A**). Combination therapy increases the likelihood of pneumonia and a large prospective clinical trial failed to demonstrate statistically significant effects on mortality[271].

Long-term treatment with oral glucocorticosteroids is not recommended in COPD (**Evidence A**). A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy[132-134], which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced COPD.

Other Pharmacologic Treatments

Vaccines. Influenza vaccines can reduce serious illness[135] and death in COPD patients by about 50%[136,137] (**Evidence A**). Vaccines containing killed or live, inactivated viruses are recommended[138] as they are more effective in elderly patients with COPD[139]. The strains are adjusted each year for appropriate effectiveness and should be given once each year[140]. Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older[141,142]. In addition, this vaccine has been shown to reduce the incidence of community-acquired pneumonia in COPD patients younger than age 65 with an FEV_1 < 40% predicted[143] (**Evidence B**).

Alpha-1 antitrypsin augmentation therapy. Young patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy. However, this therapy is very expensive, is not available in most countries, and is not recommended for patients with COPD that is unrelated to alpha-1 antitrypsin deficiency (**Evidence C**).

Antibiotics. Prophylactic, continuous use of antibiotics, has been shown to have no effect on the frequency of exacerbations in COPD[144-146] and a study that examined the efficacy of winter chemoprophylaxis chemoprophylaxis undertaken in winter monthsover a period of 5 years concluded that there was no benefit[147]. There is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful[148,149] (**Evidence A**).

Mucolytic (mucokinetic, mucoregulator) agents (ambroxol, erdosteine, carbocysteine, iodinated glycerol). The regular use of mucolytics in COPD has been evaluated in a number of long-term studies with controversial results[150-152]. Although a few patients with viscous sputum may benefit from mucolytics[153,154], the overall benefits seem to be very small, and the widespread use of these agents cannot be recommended at present (**Evidence D**).

Antioxidant agents. Antioxidants, in particular N-acetyl-cysteine, have been reported in small studies to reduce the frequency of exacerbations, leading to speculation that these medications could have a role in the treatment of patients with recurrent exacerbations[155-158] (**Evidence B**). However, a large randomized controlled trial found no effect of N-acetylcysteine on the frequency of exacerbations, except in patients not treated with inhaled glucocorticosteroids[159].

Immunoregulators (immunostimulators, immunomodulators). Studies using an immunoregulator in COPD show a decrease in the severity and frequency of exacerbations[160,161]. However, additional studies to examine the long-term effects of this therapy are required before its regular use can be recommended[162].

Antitussives. Cough, although sometimes a troublesome symptom in COPD, has a significant protective role[163]. Thus the regular use of antitussives is not recommended in stable COPD (**Evidence D**).

Vasodilators. In patients with COPD, inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-perfusion balance[164,165]. Therefore, based on the available evidence, nitric oxide is contraindicated in stable COPD.

Narcotics (morphine). Oral and parenteral opioids are effective for treating dyspnea in COPD patients with advanced disease. There are insufficient data to conclude whether nebulized opioids are effective[166]. However, some clinical studies suggest that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects[167-171].

Others. Nedocromil and leukotriene modifiers have not been adequately tested in COPD patients and cannot be recommended. There was no evidence of benefit - and some evidence of harm (malignancy and pneumonia) - from an anti-TNF-alpha antibody (infliximab) tested in moderate to severe COPD[273]. There is no evidence of the effectiveness of herbal medicines for treating COPD[274] and other alternative healing methods (e.g., acupuncture and homeopathy) have not been adequately tested.

NON-PHARMACOLOGIC TREATMENTS

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.
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[172] (**Evidence A**). Data suggest that these benefits can be sustained even after a single pulmonary rehabilitation program[173-175]. 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. Benefits have been reported from rehabilitation programs conducted in inpatient, outpatient, and home settings[176-178].

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

Oxygen Therapy: The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival[179,180]. It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state[181].

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

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

or

- PaO_2 between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg), or SaO_2 of 88%, if there is evidence

of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%) (**Evidence D**).

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. 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.

Ventilatory Support: Although long-term NIPPV cannot be recommended for the routine treatment of patients with chronic respiratory failure due to COPD, the combination of NIPPV with long-term oxygen therapy may be of some use in a selected subset of patients, particularly in those with pronounced daytime hypercapnia[182].

Surgical Treatments

Bullectomy. In carefully selected patients, this procedure is effective in reducing dyspnea and improving lung function[183] (**Evidence C**). 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.

Lung volume reduction surgery (LVRS). A large multicenter study of 1,200 patients comparing LVRS with medical treatment has shown that after 4.3 years, patients with upper-lobe emphysema and low exercise capacity who received the surgery had a greater survival rate than similar patients who received medical therapy (54% vs. 39.7%)[184]. In addition, the surgery patients experienced greater improvements in their maximal work capacity and their health-related quality of life. The advantage of surgery over medical therapy was less significant among patients who had other emphysema distribution or high exercise capacity prior to treatment. Although the results of this study showed some very positive results of surgery in a select group of patients[69,184], LVRS is an expensive palliative surgical procedure and can be recommended only in carefully selected patients.

Lung transplantation. In appropriately selected patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity[185-188] (**Evidence C**). 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[189,190].

SPECIAL CONSIDERATIONS

Surgery in COPD: Postoperative pulmonary complications are as important and common as postoperative cardiac complications and, consequently, are a key component of the increased risk posed by surgery in COPD patients. The principal potential factors contributing to the risk include smoking, poor general health status, age, obesity, and COPD severity. A comprehensive definition of postoperative pulmonary complications should include only major pulmonary respiratory complications, namely lung infections, atelectasis and/or increased airflow obstruction, all potentially resulting in acute respiratory failure and aggravation of underlying COPD[191-196].

COMPONENT 4: MANAGE EXACERBATIONS

KEY POINTS

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

INTRODUCTION

COPD is often associated with exacerbations of symptoms[197-201]. An exacerbation of COPD is defined as *an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD*[202,203]. Exacerbations are categorized in terms of either clinical presentation (number of symptoms[199]) and/or health-care resources utilization[202]. The impact of exacerbations is significant and a patient's symptoms and lung function may both take several weeks to recover to the baseline values[204].

The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution[205], but the cause of about one-third of severe exacerbations cannot be identified. The role of bacterial infections is controversial, but recent investigations have shown that at least 50% of patients have bacteria in high concentrations in their lower airways during exacerbations[206-208]. Development of specific immune responses to the infecting bacterial strains, and the association of neutrophilic inflammation with bacterial exacerbations, also support the bacterial causation of a proportion of exacerbations[209-212].

DIAGNOSIS AND ASSESSMENT OF SEVERITY

Medical History: Increased breathlessness, the main symptom of an exacerbation, is often accompanied by wheezing and chest tightness, increased cough and sputum, change of the color and/or tenacity of sputum, and fever. Exacerbations may also be accompanied by a number of nonspecific complaints, such as tachycardia and tachypnea, malaise, insomnia, sleepiness, fatigue, depression, and confusion. A decrease in exercise tolerance, fever, and/or new radiological anomalies suggestive of pulmonary disease may herald a COPD exacerbation. An increase in sputum volume and purulence points to a bacterial cause, as does prior history of chronic sputum production[199,212].

Assessment of Severity: Assessment of the severity of an exacerbation is based on the patient's medical history before the exacerbation, preexisting comorbidities, symptoms, physical examination, arterial blood gas measurements, and other laboratory tests. Specific information is required on the frequency and severity of attacks of breathlessness and cough, sputum volume and color, and limitation of daily activities. When available, prior arterial blood gas measurements are extremely useful for comparison with those made during the acute episode, as an acute change in these tests is more important than their absolute values. Thus, where possible, physicians should instruct their patients to bring the summary of their last evaluation when they come to the hospital with an exacerbation. In patients with *Stage IV: Very Severe COPD*, the most important sign of a severe exacerbation is a change in the mental status of the patient and this signals a need for immediate evaluation in the hospital.

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

Pulse oximetry and arterial blood gas measurement. Pulse oximetry can be used to evaluate a patient's oxygen saturation and need for supplemental oxygen therapy. For patients that require hospitalization, measurement of arterial blood gases is important to assess the severity of an exacerbation. A PaO_2 < 8.0 kPa (60 mm Hg) and/or SaO_2 < 90% with or without $PaCO_2$ > 6.7 kPa (50 mm Hg) when breathing room air indicate respiratory failure. In addition, moderate-to-severe acidosis (pH < 7.36) plus hypercapnia ($PaCO_2$ > 6-8 kPa, 45-60 mm Hg) in a patient with respiratory failure is an indication for mechanical ventilation[196,213].

Chest X-ray and ECG. Chest radiographs (posterior/anterior plus lateral) are useful in identifying alternative diagnoses that can mimic the symptoms of an exacerbation. An ECG aids in the diagnosis of right heart hypertrophy, arrhythmias, and ischemic episodes. Pulmonary embolism can be very difficult to distinguish from an exacerbation, especially in advanced COPD, because right ventricular hypertrophy and large pulmonary arteries lead to confusing ECG and radiographic results. A low systolic blood pressure and an inability to increase the PaO_2 above 8.0 kPa (60 mm Hg) despite high-flow oxygen also suggest pulmonary embolism. If there are strong indications that pulmonary embolism has occurred, it is best to treat for this along with the exacerbation.

Other laboratory tests. The whole blood count may identify polycythemia (hematocrit > 55%) or bleeding. White blood cell counts are usually not very informative. The presence of purulent sputum during an exacerbation of symptoms is sufficient indication for starting empirical antibiotic treatment[33]. *Streptococcus pneumoniae, Hemophilus influenzae,* and *Moraxella catarrhalis* are the most common bacterial pathogens involved in COPD exacerbations. If an infectious exacerbation does not respond to the initial antibiotic treatment, a sputum culture and an antibiogram should be performed. Biochemical test abnormalities can be associated with an exacerbation and include electrolyte disturbance(s) (e.g., hyponatremia, hypokalemia), poor glucose control, metabolic acid-base disorder. These abnormalities can also be due to associated co-morbid conditions.

Differential Diagnoses: Patients with apparent exacerbations of COPD that do not respond to treatment[204,214] should be re-evaluated for other medical conditions that can aggravate symptoms or mimic COPD exacerbations[153], including pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, and cardiac arrhythmia. Non-compliance with the prescribed medication regimen can also cause increased symptoms that may be confused with a true exacerbation. Elevated serum levels of brain-type natriuretic peptide, in conjunction with other clinical information, identifies patients with acute dyspnea secondary to congestive heart failure and enables them to be distinguished from patients with COPD exacerbations[215,216].

HOME MANAGEMENT

There is increasing interest in home care for end-stage COPD patients, although the exact criteria for this approach as opposed to hospital treatment remain uncertain and will vary by health care setting[217-220].

Bronchodilator Therapy: Home management of COPD exacerbations involves increasing the dose and/or frequency of existing short-acting bronchodilator therapy, preferably with a β_2-agonist (**Evidence A**). If not already used, an anticholinergic can be added until the symptoms improve.

Glucocorticosteroids: Systemic glucocorticosteroids are beneficial in the management of exacerbations of COPD. They shorten recovery time, improve lung function (FEV_1) and hypoxemia (PaO_2)[221-224] (**Evidence A**), and may reduce the risk of early relapse, treatment failure, and length of hospital stay[225]. They should be considered in addition to bronchodilators if the patient's baseline FEV_1 is < 50% predicted. A dose of 30-40 mg prednisolone per day for 7-10 days is recommended[221,222,226].

Antibiotics: The use of antibiotics in the management of COPD exacerbations is discussed below in the hospital management section.

HOSPITAL MANAGEMENT

The risk of dying from an exacerbation of COPD is closely related to the development of respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support[227]. 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[228], 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[229]. Savings on inpatient expenditures[230] offset the additional costs of

maintaining a community-based COPD nursing team. However, detailed cost-benefit analyses of these approaches are awaited.

A range of criteria to consider for hospital assessment/admission for exacerbations of COPD are shown in **Figure 10**. Some patients need immediate admission to an intensive care unit (ICU) (**Figure 11**). 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.

The first actions when a patient reaches the emergency department are to provide supplemental oxygen therapy and to determine whether the exacerbation is life threatening. If so, the patient should be admitted to the ICU immediately. Otherwise, the patient may be managed in the emergency department or hospital (**Figure 12**).

Figure 10. Indications for Hospital Assessment or Admission for Exacerbations of COPD*

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

**Local resources need to be considered.*

Figure 11. Indications for ICU Admission of Patients with Exacerbations of COPD*

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

**Local resources need to be considered.*

Figure 12. Management of Severe but Not Life-Threatening Exacerbations of COPD in the Emergency Department or the Hospital[226]*

- Assess severity of symptoms, blood gases, chest X-ray
- Administer controlled oxygen therapy and repeat arterial blood gas measurement after 30-60 minutes
- Bronchodilators:
  - Increase doses and/or frequency
  - Combine β_2-agonists and anticholinergics
    - Use spacers or air-driven nebulizers
    - Consider adding intravenous mehylxanthines, if needed
- Add oral or intravenous glucocorticosteroids
- Consider antibiotics (oral or occasionally intravenous) when signs of bacterial infection
- Consider noninvasive mechanical ventilation
- At all times:
  - Monitor fluid balance and nutrition
  - Consider subcutaneous heparin
  - Identify and treat associated conditions (e.g., heart failure, arrhythmias)
  - Closely monitor condition of the patient

**Local resources need to be considered.*

Controlled oxygen therapy. Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Supplemental oxygen should be titrated to improve the patient's hypoxemia. Adequate levels of oxygenation (PaO_2 > 8.0 kPa, 60 mm Hg, or SaO_2 > 90%) are easy to achieve in uncomplicated exacerbations, but CO_2 retention can occur insidiously with little change in symptoms. Once oxygen is started, arterial blood gases should be checked 30-60 minutes later to ensure satisfactory oxygenation without CO_2 retention or acidosis. Venturi masks (high-flow devices) offer more accurate delivery of controlled oxygen than do nasal prongs but are less likely to be tolerated by the patient[196].

Bronchodilator therapy. Short-acting inhaled β_2-agonists are usually the preferred bronchodilators for treatment of exacerbations of COPD[153,196,231] (**Evidence A**). If a prompt response to these drugs does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the effectiveness of this combination is controversial. Despite its widespread clinical use, the role of methylxanthines in the treatment of exacerbations of COPD remains controversial. Methylxanthines (theophylline or aminohylline) is currently considered

second-line intravenous therapy, used when there is inadequate or insufficient response to short-acting bronchodilators[232-236] (**Evidence B**). Possible beneficial effects in terms of lung function and clinical endpoints are modest and inconsistent, whereas adverse effects are significantly increased[237,238]. There are no clinical studies that have evaluated the use of inhaled long-acting bronchodilators (either β_2-agonists or anticholinergics) with or without inhaled glucocorticosteroids during an acute exacerbation.

Glucocorticosteroids. Oral or intravenous glucocorticosteroids are recommended as an addition to other therapies in the hospital management of exacerbations of COPD[222,223] (**Evidence A**). The exact dose that should be recommended is not known, but high doses are associated with a significant risk of side effects. Thirty to 40 mg of oral prednisolone daily for 7-10 days is effective and safe (**Evidence C**). Prolonged treatment does not result in greater efficacy and increases the risk of side effects.

Antibiotics. Based on the current available evidence[196,62], antibiotics should be given to:

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

The infectious agents in COPD exacerbations can be viral or bacterial[140,239]. The predominant bacteria recovered from the lower airways of patients with COPD exacerbations are *H. influenzae, S. pneumoniae*, and *M. catarrhalis*[140,206,207,240]. So-called atypical pathogens, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*[240,241], have been identified in patients with COPD exacerbations, but because of diagnostic limitations the true prevalence of these organisms is not known.

Respiratory Stimulants. Respiratory stimulants are not recommended for acute respiratory failure[231]. Doxapram, a nonspecific but relatively safe respiratory stimulant available in some countries as an intravenous formulation, should be used only when noninvasive intermittent ventilation is not available or not recommended[242].

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

Noninvasive mechanical ventilation. Noninvasive intermittent ventilation (NIV) has been studied in several randomized controlled trials in acute respiratory failure, consistently providing positive results with success rates of 80-85%[182,243-245]. These studies provide evidence that NIV improves respiratory acidosis (increases pH, and decreases $PaCO_2$) , decreases respiratory rate, severity of breathlessness, and length of hospital stay (**Evidence A**). More importantly, mortality—or its surrogate, intubation rate—is reduced by this intervention[245-248]. However, NIV is not appropriate for all patients, as summarized in **Figure 13**[182].

Figure 13. Indications and Relative Contraindications for NIV[196,243,249,250]

Selection criteria

- Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Moderate to severe acidosis (pH ≤ 7.35) and/ or hypercapnia ($PaCO_2$ > 6.0 kPa, 45 mm Hg)[251]
- Respiratory frequency > 25 breaths per minute

Exclusion criteria (any may be present)

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

Invasive mechanical ventilation: The indications for initiating invasive mechanical ventilation during exacerbations of COPD are shown in **Figure 14**, including failure of an initial trial of NIV[252]. As experience is being gained with the generalized clinical use of NIV in COPD, several of the indications for invasive mechanical ventilation are being successfully treated with NIV.

The use of invasive ventilation in end-stage COPD patients is influenced by the likely reversibility of the precipitating event, the patient's wishes, and the availability of intensive care facilities. Major hazards include the risk of ventilator-acquired pneumonia (especially when

multi-resistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation. Contrary to some opinions, acute mortality among COPD patients with respiratory failure is lower than mortality among patients ventilated for non-COPD causes[253]. 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.

Figure 14. Indications for Invasive Mechanical Ventilation

- Unable to tolerate NIV or NIV failure (for exclusion criteria, see **Figure 13**)
- Severe dyspnea with use of accessory muscles and paradoxical abdominal motion.
- Respiratory frequency > 35 breaths per minute
- Life-threatening hypoxemia
- Severe acidosis (pH < 7.25) and/or hypercapnia ($PaCO_2$ > 8.0 kPa, 60 mm Hg)
- Respiratory arrest
- Somnolence, impaired mental status
- Cardiovascular complications (hypotension, shock)
- Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion)

Weaning or discontinuation from mechanical ventilation can be particularly difficult and hazardous in patients with COPD and the best method (pressure support or a T-piece trial) remains a matter of debate[254-256]. In COPD patients that failed extubation, noninvasive ventilation facilitates weaning and prevents reintubation, but does not reduce mortality[89,92].

Other measures. Further treatments that can be used in the hospital include: fluid administration (accurate monitoring of fluid balance is essential); nutrition (supplementary when needed); deep venous thrombosis prophylaxis (mechanical devices, heparins, etc.) in immobilized, polycythemic, or dehydrated patients with or without a history of thromboembolic disease; and sputum clearance (by stimulating coughing and low-volume forced expirations as in home management). Manual or mechanical chest percussion and postural drainage may be beneficial in patients producing > 25 ml sputum per day or with lobar atelectasis.

HOSPITAL DISCHARGE AND FOLLOW-UP

Insufficient clinical data exist to establish the optimal duration of hospitalization in individual patients developing an exacerbation of COPD[197,257,258] although units with more respiratory consultants and better quality organized care have lower mortality and reduced length of hospital stay following admission for acute COPD exacerbation[275]. Consensus and limited data support the discharge criteria listed in **Figure 15**. **Figure 16** 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[229]. Home visits by a community nurse may permit earlier discharge of patients hospitalized with an exacerbation of COPD, without increasing readmission rates[153,259-261]. Use of a written action plan in COPD increased appropriate therapeutic interventions for exacerbations of COPD, an effect that does not decrease health-care resource utilization[276] (**Evidence B**).

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

Figure 15. Discharge Criteria for Patients with Exacerbations of COPD

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

Figure 16. Items to Assess at Follow-Up Visit 4-6 Weeks After Discharge from Hospital for Exacerbations of COPD

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

Opportunities for prevention of future exacerbations should be reviewed before discharge, with particular attention to smoking cessation, current vaccination (influenza, pneumococcal vaccines), knowledge of current therapy including inhaler technique[32,262,263], and how to recognize symptoms of exacerbations. Pharmacotherapy known to reduce the number of exacerbations and hospitalizations and delay the time of first/next hospitalization, such as long-acting inhaled bronchodilators, inhaled glucocorticosteroids, and combination inhalers, should be specifically considered. Social problems should be discussed and principal caregivers identified if the patient has a significant persisting disability.

4. TRANSLATING GUIDELINE RECOMMENDATIONS TO THE CONTEXT OF (PRIMARY) CARE

KEY POINTS

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

The recommendations provided in Chapters 1 through 3 define—from a disease perspective—best practices in the diagnosis, monitoring, and treatment of COPD. However, (primary) medical care is based on an engagement with *patients*, and this engagement determines the success or failure of pursuing best practice. For this reason, medical practice requires a translation of disease-specific recommendations to the circumstances of individual patients—the local communities in which they live, and the health systems from which they receive medical care.

DIAGNOSIS

In pursuing early diagnosis, a policy of identifying patients at high risk of COPD, followed by watchful surveillance of these patients, is advised.

Respiratory Symptoms: Of the chronic symptoms characteristic of COPD (dyspnea, cough, sputum production), dyspnea is the symptom that interferes most with a patient's daily life and health status. When taking the medical history of the patient, it is therefore important to explore the impact of dyspnea and other symptoms on daily activities, work, and social activities, and provide treatment accordingly.

Spirometry: High-quality spirometry in primary care is possible[264,265], provided that good skills training and an ongoing quality assurance program are provided. An alternative is to ensure that high quality spirometry is available in the community, for example, within the primary care practice itself, in a primary care laboratory, or in a hospital setting, depending on the structure of the local health care system[266]. Ongoing collaboration between primary care and respiratory care also helps assure quality control.

COMORBIDITIES

Older patients frequently have multiple chronic health conditions and the severity of comorbid conditions and their impact on a patient's health status will vary between patients and in the same patient over time. Comorbidities for patients with COPD may include other smoking-related diseases such as ischemic heart disease and lung cancer; conditions that arise as a complication of a specific pre-existing disease such as pulmonary hypertension and consequent heart failure; coexisting chronic conditions with unrelated pathogenesis related to aging, such as bowel or prostate cancer, depression, diabetes mellitus, Parkinson's disease, dementia, and arthritis; or acute illnesses that may have a more severe impact in patients with a given chronic disease. For example, upper respiratory tract infections are the most frequent health problem in all age groups, but they may have a more severe impact or require different treatment in patients with COPD.

REDUCING EXPOSURE TO RISK FACTORS

Reduction of total personal exposure to tobacco smoke, occupational dusts and chemicals, and indoor and outdoor air pollutants, including smoke from cooking over biomass fueled fires, are important goals to prevent the onset and progression of COPD. In many health care systems, primary care practitioners may be actively

involved in public health campaigns and can play an important part in bringing messages about reducing exposure to risk factors to patients and the public. Primary care practitioners can also play a very important role in reinforcing the dangers of passive smoking and the importance of implementing smoke-free work environments.

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

IMPLEMENTATION OF COPD GUIDELINES

GOLD National Leaders play an essential role in the dissemination of information about prevention, early diagnosis, and management of COPD in health systems around the world. A major GOLD program activity that has helped to bring together health care teams at the local level is World COPD Day, held annually on the third Wednesday in November*. GOLD National Leaders, often in concert with local physicians, nurses, and health care planners, have hosted many types of activities to raise awareness of COPD. WONCA (the World Organization of Family Doctors) is also an active collaborator in organizing World COPD Day activities. Increased participation of a wide variety of health care professionals in World COPD Day activities in many countries would help to increase awareness of COPD.

GOLD is a partner organization in the World Health Organization Global Alliance Against Chronic Respiratory Diseases (GARD) with the goal *is* to raise awareness of the burden of chronic respiratory diseases in all countries of the world, and to disseminate and implement recommendations from international guidelines.

Although awareness and dissemination of guidelines are important goals, the actual implementation of a comprehensive care system in which to coordinate the management of COPD will be important to pursue. Evidence is increasing that a chronic disease management program for COPD patients that incorporates a variety of interventions, includes pulmonary rehabilitation, and is implemented by primary care reduce hospital admissions and bed days. Key elements are patient participation and information sharing among health care providers[267].

**For further information on World COPD Day: http://www.goldcopd.org/WCDindex.asp.*

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