Pulmonary Perspective

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

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Chronic obstructive pulmonary disease (COPD) is a global health problem, and since 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has published its strategy document for the diagnosis and management of COPD. This executive summary presents the main contents of the second 5-year revision of the GOLD document that has implemented some of the vast knowledge about COPD accumulated over the last years. Today, GOLD recommends that spirometry is *required* for the clinical diagnosis of COPD to avoid misdiagnosis and to ensure proper evaluation of severity of airflow limitation. The document highlights that the assessment of the patient with COPD should always include assessment of (*1*) symptoms, (*2*) severity of airflow limitation, (*3*) history of exacerbations, and (*4*) comorbidities. The first three points can be used to evaluate level of symptoms and risk of future exacerbations, and this is done in a way that splits patients with COPD into four categories—A, B, C, and D. Nonpharmacologic and pharmacologic management of COPD match this assessment in an evidence-based attempt to relieve symptoms and reduce risk of exacerbations. Identification and treatment of comorbidities must have high priority, and a separate section in the document addresses management of comorbidities as well as COPD in the presence of comorbidities. The revised document also contains a new section on exacerbations of COPD. The GOLD initiative will continue to bring COPD to the attention of all relevant shareholders and will hopefully inspire future national and local guidelines on the management of COPD.

Keywords: COPD; clinical assessment; COPD management; exacerbations; comorbidities

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major public health problem. In 2020, COPD is projected to rank fifth worldwide

in terms of burden of disease and third in terms of mortality. Although COPD has received increasing attention from the medical community in recent years, it is still relatively unknown or ignored by the public as well as public health and government officials.

In 1998, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was formed to bring more attention to the management and prevention of COPD. 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. In 2001, the GOLD program released a consensus report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*; this document was revised in 2006, and now we present the 2011 version.

The GOLD document is a global document and for that reason alone should not be regarded a clinical guideline. It is impossible to make the same guidelines for developing countries as for, for example, Europe and North America. A strategy document provides advice on diagnosis and management that can be implemented in national guidelines. It can be expanded for rich countries and restricted for poorer ones. It provides guidance on principles and drug classes to be applied, and national guidelines can therefore build on the assessment and management principles suggested by GOLD—and then modify it to fit their country's needs.

Based on multiple scientific and clinical achievements in the 10 years since the 2001 GOLD report was published, this revised edition provides a new paradigm for treatment of stable COPD. This major revision builds on the strengths from the original recommendations and incorporates new knowledge to make three important new recommendations:

1. One of the strengths was the treatment objectives. These have stood the test of time, but are now organized into two groups: objectives that are directed toward immediately relieving and reducing the impact of symptoms, and objectives that reduce the risk of adverse health events in the future. This emphasizes the need for clinicians to maintain a focus on both the short-term and long-term impact of COPD on their patients.

2. A second strength of the original strategy was the simple, intuitive system for classifying COPD severity. This was based on the FEV_1 and was called a staging system because it was believed, at the time, that the majority of patients followed a path of disease progression that tracked the severity of the airflow limitation. Much is now known about the characteristics of patients in the different GOLD stages—for example, their level of risk of exacerbations, hospitalization, and death. However at an individual patient level, the FEV_1 is an unreliable marker of the severity of breathlessness, exercise limitation, and health status impairment. This report retains the GOLD classification system of airflow limitation because it is a predictor of future adverse events, but the term "stage" is now replaced by "grade."

3. At the time of the original report, improvement in both symptoms and health status was a GOLD treatment objective, but symptom assessment did not have a direct relation to the choice of management, and health status measurement was a complex process largely confined to clinical studies. Now, there are simple and reliable questionnaires designed for use in routine daily clinical practice. These have been validated in many languages, which has enabled the development of a new assessment system that integrates patient symptoms and their risk for serious adverse health events in the future. In turn, this new assessment system has led to the construction of a new approach to management— one that matches assessment to treatment objectives. The new management approach can be used in any clinical setting anywhere in the world and moves COPD treatment toward individualized medicine—matching the patient's therapy more closely to his or her needs. Whereas recommendations on treatment are evidence based, a novel assessment system will have to be consensus based, with the aim that future studies will test the value of this system.

Summary of New Recommendations

A summary of the new issues presented in this report follows:

1. This document has been considerably shortened in length by limiting section 1 to the essential background data on COPD. Readers who wish to access more comprehensive information are referred to a variety of excellent textbooks that have appeared in the last decade.

2. Section 2 includes information on diagnosis and assessment of COPD. The definition of COPD has not been significantly modified but has been reworded for clarity.

3. Assessment of COPD is based on the patient's level of symptoms, exacerbation history, the severity of the spirometric abnormality, and the identification of comorbidities. Whereas spirometry was previously used to support a diagnosis of COPD, spirometry is now required to make a confident diagnosis of COPD.

4. Airflow limitation as determined by spirometry is divided into four grades (GOLD 1, mild; GOLD 2, moderate; GOLD 3, severe; and GOLD 4, very severe) using the fixed ratio, post-bronchodilator $FEV_1/FVC < 0.7$, to define airflow limitation. It is recognized that the use of the fixed ratio (FEV_1/FVC) may lead to more frequent diagnoses of COPD in older adults with mild COPD as the normal process of aging affects lung volumes and flows, and may lead to underdiagnosis in adults younger than 45 years. The concept of staging has been abandoned because a staging system based on FEV_1 alone was inadequate and the evidence for an alternative staging system does not exist. The most severe spirometric grade, GOLD 4, does not include reference to respiratory failure as this seemed to be an arbitrary inclusion.

5. A new section (section 3) on therapeutic approaches has been added. This includes descriptive information on both pharmacologic and nonpharmacologic therapies, and identifying any adverse effects.

6. Management of COPD is presented in three sections: MANAGEMENT OF STABLE COPD (section 4); MANAGEMENT OF EXACERBATIONS (section 5); and COPD AND COMORBIDITIES (section 6), covering both management of comorbidities in patients with COPD and of COPD in patients with comorbidities.

7. In section 4, MANAGEMENT OF STABLE COPD, recommended approaches to both pharmacologic and nonpharmacologic treatment of COPD are presented. In previous GOLD documents, recommendations for management of COPD were based solely on spirometric category. However, there is considerable evidence that the level of FEV_1 is a poor descriptor of disease status, and for this reason, the management of stable COPD based on a strategy considering both disease impact (determined mainly by symptom burden and activity limitation) and future risk of disease progression (especially of exacerbations) is recommended.

8. Section 5, MANAGEMENT OF EXACERBATIONS, presents a revised definition of a COPD exacerbation.

9. Section 6, COMORBIDITIES AND COPD, focuses on cardiovascular diseases, osteoporosis, anxiety and depression, lung cancer, infections, and metabolic syndrome and diabetes.

Levels of Evidence

Levels of evidence are assigned to management recommendations where appropriate with the system used in previous reports. Evidence levels are enclosed in parentheses after the relevant statement, for example, "(Evidence A)." Levels of evidence used in this document have not changed with respect to previous releases and are listed in the original document (www.goldcopd.org).

1. DEFINITION AND OVERVIEW

> ### KEY POINTS
>
> - COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.
>
> - COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing.
>
> - Inhaled cigarette smoke and other noxious particles such as smoke from biomass fuels cause lung inflammation, a normal response that appears to be modified in patients who develop COPD. This chronic inflammatory response may induce parenchymal tissue destruction (resulting in emphysema) and disrupt normal repair and defense mechanisms (resulting in small airway fibrosis). These pathological changes lead to air trapping and progressive airflow limitation, and in turn to breathlessness and other characteristic symptoms of COPD.

Definition

COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

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

Burden of COPD

COPD prevalence, morbidity, and mortality vary across countries and across different groups within countries. COPD is the result of cumulative exposures over decades. Often, the prevalence of COPD is directly related to the prevalence of tobacco smoking, although in many countries, outdoor, occupational, and indoor air pollution—the latter resulting from the burning of wood and other biomass fuels—are major COPD risk factors (1). The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the aging of the world's population.

Prevalence. Existing COPD prevalence data show remarkable variation due to differences in survey methods, diagnostic criteria, and analytic approaches (2). Despite the complexities and the widespread underrecognition and underdiagnosis of COPD (3), data from the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) and the Burden of Obstructive Lung Diseases program (BOLD) have documented more severe disease than previously found and a substantial prevalence (3–11%) of COPD among never-smokers (4).

Morbidity. Morbidity measures traditionally include physician visits, emergency department visits, and hospitalizations. Morbidity due to COPD increases with age (5–7) and may be affected by other comorbid chronic conditions (e.g., cardiovascular disease, musculoskeletal impairment, or diabetes mellitus) that are frequent in patients with COPD and may impact on the patient's health status, as well as interfere with COPD management.

Mortality. Underrecognition and underdiagnosis of COPD still affect the accuracy of mortality data (8, 9) with COPD often listed as a *contributory* cause of death or omitted from the death certificate entirely (10). The Global Burden of Disease Study projected that COPD, which ranked sixth as a cause of death in 1990, will become the third leading cause of death worldwide by 2020; a newer projection estimated COPD will be the fourth leading cause of death in 2030 (11). This increased mortality is mainly driven by the expanding epidemic of smoking, reduced mortality from other common causes of death, and aging of the world population.

Economic and social burden. COPD is associated with significant economic burden. There is a direct relationship between the severity of COPD and the cost of care, and the distribution of costs changes as the disease progresses. For example, hospitalization and ambulatory oxygen costs soar as COPD severity increases. In developing countries, direct medical costs may be less important than the impact of COPD on workplace and home productivity. In 1990, COPD was the 12th leading cause of disability-adjusted life years (DALYs) lost in the world, responsible for 2.1% of the total. According to the projections, COPD will be the seventh leading cause of DALYs lost worldwide in 2030 (11).

Factors That Influence Disease Development and Progression

Although cigarette smoking is the best-studied COPD risk factor, there is consistent epidemiological evidence that nonsmokers may also develop chronic airflow limitation (5–7, 12). Besides, among people with the same smoking history, not all will develop COPD, for reasons that are still unclear but likely involve differences in genetic backgrounds and other exposures.

Across the world, cigarette smoking is the most commonly encountered risk factor for COPD. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV_1, and a greater COPD mortality rate than nonsmokers (13). Other types of tobacco (e.g., pipe, cigar, water pipe [14]) and marijuana (15) are also risk factors for COPD (16, 17). Passive exposure to cigarette smoke (also known as environmental tobacco smoke) may also contribute to respiratory symptoms (18) and COPD (19) by increasing the lung's total burden of inhaled particles and gases (20, 21). 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 (22, 23).

Occupational exposures, including organic and inorganic dusts and chemical agents and fumes, are an underappreciated risk factor for COPD (24–26). Wood, animal dung, crop residues, and coal, typically burned in open fires or poorly functioning stoves, may lead to very high levels of indoor air pollution. Evidence continues to grow that indoor pollution from biomass cooking and heating in poorly ventilated dwellings is an important risk factor for COPD (27–33). Almost 3 billion people worldwide use biomass and coal as their main source of energy for cooking, heating, and other household needs, so the population at risk worldwide is very large (30, 34).

Other factors associated with development and progression of COPD, such as genetics, lung development abnormalities, accelerated aging, bronchial hyperreactivity, and socioeconomic status, among others, are listed in recent reviews and in the full document (www.goldcopd.org).

Pathology, Pathogenesis, and Pathophysiology[1]

Inhaled particles (from cigarette smoke or other sources) cause lung inflammation, a normal response that appears to be modified in individuals who develop COPD. This chronic inflammatory response may induce parenchymal tissue destruction (resulting in emphysema), and disrupt normal repair and defense mechanisms (resulting in small airway fibrosis), which in turn lead to air trapping and progressive airflow limitation.

Pathology. Chronic inflammatory changes with increased numbers of inflammatory cell types, and structural changes resulting from repeated injury and repair, are found in the airways, lung parenchyma, and pulmonary vasculature of patients with COPD (35). In general, these changes increase with disease severity and persist despite smoking cessation.

Pathogenesis. The above-mentioned pathological changes appears to be an enhancement of the normal, physiological, inflammatory response of the respiratory tract to chronic irritants. The mechanisms for this amplified inflammation in COPD are not yet understood but may be genetically determined. Lung inflammation persists after smoking cessation through unknown mechanisms, although autoantigens and persistent microorganisms may play a role (36). Patients can clearly develop COPD without smoking, but the nature of the inflammatory response in these patients is unknown.

Pathophysiology. AIRFLOW LIMITATION AND GAS TRAPPING. Inflammation and narrowing of peripheral airways leads to decreased FEV_1. Parenchymal destruction due to emphysema also contributes to airflow limitation due to reduced elastic recoil (37). In combination, both progressively lead to gas trapping during expiration, resulting in hyperinflation.

GAS EXCHANGE ABNORMALITIES. Gas exchange abnormalities may result in hypoxemia and hypercapnia, and have several mechanisms in COPD. The main one is ventilation–perfusion (V_A/Q) abnormalities (38).

Reduced ventilatory drive may lead to carbon dioxide retention, particularly when combined with reduced ventilation.

MUCUS HYPERSECRETION. Mucus hypersecretion, resulting in a chronic productive cough, is a feature of chronic bronchitis and is not necessarily associated with airflow limitation. Conversely, not all patients with COPD have symptomatic mucus hypersecretion. When present, it is due to an increased number of goblet cells and enlarged submucosal glands in response to chronic airway irritation.

PULMONARY HYPERTENSION. Pulmonary hypertension may develop late in the course of COPD. It can be due to hypoxic vasoconstriction of small pulmonary arteries, eventually resulting in

structural changes that include intimal hyperplasia and later smooth muscle hypertrophy/hyperplasia, and/or loss of pulmonary capillary bed due to emphysema (39). In pulmonary vessels, an inflammatory response similar to that seen in the airways (and evidence of endothelial dysfunction) has been identified. Severe pulmonary hypertension may lead to right ventricular hypertrophy and eventually to right-side cardiac failure.

EXACERBATIONS. Exacerbations of respiratory symptoms often occur in patients with COPD, triggered by infection with bacteria or viruses (which may coexist), environmental pollutants, or unknown factors. During exacerbations, there is a flare-up of inflammation, increased hyperinflation and gas trapping, reduced expiratory flow, and increased dyspnea (40). There is also worsening of V_A/Q abnormalities, which can result in hypoxemia and hypercapnia (41). Other medical conditions (pneumonia, thromboembolism, and acute cardiac failure) may mimic or aggravate an exacerbation of COPD.

COMORBIDITIES. It is increasingly recognized that many patients with COPD have comorbidities and that these have a major impact on their quality of life and survival (42). The precise pathobiology of this association is under investigation but may involve mechanical as well as biological or genetic mechanisms. For instance, airflow limitation and hyperinflation affect cardiac function and gas exchange (43).

2. DIAGNOSIS AND ASSESSMENT

> ### KEY POINTS
> - A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough and/or sputum production, and a history of exposure to risk factors for the disease.
>
> - Spirometry is required to make the diagnosis in this clinical context; the presence of a post-bronchodilator FEV_1/FVC less than 0.70 confirms the presence of persistent airflow limitation and thus of COPD.
>
> - The goals of COPD assessment are to determine: (*1*) the impact of the disease on the patient's health status, (*2*) the severity of airflow limitation, and (*3*) the risk of future exacerbations, in order to guide therapy. The risk of future exacerbations is estimated by the severity of airflow limitation and the history of previous exacerbations.
>
> - Comorbidities, including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, and lung cancer, occur frequently in patients with COPD. Comorbidities should be actively looked for, and treated appropriately if present.

Diagnosis

A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough and/or sputum production, and a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis in this clinical context; the presence of a post-bronchodilator FEV_1/FVC less than 0.70 confirms the presence of persistent airflow limitation and thus of COPD.

The spirometric criterion for airflow limitation remains a post-bronchodilator fixed ratio of FEV_1/FVC less than 0.70. This criterion is simple, independent of reference values, and has been used in numerous clinical trials forming the evidence base from which most of our treatment recommendations are drawn. Diagnostic simplicity and consistency are key for the busy nonspecialist clinician. Although post-bronchodilator spirometry

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[1] Illustrations of many of the topics covered in this section can be found in the Teaching Slide Set on the GOLD website: http://www.goldcopd.org.

is required for the diagnosis and assessment of severity of COPD, the degree of reversibility of airflow limitation (e.g., measuring FEV_1 before and after bronchodilator or corticosteroids) is no longer recommended.

Symptoms. 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. Individuals, particularly those exposed to COPD risk factors, who present with these symptoms should be examined to search for an underlying cause(s) and appropriate interventions taken. Conversely, significant airflow limitation may develop without chronic cough and sputum production.

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
- Family history of COPD or other chronic respiratory disease
- Pattern of symptom development
- History of exacerbations or previous hospitalizations for respiratory disorder
- Presence of comorbidities
- Impact of the disease on the patient's life
- Social and family support available to the patient
- Possibilities for reducing risk factors, especially smoking cessation

Physical examination. Although 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 (44, 45), and their detection has a relatively low sensitivity and specificity.

Spirometry. Spirometry is the most reproducible and objective measurement of airflow limitation available. Peak expiratory flow measurement alone cannot be reliably used as the only diagnostic test, despite its good sensitivity, because of its weak specificity (46). Good-quality spirometric measurement is possible in any health care setting, and all health care workers who care for patients with COPD should have access to spirometry.

Assessment of Disease

The goals of COPD assessment are to determine: (*1*) the impact of the disease on the patient's health status, (*2*) the severity of airflow limitation, and (*3*) the risk of future events (such as exacerbations, hospital admissions, or death), to, eventually, guide therapy. To achieve these goals, COPD assessment must consider the following aspects of the disease separately:

- Current level of patient's symptoms
- Severity of airflow limitation
- Exacerbation risk
- Presence of comorbidities

Assessment of symptoms. There are several validated questionnaires to assess symptoms in patients with COPD that can be used to distinguish patients with less severe symptoms from patients with more severe symptoms. GOLD primarily recommends the use of the Modified British Medical Research Council (mMRC) questionnaire on breathlessness or the COPD Assessment

Test (CAT), the latter having a broader coverage of the impact of COPD on the patient's daily life and well-being. Other symptoms scales can be used where available, for example, the Clinical COPD Questionnaire, and future GOLD updates are likely to expand in this area.

Assessment of airflow limitation severity. Table 1 shows the classification of airflow limitation severity in COPD. Specific spirometric cut points are used for purposes of simplicity. Spirometry should be performed after the administration of an adequate dose of a short-acting inhaled bronchodilator to minimize variability. Worsening airflow limitation is associated with an increasing prevalence of exacerbations (*see below*) and risk of death.

Assessment of exacerbation risk. An exacerbation of COPD is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication (47–49). The rate at which exacerbations occur varies greatly between patients (50). The best predictor of having frequent exacerbations (two or more exacerbations per year) is a history of previous treated events (51). Severity of exacerbations is usually classified as mild when exacerbations of respiratory symptoms require change of inhaled treatment by the patient, moderate when exacerbations of respiratory symptoms require medical intervention including a short course of antibiotic and/or oral steroids, and severe when exacerbations of respiratory symptoms require hospitalization.

Assessment of comorbidities. Comorbidities occur frequently in COPD and include cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, and lung cancer. The existence of COPD may actually increase the risk for other concomitant diseases; this is particularly striking for COPD and lung cancer (52–55).

Combined COPD assessment. Figure 1 illustrates the proposed combined assessment of COPD. The MRC or CAT scale is recommended for assessing symptoms, with an mMRC grade greater than or equal to 2 or a CAT score greater than or equal to 10 indicating a high level of symptoms. These cutoffs should be used as indicators; the primary aim is to separate patients with a significant symptom burden from those with less symptoms. There are two methods of assessing exacerbation risk. One is a population-based method using the GOLD spirometric classification (Table 1), with GOLD 3 or GOLD 4 categories indicating high risk. The other is based on the individual patient's history of exacerbations (51, 56), with two or more exacerbations in the preceding year indicating high risk. Given the significance of an exacerbation leading to hospital admission (57), hospitalization will often be an indicator of high risk as well. If there is a discrepancy between the risk category as assessed by spirometric classification and that derived from exacerbation history, the assessment pointing to the highest risk should be used.

To use Figure 1, first assess symptoms and determine if the patient belongs to the left side of the box—less symptoms (as indicated by mMRC grade 0–1 or CAT < 10)—or the right side—more symptoms (as indicated by mMRC ⩾ 2 or CAT ⩾ 10). Next, assess the risk of exacerbations to determine if the patient belongs to the

TABLE 1. GRADING OF SEVERITY OF AIRFLOW LIMITATION IN COPD (BASED ON POST-BRONCHODILATOR FEV_1)

In patients with FEV_1/FVC < 0.70:		
GOLD 1:	Mild	FEV_1 ⩾ 80% predicted
GOLD 2:	Moderate	50% ⩽ FEV_1 < 80% predicted
GOLD 3:	Severe	30% ⩽ FEV_1 < 50% predicted
GOLD 4:	Very severe	FEV_1 < 30% predicted

Definition of abbreviation: COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease.
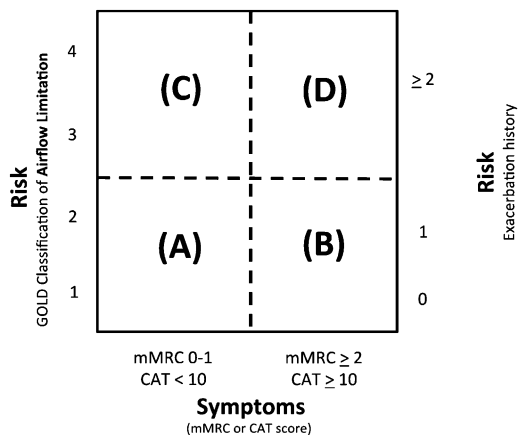
Figure 1. Combined COPD assessment. When assessing risk, choose the highest risk according to GOLD spirometric grade or exacerbation history.

lower part of the box—low risk—or the upper part of the box—high risk. This can be done by either of two methods: (*1*) use spirometry to determine the GOLD grade of airflow limitation (GOLD 1 and 2 indicate low risk, whereas GOLD 3 and 4 indicate high risk); or (*2*) assess the number of exacerbations the patient has had within the previous 12 months (zero or one indicates low risk, whereas two or more exacerbations indicates high risk). In some patients, these two ways of assessing risk of exacerbations will not lead to the same level of risk; in this case, the risk should be determined by the method indicating high risk.

The groups can be summarized as follows:

Patient group A—low risk, less symptoms
GOLD 1–2 (mild or moderate airflow limitation)
and 0–1 exacerbation per year *and* mMRC grade 0–1 or CAT score < 10

Patient group B—low risk, more symptoms
GOLD 1–2 (mild or moderate airflow limitation)
and 0–1 exacerbation per year *and* mMRC grade $\geqslant$ 2 or CAT score $\geqslant$ 10

Patient group C—high risk, less symptoms
GOLD 3–4 (severe or very severe airflow limitation)
and/or $\geqslant$ 2 exacerbations per year and/or $\geqslant$ 1 hospitalized exacerbation per year *and* mMRC grade 0–1 or CAT score < 10

Patient group D—high risk, more symptoms
GOLD 3–4 (severe or very severe airflow limitation)
and/or $\geqslant$ 2 exacerbations per year / $\geqslant$ 1 hospitalized exacerbation per year *and* mMRC grade $\geqslant$ 2 or CAT score $\geqslant$ 10

This approach, combined with an assessment of potential comorbidities, reflects the complexity of COPD better than the unidimensional analysis of airflow limitation previously used for staging the disease and forms the basis of the guide to individualized management provided in section 4.

Additional investigations. The following additional investigations may be considered as part of the diagnosis and assessment of COPD:

IMAGING. A chest X-ray is not useful to establish a diagnosis in COPD, but it is valuable in excluding alternative diagnoses and establishing the presence of significant comorbidities.

LUNG VOLUMES AND DIFFUSING CAPACITY. Patients with COPD exhibit gas trapping (a rise in residual volume) from early in the disease, and as airflow limitation worsens, static hyperinflation (an increase in total lung capacity) occurs. These changes can be documented by body plethysmography, or less accurately by helium dilution lung volume measurement. Diffusing capacity can be assessed by the uptake of carbon monoxide using the single-breath method. These measurements help characterize the severity of COPD but are not essential to patient management.

OXIMETRY AND ARTERIAL BLOOD GAS MEASUREMENT. Pulse oximetry can be used to evaluate a patient's oxygen saturation and need for supplemental oxygen therapy. Pulse oximetry should be used to assess all stable patients with FEV_1 less than 35% predicted or with clinical signs suggestive of respiratory failure or right heart failure. If peripheral saturation is less than 92%, arterial blood gases should be assessed (58).

α_1-ANTITRYPSIN DEFICIENCY SCREENING. The World Health Organization recommends that patients with COPD from areas with a particularly high prevalence of α_1-antitrypsin deficiency should be screened for this genetic disorder (59). The typical patient tends to present at a younger age (<45 yr) with lower lobe emphysema. A serum concentration of α_1-antitrypsin below 15 to 20% of the normal value is highly suggestive of homozygous α_1-antitrypsin deficiency.

EXERCISE TESTING. Objectively measured exercise impairment, assessed by a reduction in self-paced walking distance (60) or during incremental exercise testing in a laboratory (61), is a powerful indicator of health status impairment and predictor of prognosis (62). Monitoring of physical activity may be more relevant regarding prognosis than evaluating exercise capacity (63).

COMPOSITE SCORES. Several variables, including age, dyspnea, FEV_1, body mass index, exercise tolerance assessed by walking distance or peak oxygen consumption, and/or arterial hypoxemia, identify patients at increased risk for mortality (64–66).

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 will include use of antiinflammatory drugs, and other treatments need to be individualized. Other potential diagnoses are usually easier to distinguish from COPD (Table 2).

3. THERAPEUTIC OPTIONS

KEY POINTS
- In patients who continue to smoke, smoking cessation is a key therapeutic measure. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.

- Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.

- To date, none of the existing medications for COPD has been shown conclusively to modify the long-term decline in lung function.

- Each pharmacological treatment regimen needs to be patient specific, guided by severity of symptoms, risk of exacerbations, comorbidities, drug availability, and the patient's response.

- Influenza and pneumococcal vaccination should be offered to every patient with COPD; they appear to be more effective in older patients and those with more severe disease or cardiac comorbidity.

- All patients who get short of breath when walking on their own pace on level ground should be offered rehabilitation; it can improve symptoms, quality of life, and physical and emotional participation in everyday activities.

All text of this section can be found in the online supplement.

4. MANAGEMENT OF STABLE COPD

> ### KEY POINTS
>
> - Identification and reduction of exposure to risk factors are important in the prevention and treatment of COPD. All individuals who smoke should be encouraged to quit.
>
> - The level of FEV_1 is an inadequate descriptor of the impact of the disease on patients, and for this reason, individualized assessment of symptoms and future risk of exacerbation should also be incorporated into the management strategy for stable COPD.
>
> - Regular physical activity is recommended for all patients with COPD.
>
> - All patients with COPD with breathlessness when walking at their own pace on level ground benefit from rehabilitation and maintenance of physical activity, improving their exercise tolerance and quality of life, and reducing symptoms of dyspnea and fatigue.
>
> - Pharmacologic therapy is used to reduce symptoms, reduce frequency and severity of exacerbations, and improve health status and exercise tolerance. Existing medications for COPD have not been conclusively shown to modify the long-term decline in lung function that is the hallmark of this disease.
>
> - For both β_2-agonists and anticholinergics, long-acting formulations are preferred over short-acting formulations. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators.
>
> - Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients at high risk of exacerbations.
>
> - Long-term monotherapy with oral or inhaled corticosteroids is not recommended in COPD.
>
> - The phospodiesterase-4 inhibitor roflumilast may be useful to reduce exacerbations for patients with FEV_1 less than 50% predicted, chronic bronchitis, and frequent exacerbations.
>
> - Influenza vaccines can reduce the risk of serious illness (such as hospitalization due to lower respiratory tract infections) and death in patients with COPD.
>
> - The routine use of antibiotics is not indicated in patients with clinically stable COPD, other than for treating infectious exacerbations of COPD and other bacterial infections.

Introduction

Once COPD has been diagnosed, effective management should be based on an individualized assessment of the disease having two goals in mind:

1. Reduce current symptoms
2. Reduce the risk of future events (Table 3)

These goals should be reached with minimal side effects from treatment, a particular challenge in patients with COPD because they commonly have comorbidities that also need to be carefully identified and treated.

Identify and Reduce Exposures

Identification and reduction of exposure to risk factors are important in the treatment (and prevention) of COPD. Since cigarette smoking is the most commonly encountered and easily identifiable risk factor, smoking cessation should be encouraged for all individuals who smoke. Reduction of total personal exposure to occupational dusts, fumes, and gases and to indoor and outdoor air pollutants may be more difficult but should be attempted.

Treatment of Stable COPD

In previous versions of the GOLD report, COPD treatment recommendations were based on spirometry only. This is in keeping with the fact that most of the clinical trial evidence about treatment efficacy in COPD is oriented around baseline FEV_1. However, FEV_1 alone is a poor descriptor of disease status, and for this reason, the treatment strategy for stable COPD should consider also an individual patient's symptoms and future risk of exacerbations as illustrated in Figure 1.

Nonpharmacologic Treatment

Physical activity. Regular physical activity is recommended for all patients with COPD.

   Rehabilitation. Although more information is needed on criteria for patient selection for pulmonary rehabilitation programs, all patients with COPD appear to benefit from rehabilitation and maintenance of physical activity, improving their exercise tolerance and experiencing decreased dyspnea and fatigue (67) (Evidence A).

   Vaccination. Decisions about vaccination in patients with COPD depend on local policies, availability, and affordability.

   Nonpharmacologic management of COPD according to the individualized assessment of symptoms and exacerbation risk (Figure 1) is shown in Table 4.

Pharmacologic Treatment

The classes of medications commonly used in treating COPD are shown in Table E1 in the online supplement, and a detailed description of the effects of these medications is given in section 3 in the online supplement. The choice within each class depends on the availability of medication and the patient's response. A proposed model for initial pharmacological management of COPD according to the individualized assessment of symptoms and exacerbation risk (Figure 1) is shown in Table 5.

   Group A. Group A patients have few symptoms and a low risk of exacerbations. Specific evidence for the effectiveness of pharmacologic treatments is not available for patients with FEV_1 greater than 80% predicted (GOLD 1). However, for all group A patients, a short-acting bronchodilator is recommended as first choice based on its effect on lung function and breathlessness. Second choice is a combination of short-acting bronchodilators or the introduction of a long-acting bronchodilator. The evidence for this step-up is weak; few studies of the combination exist (68, 69), and most trials of therapy with long-acting bronchodilators have been performed in patients with more severe airflow limitation (70, 71).

   Group B. Group B patients have more significant symptoms but still a low risk of exacerbations. Long-acting bronchodilators are superior to short-acting bronchodilators (taken as needed) and are therefore recommended (70, 71). There is no evidence to recommend one class of long-acting bronchodilators over another for initial treatment. In the individual patient, the choice should depend on the patient's perception of symptom relief. For patients with severe breathlessness, the second choice is a combination of long-acting bronchodilators (72, 73). Only short-term studies of this treatment option have been reported, and patients on a combination of long-acting bronchodilators should be carefully followed and their treatment effect evaluated.

TABLE 2. COPD AND ITS DIFFERENTIAL DIAGNOSES

Diagnosis	Suggestive Features
COPD	Onset in midlife
	Symptoms slowly progressive
	History of tobacco smoking or exposure to other types of smoke
Asthma	Onset early in life (often childhood)
	Symptoms vary widely from day to day
	Symptoms worse at night/early morning
	Allergy, rhinitis, and/or eczema also present
	Family history of asthma
Congestive heart failure	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
	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 at younger age, nonsmokers
	May have history of rheumatoid arthritis or acute fume exposure
	Seen after lung or bone marrow transplantation
	CT on expiration shows hypodense areas
Diffuse panbronchiolitis	Predominantly seen in patients of Asian descent
	Most patients are male and nonsmokers
	Almost all have chronic sinusitis
	Chest X-ray and HRCT show diffuse small centrilobular nodular opacities and hyperinflation

Definition of abbreviations: CT = computer tomography; HRCT = high-resolution computer tomography.

These features tend to be characteristic of the respective diseases, but are not mandatory. 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 in elderly patients.

Alternative choices include short-acting bronchodilators and theophylline, the latter of which can be used if inhaled bronchodilators are unavailable or unaffordable.

Group C. Group C patients have few symptoms but a high risk of exacerbations. As first choice, a long-acting anticholinergic or a combination of inhaled corticosteroid/long-acting β_2-agonist is recommended (71, 74–79). Unfortunately, there is only one study directly comparing these treatments, which makes differentiation difficult (80). Both long-acting anticholinergic and long-acting β_2-agonist reduce the risk of exacerbations (70, 71), and although good long-term studies are lacking, this principle of combination treatment seems sound (although in many countries expensive). The recommendation for a combination of inhaled corticosteroid/long-acting anticholinergic is not evidence based. A phosphodiesterase-4 inhibitor may be

TABLE 3. GOALS FOR TREATMENT OF STABLE COPD

Reduce symptoms
- Relieve symptoms
- Improve exercise tolerance
- Improve health status

Reduce risk
- Prevent disease progression
- Prevent exacerbations
- Reduce mortality

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

considered if the patient has chronic bronchitis (81, 82). Alternative choices include short-acting bronchodilators and theophylline if long-acting inhaled bronchodilators are unavailable or unaffordable.

Group D. Group D patients have many symptoms and a high risk of exacerbations. The rationale for the first choice of therapy is the same as that for patients in group C, as reduction of exacerbation risk seems most important. As second choice, a combination of all three classes of drugs (inhaled corticosteroid/long-acting β_2-agonist/long-acting anticholinergic) is recommended (83), although there are conflicting findings concerning this treatment (84); support for it mainly comes from short-term studies (85). It is also possible to add a phosphodiesterase-4 inhibitor to the treatment chosen as first choice, provided the patient has chronic bronchitis (81). A phosphodiesterase-4 inhibitor is effective when added to a long-acting bronchodilator (82), whereas evidence of its benefit when added to inhaled corticosteroid comes from less valid secondary analyses. Alternative choices include short-acting bronchodilators, and theophylline or carbocysteine (86) can be used if long-acting inhaled bronchodilators are unavailable or unaffordable.

Bronchodilators—recommendations

- For both β_2-agonists and anticholinergics, long-acting formulations are preferred over short-acting formulations (Evidence A).

- The combined use of short- or long-acting β_2-agonists and anticholinergics may be considered if symptoms are not improved with single agents (Evidence B).

- Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators (Evidence A).

- Based on evidence of relatively low efficacy and more side effects, treatment with theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable (Evidence B).

Corticosteroids and phosphodiesterase-4 inhibitors—recommendations

- There is no evidence to recommend a short-term therapeutic trial with oral corticosteroids in patients with COPD to identify those who will respond to inhaled corticosteroids or other medications.

- Long-term treatment with inhaled corticosteroids is recommended for patients with FEV_1 less than 50% of predicted and/or frequent exacerbations that are not adequately controlled by long-acting bronchodilators (Evidence A).

- Long-term monotherapy with oral corticosteroids is not recommended in COPD (Evidence A).

- Long-term monotherapy with inhaled corticosteroids is not recommended in COPD because it is less effective than the combination of inhaled corticosteroids with long-acting β_2-agonists (Evidence A).

- The phosphodiesterase-4 inhibitor roflumilast may also be used to reduce exacerbations for patients with chronic bronchitis, FEV_1 less than 50% of predicted, and frequent exacerbations that are not adequately controlled by long-acting bronchodilators (Evidence B).

Monitoring and Follow-up

Routine follow-up is essential in COPD. The frequency of follow-up visits and type of examinations needs to be individualized. In general, the following aspects need to be considered:

TABLE 4. NONPHARMACOLOGIC MANAGEMENT OF COPD

Patient Group	Essential	Recommended	Depending on Local Guidelines
A	Smoking cessation (can include pharmacologic treatment)	Physical activity	Flu vaccination Pneumococcal vaccination
B–D	Smoking cessation (can include pharmacologic treatment) Pulmonary rehabilitation	Physical activity	Flu vaccination Pneumococcal vaccination

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

Symptoms. At each visit, inquire about changes in symptoms since the last visit, including cough and sputum, breathlessness, fatigue, activity limitation, and sleep disturbances. Questionnaires such as the CAT (87) can be performed every 2 to 3 months; trends and changes are more valuable than single measurements.

Smoking status. At each visit, determine current smoking status and smoke exposure; strongly encourage participation in programs to reduce and eliminate wherever possible exposure to COPD risk factors.

Lung function. It may worsen over time, even with the best available care. Decline in lung function is best tracked by spirometry performed at least once a year to identify patients whose lung function is declining quickly.

Pharmacotherapy and other medical treatment. 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. Treatment modifications should be recommended as appropriate with a focus on avoiding unnecessary polypharmacy.

Exacerbation history. Evaluate the frequency, severity, and likely causes of any exacerbations (88). Specific inquiry into unscheduled visits to providers, telephone calls for assistance, and use of urgent or emergency care facilities is important. Severity of exacerbations can be estimated by the increased need for bronchodilator medication or corticosteroids, by the need for antibiotic treatment, or by documenting hospitalizations.

Comorbidities. Identification and manage them in line with local treatment guidance (*see* section 6).

Surgery in the patient with COPD. General surgical risk increases in patients with COPD due to smoking, poor general health status, age, obesity, and COPD severity (89). Postoperative pulmonary complications include lung infections, atelectasis, and/or increased airflow limitation, which all potentially result in acute respiratory failure (90–93). The surgical site is the most important predictor of postoperative pulmonary complications and risk increases as the incision approaches the diaphragm (92). Epidural or spinal anesthesia appears to have a lower risk than general anesthesia. To prevent postoperative pulmonary complications, patients with COPD should be optimally treated before surgery. Surgery should be postponed if an exacerbation is present.

For lung resection, the individual patient's risk factors should be identified by careful history, physical examination, chest radiography, and a complete battery of pulmonary function tests, including spirometry with bronchodilator response, static lung volumes, diffusing capacity, and arterial blood gases at rest (94, 95). The risk of postoperative complications is particularly high in patients with decreased predicted postoperative pulmonary function (FEV_1 or $D_{L_{CO}} < 30–40\%$ predicted). These patients should undergo further lung function assessment, for example, tests of regional distribution of perfusion and exercise capacity (94, 95). Poor exercise capacity (peak $V_{O_2} < 10$ ml/kg/min or 35% predicted) identifies a group of patients at very high risk. The final decision to pursue surgery should be made after discussion with the surgeon, pulmonary specialist, primary clinician, and the patient.

5. MANAGEMENT OF EXACERBATIONS

KEY POINTS

- An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.

- Exacerbations of COPD can be precipitated by several factors. The most common causes appear to be viral upper respiratory tract infections and infection of the tracheobronchial tree.

- The diagnosis of an exacerbation relies exclusively on the clinical presentation of the patient complaining of an acute change of symptoms (baseline dyspnea, cough, and/or sputum production) that is beyond normal day-to-day variation.

- The goal of treatment in COPD exacerbations is to minimize the impact of the current exacerbation and to prevent the development of subsequent exacerbations.

- Short-acting inhaled β_2-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment of an exacerbation.

- Systemic corticosteroids and antibiotics can shorten recovery time, improve lung function (FEV_1) and arterial hypoxemia (Pa_{O_2}), and reduce the risk of early relapse, treatment failure, and length of hospital stay.

- COPD exacerbations can often be prevented. Smoking cessation, influenza and pneumococcal vaccination, knowledge of current therapy including inhaler technique, and appropriate treatment are all interventions that reduce the number of exacerbations and hospitalizations.

Definition

An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication (47–49).

Exacerbations of COPD are important events in the course of the disease because they:

- Negatively affect a patient's quality of life (88, 96)
- Have effects on symptoms and lung function that take several weeks to recover (97)
- Accelerate the rate of decline of lung function (98, 99)
- Are associated with significant mortality, particularly in those requiring hospitalization
- Have high socioeconomic costs (100)

In-hospital mortality of patients admitted for a hypercapnic exacerbation with acidosis is approximately 10% (101). Mortality

reaches 40% at 1 year after discharge in those needing mechanical ventilator support, and all-cause mortality 3 years after hospitalization is as high as 49% (100–104). Prevention, early detection, and prompt treatment of exacerbations are vital to reduce the burden of COPD (105).

Exacerbations of COPD can be precipitated by several factors. The most common causes appear to be respiratory tract infections (viral or bacterial) (106–112). Air pollution can also precipitate exacerbations of COPD (113–115). However, the cause of about one-third of severe exacerbations of COPD cannot be identified. Some patients appear particularly prone to developing exacerbations of COPD, whereas others do not. Those reporting two or more exacerbations of COPD per year are often defined as "frequent exacerbators" (51, 56), a phenotype that appears stable over time. Severity of exacerbations is usually classified as mild when exacerbations of respiratory symptoms require change of inhaled treatment by the patient, moderate when exacerbations of respiratory symptoms require medical intervention including a short course of antibiotic and/or oral steroids, and severe when exacerbations of respiratory symptoms require hospitalization.

In addition to infections and exposure to pollutants, exacerbations of respiratory symptoms (especially dyspnea) in patients with COPD may be due to different mechanisms that may overlap in the same patients. Conditions that may mimic and/or aggravate exacerbations, including pneumonia, pulmonary embolism, congestive heart failure, cardiac arrhythmia, pneumothorax, and pleural effusion, need to be considered in the differential diagnosis and treated if present (47, 90, 97, 116). Interruption of maintenance therapy has also been shown to lead to exacerbations.

Diagnosis

Currently, the diagnosis of an exacerbation relies exclusively on the clinical presentation of the patient complaining of an acute change of symptoms (baseline dyspnea, cough, and/or sputum production) that is beyond normal day-to-day variation. In the future, a biomarker or panel of biomarkers that allows a more precise etiologic diagnosis would be desirable.

Assessment

The assessment of an exacerbation is based on the patient's medical history and clinical signs of severity and some laboratory tests, if available. The following tests may be considered to assess the severity of an exacerbation:

- Pulse oximetry for tracking and/or adjusting supplemental oxygen therapy. The measurement of arterial blood gases is required if the coexistence of acute or acute-on-chronic respiratory failure is suspected ($Pa_{O_2} < 8.0$ kPa [60 mm Hg] with or without $Pa_{CO_2} > 6.7$ kPa [50 mm Hg] breathing ambient air). Assessment of the acid–base status is necessary before initiating mechanical ventilation (90, 117).

- Chest radiographs are useful in excluding alternative diagnoses.

- An ECG may aid in the diagnosis of coexisting cardiac problems.

- Whole-blood count may identify polycythemia (hematocrit > 55%), anemia, or leukocytosis.

- The presence of purulent sputum during an exacerbation can be sufficient indication for starting empirical antibiotic treatment (118). *Haemophilus influenzae*, *Streptococcus pneumoniae,* and *Moraxella catarrhalis* are the most common

bacterial pathogens involved in an exacerbation (108); in GOLD 3 and GOLD 4 patients, *Pseudomonas aeruginosa* becomes important.

- Biochemical test abnormalities, including electrolyte disturbances and hyperglycemia, can be associated with exacerbations. However, these abnormalities can also be due to associated comorbidities.

Spirometry is not recommended during an exacerbation because it can be difficult to perform and measurements are not accurate enough.

Treatment Options

Treatment setting. The goals of treatment for COPD exacerbations are to minimize the impact of the current exacerbation and prevent the development of subsequent exacerbations (119). Depending on the severity of an exacerbation and/or the severity of the underlying disease, an exacerbation can be managed in an outpatient or inpatient setting. More than 80% of exacerbations can be managed on an outpatient basis (51, 79, 120) with pharmacologic therapies including bronchodilators, corticosteroids, and antibiotics.

Table 6 shows the indications for hospital assessment and potential admission of a patient with a COPD exacerbation. When a patient comes to the emergency department, the first actions are to provide controlled oxygen therapy and to determine whether the exacerbation is life threatening (Table 7). If so, the patient should be admitted to the intensive care unit (ICU) immediately. Otherwise, the patient may be managed in the emergency department or hospital. In addition to pharmacologic therapy, hospital management of exacerbations includes respiratory support (oxygen therapy, ventilation).

Pharmacologic treatment. The three classes of medications most commonly used for exacerbations of COPD are bronchodilators, corticosteroids, and antibiotics.

SHORT-ACTING BRONCHODILATORS. Although there are no controlled trials, short-acting inhaled β₂-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment of an exacerbation (90, 121) (Evidence C). A systematic review of the route of delivery of short-acting bronchodilators found no significant differences in FEV_1 between metered-dose inhalers (with or without a spacer device) and nebulizers (122), although the latter can be more convenient for sicker or frail patients. Intravenous methylxanthines (theophylline or aminophylline) are only to be used in selected cases when there is insufficient response to short-acting bronchodilators (123–127) (Evidence B). Side effects of methylxanthines are significant, and their beneficial effects in terms of lung function and clinical endpoints are modest and inconsistent (128, 129).

CORTICOSTEROIDS. Data from studies in secondary health care indicate that systemic corticosteroids in COPD exacerbations shorten recovery time, improve lung function (FEV_1) and arterial hypoxemia (Pa_{O_2}) (130–133) (Evidence A), and reduce the risk of early relapse, treatment failure, and length of hospital stay (130, 132, 134). A dose of 30–40 mg prednisolone per day for 10–14 days is recommended (Evidence D). Therapy with oral prednisolone is preferable (135). Nebulized budesonide alone may be an alternative (although more expensive) to oral corticosteroids in the treatment of exacerbations (131, 136, 137).

ANTIBIOTICS. There is evidence supporting the use of antibiotics in exacerbations when patients have clinical signs of a bacterial infection, for example, increase in sputum purulence (118). A systematic review of the very few available placebo-controlled studies has shown that antibiotics reduce the risk of short-term mortality by 77%, treatment failure by 53%, and sputum purulence by 44%. This review supports antibiotics

TABLE 5. INITIAL PHARMACOLOGIC MANAGEMENT OF COPD*

Patient Group	Recommended First Choice	Alternative Choice	Other Possible Treatments[†]
A	Short-acting anticholinergic prn *or* Short-acting β₂-agonist prn	Long-acting anticholinergic *or* Long-acting β₂-agonist *or* Short-acting anticholinergic and short-acting β₂-agonist	Theophylline
B	Long-acting anticholinergic *or* Long-acting β₂-agonist	Long-acting anticholinergic and long-acting β₂-agonist	Short-acting anticholinergic *and/or* Short-acting β₂-agonist *and/or* Theophylline
C	Inhaled corticosteroid and long-acting β₂-agonist *or* Long-acting anticholinergic	Long-acting anticholinergic and long-acting β₂-agonist	Phosphodiesterase-4 inhibitor *and/or* Short-acting β₂-agonist *and/or* Short-acting anticholinergic *and/or* Theophylline
D	Inhaled corticosteroid and long-acting β₂-agonist *or* Long-acting anticholinergic	Inhaled corticosteroid, long-acting β₂-agonist, and long-acting anticholinergic *or* Inhaled corticosteroid, long-acting β₂-agonist, and phosphodiesterase-4 inhibitor *or* Long-acting anticholinergic and long-acting β₂-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine *and/or* Short-acting β₂-agonist *and/or* Short-acting anticholinergic *and/or* Theophylline

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

* Medications in each cell are mentioned in alphabetical order and therefore not necessarily in order of preference.

[†] Medications in this column can be used alone or in combination with other options in the First and Alternative Choice columns.

for only moderately or severely ill patients with COPD exacerbations with increased cough and sputum purulence (138, 139). Procalcitonin III, a marker that is specific for bacterial infections, may be of value in the decision to use antibiotics (140), but this test is expensive and thus not widely established. A study in patients with COPD with exacerbations requiring mechanical ventilation (invasive or noninvasive) indicated that not giving antibiotics was associated with increased mortality and a greater incidence of secondary nosocomial pneumonia (141). In summary, antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms—increase in dyspnea, sputum volume, and sputum purulence (Evidence B); patients who have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms (Evidence C); or require mechanical ventilation (invasive or noninvasive) (Evidence B) (142). The recommended length of antibiotic therapy is usually 5–10 days (Evidence D). The choice of the antibiotic should be based on the local bacterial resistance pattern.

ADJUNCT THERAPIES. Depending on the clinical condition of the patient, an appropriate fluid balance with special attention to the administration of diuretics, anticoagulants, treatment of comorbidities, and nutritional aspects should be considered. At all times, health care providers should strongly enforce stringent measures against active cigarette smoking.

Respiratory support. OXYGEN THERAPY. Controlled oxygen should be titrated to improve the patient's hypoxemia with a target saturation of 88–92% (143). Once oxygen is started, arterial blood gases should be checked 30 to 60 minutes later to ensure satisfactory oxygenation without carbon dioxide retention or acidosis. Venturi masks (high-flow devices) offer more accurate

and controlled delivery of oxygen than do nasal prongs but are less likely to be tolerated by the patient (90).

VENTILATORY SUPPORT. Some patients need immediate admission to an ICU (Table 8). Admission of patients with severe 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.

Ventilatory support in an exacerbation can be provided by either noninvasive (by nasal or facial mask) or invasive (by orotracheal tube or tracheostomy) ventilation. Respiratory stimulants are not recommended for acute respiratory failure (121).

NONINVASIVE MECHANICAL VENTILATION. Noninvasive mechanical ventilation (NIV) has been studied in several randomized, controlled trials in acute respiratory failure, consistently providing success rates of 80 to 85% (144–147). NIV improves respiratory acidosis (increases pH and decreases Pa_{CO_2}) and decreases respiratory rate, severity of breathlessness, complications such as ventilator-associated pneumonia, and length of hospital stay (Evidence A). More importantly, mortality and intubation rates are reduced by this intervention (145, 148–150) (Evidence A). Table 9 summarizes the indications for NIV (90, 144, 146, 151, 152).

INVASIVE MECHANICAL VENTILATION. The indications for initiating invasive mechanical ventilation during an exacerbation are shown in Table 10, and include failure of an initial trial of NIV (153). As experience is being gained with the generalized clinical use of NIV in COPD, several indications for invasive mechanical ventilation are being successfully treated with NIV, and in all but a few situations, there is nothing to be lost by a trial of noninvasive ventilation (153).

TABLE 6. POTENTIAL INDICATIONS FOR HOSPITAL ASSESSMENT OR ADMISSION*

- 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 an exacerbation to respond to initial medical management
- Presence of serious comorbidities (e.g., heart failure or newly occurring arrhythmias)
- Frequent exacerbations
- Older age
- Insufficient home support

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.
* Local resources need to be considered.

The use of invasive ventilation in patients with very severe COPD is influenced by the likely reversibility of the precipitating event, the patient's wishes, and availability of intensive care facilities. When possible, a clear statement of the patient's own treatment wishes—an advance directive or "living will"—makes these difficult decisions much easier to resolve. Major hazards include the risk of ventilator-acquired pneumonia (especially when multiresistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation.

Contrary to some opinions, acute mortality among patients with COPD with respiratory failure is lower than mortality among patients ventilated for non-COPD causes (154). Despite this, there is evidence that patients who might otherwise survive may be denied admission to intensive care for intubation because of unwarranted prognostic pessimism (155).

Hospital Discharge and Follow-up

Insufficient clinical data exist to establish the optimal duration of hospitalization in individual patients with an exacerbation of COPD (156–158), although units with more respiratory consultants and better-organized care have lower mortality and reduced length of hospital stay after admission for an exacerbation (159). In the hospital prior to discharge, patients should start long-acting bronchodilators, either anticholinergics and/or β₂-agonists with or without inhaled corticosteroids. Hospitalization offers a unique window of opportunity to reinforce smoking cessation measures if necessary. Table 11 provides a checklist of items to assess at time of discharge and Table 12 shows items to assess at follow-up 4 to 6 weeks after discharge from the hospital.

Home visits by a community nurse may permit earlier discharge of patients hospitalized with an exacerbation without

TABLE 7. MANAGEMENT OF SEVERE BUT NOT LIFE-THREATENING EXACERBATIONS*

- Assess severity of symptoms, blood gases, chest radiograph
- Administer controlled oxygen therapy and obtain serial arterial blood gas measurement
- Bronchodilators:
  - Increase doses and/or frequency of short-acting bronchodilators
  - Combine short-acting β₂-agonists and anticholinergics
  - Use spacers or air-driven nebulizers
- Add oral or intravenous corticosteroids
- 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 or low molecular weight heparin
  - Identify and treat associated conditions (e.g., heart failure, arrhythmias)
  - Closely monitor condition of the patient

* Local resources need to be considered.

increasing readmission rates (90, 160–163). Use of a written action plan increases appropriate therapeutic interventions for an exacerbation, an effect that does not decrease health care resource use (164) (Evidence B) but may shorten recovery time (165).

For patients who are hypoxemic during an 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.

Home Management of Exacerbations

Nurse-administered home care (also known as "hospital-at-home" care) represents an effective and practical alternative to hospitalization in selected patients with exacerbations of COPD without acidotic respiratory failure (160, 161) (Evidence A). However, the exact criteria for this approach as opposed to hospital treatment remain uncertain and will vary by health care setting. Treatment recommendations are the same as for hospitalized patients.

Prevention of COPD Exacerbations

COPD exacerbations can often be prevented. Smoking cessation, influenza and pneumococcal vaccines, knowledge of current therapy including inhaler technique, and treatment with long-acting inhaled bronchodilators, with or without inhaled corticosteroids, and phosphodiesterase-4 inhibitors are all therapies that reduce the number of exacerbations and hospitalizations (75, 79, 81, 82, 166, 167). Early outpatient pulmonary rehabilitation after hospitalization for an exacerbation is safe and results in clinically significant improvements in exercise capacity and health status at 3 months (168). Patients should be encouraged to maintain physical activity, and anxiety, depression, and social problems should be discussed. Principal caregivers should be identified if the patient has a significant persisting disability.

6. COPD AND COMORBIDITIES

KEY POINTS

- COPD often coexists with other diseases (comorbidities) that may have a significant impact on prognosis.
- In general, the presence of comorbidities should not alter COPD treatment, and comorbidities should be treated as if the patient did not have COPD.
- Cardiovascular diseases are major comorbidities in COPD and probably both the most frequent and most important diseases coexisting with COPD.
- Osteoporosis and depression are also major comorbidities in COPD, are often underdiagnosed, and are associated with poor health status and prognosis.
- Lung cancer is frequently seen in patients with COPD and has been found to be the most frequent cause of death in patients with mild COPD.

Introduction

COPD often coexists with other diseases (comorbidities) that may have a significant impact on prognosis (42, 169–171). Comorbidities can occur at any COPD grade (50). Differential diagnosis may be difficult because comorbidities may mimic COPD

TABLE 8. INDICATIONS FOR ICU ADMISSION*

- Severe dyspnea that responds inadequately to initial emergency therapy
- Changes in mental status (confusion, lethargy, coma)
- Persistent or worsening hypoxemia ($Pa_{O_2} < 5.3$ kPa, 40 mm Hg) 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.

symptoms, for example, heart failure and lung cancer (breathlessness) or depression (fatigue and reduced physical activity). Below is a brief guide to management of COPD and some comorbidities in stable disease. The recommendations reported in this document may be insufficient for the management of all patients and cannot substitute for the use of guidelines for the management of each comorbidity. In general, the presence of comorbidities should not alter COPD treatment and comorbidities should be treated as if the patient did not have COPD.

Cardiovascular Diseases

Cardiovascular diseases are the most frequent and important disease coexisting with COPD (171, 172) and include four separate entities: ischemic heart disease, heart failure, atrial fibrillation, and hypertension.

Ischemic heart disease. The prevalence of ischemic heart disease (IHD) is increased in COPD, to some extent because of an unfavorable IHD risk profile in patients with COPD (173, 174). Yet, it is often underdiagnosed in patients with COPD (175).

TREATMENT OF IHD IN PATIENTS WITH COPD. IHD should be treated according to usual IHD guidelines, as there is no evidence that IHD should be treated differently in the presence of COPD than recommended in the usual IHD guidelines. This includes treatment with selective β_1-blockers, which are considered safe in patients with COPD (176), although this is based on relatively few short-term studies. The benefits of selective β_1-blockers when indicated in IHD are, however, considerably larger than the potential risks associated with treatment, even in patients with severe COPD.

TREATMENT OF COPD IN PATIENTS WITH IHD. COPD should be treated as usual, as there is no evidence that COPD should be treated differently in the presence of IHD (75, 79, 177). Although no large, long-term studies on COPD medications in patients with unstable angina have been published, it seems reasonable to avoid high doses of β-agonists.

Heart failure. Roughly 30% of patients with stable COPD will have some degree of heart failure (HF) (178), and worsening of HF is a significant differential diagnosis to an exacerbation of COPD. Conversely, approximately 30% of patients in a HF clinic have COPD (179), and comorbid COPD is often the cause of admission for acute HF (180)—with significant implications for prognosis as FEV_1 is a strong predictor of mortality in HF (181). HF, COPD, and asthma may be confused because of the common cardinal symptom of breathlessness.

TABLE 9. INDICATIONS FOR NONINVASIVE MECHANICAL VENTILATION

At least one of the following:
- Respiratory acidosis (arterial pH $\leqslant$ 7.35 and/or $Pa_{CO_2} \geqslant 6.0$ kPa, 45 mm Hg)
- Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces

TABLE 10. INDICATIONS FOR INVASIVE MECHANICAL VENTILATION

- Unable to tolerate NIV or NIV failure
- Respiratory or cardiac arrest
- Respiratory pauses with loss of consciousness or gasping for air
- Diminished consciousness, psychomotor agitation inadequately controlled by sedation
- Massive aspiration
- Persistent inability to remove respiratory secretions
- Heart rate < 50 min^{-1} with loss of alertness
- Severe hemodynamic instability without response to fluids and vasoactive drugs
- Severe ventricular arrhythmias
- Life-threatening hypoxemia in patients unable to tolerate NIV

Definition of abbreviation: NIV = noninvasive mechanical ventilation.

TREATMENT OF HF IN PATIENTS WITH COPD. HF should be treated according to usual HF guidelines as there is no evidence that HF should be treated differently in the presence of COPD. Treatment with selective β_1-blockers has a significant impact on survival in HF, and the presence of COPD is the most significant reason for patients not receiving sufficient therapy (182). However, as in IHD, treatment with selective β_1-blockers is considered safe for heart failure patients who also have COPD (176). The benefits of selective β_1-blocker treatment in HF clearly outweigh any potential risk associated with treatment even in patients with severe COPD.

TREATMENT OF COPD IN PATIENTS WITH HF. COPD should be treated as usual, as there is no direct evidence that COPD should be treated differently in the presence of HF. As for IHD, this statement is based on findings from large long-term studies in patients with HF and comorbid COPD (75, 79, 177). An observational study found an increased risk of death and hospital admission among patients with HF treated with inhaled β-agonists (183), possibly indicating a need for close follow-up of patients with severe HF who are on this treatment for COPD.

Atrial fibrillation. Atrial fibrillation (AF) is the most frequent cardiac arrhythmia, and patients with COPD have an increased incidence of AF (184). COPD with AF presents a challenge to clinicians because of the breathlessness and disability resulting from their coexistence.

TREATMENT OF AF IN PATIENTS WITH COPD. AF should be treated according to usual AF guidelines, as there is no evidence that patients with COPD should be treated differently. If β-blockers are used, β_1-selective drugs are preferred (see considerations under IHD and HF above).

TREATMENT OF COPD IN PATIENTS WITH AF. COPD should be treated as usual; however, there are no good data on the use of COPD medication in patients with AF, and these patients have often been excluded from clinical trials. It is a clinical impression that care should be taken when using high doses of β_2-agonists as this can make appropriate heart rate control difficult.

TABLE 11. CHECKLIST AT TIME OF DISCHARGE FROM HOSPITAL

- Reinforce smoking cessation measures
- Assure effective home maintenance of pharmacotherapy regimen
- Reassess inhaler technique
- Educate about maintenance regimen
- Give instruction regarding completion of steroid therapy and antibiotics, if prescribed
- Assess need for long-term oxygen therapy
- Assure follow-up visit in 4–6 wk
- Provide a management plan for comorbidities and their follow-up

TABLE 12. ITEMS TO ASSESS AT FOLLOW-UP VISIT 4–6 WEEKS AFTER DISCHARGE FROM HOSPITAL

- Smoking cessation measures
- Ability to cope in usual environment
- Measurement of FEV_1
- Inhaler technique
- Understanding of recommended treatment regimen
- Need for long-term oxygen therapy and/or home nebulizer
- Capacity to do physical activity and activities of daily living
- CAT or mMRC
- Status of comorbidities

Definition of abbreviations: CAT = Chronic Obstructive Pulmonary Disease Assessment Test; mMRC = Modified British Medical Research Council questionnaire on breathlessness.

Hypertension. Hypertension is likely to be the most frequently occurring comorbidity in COPD and has implications for prognosis (172).

TREATMENT OF HYPERTENSION IN PATIENTS WITH COPD. Hypertension should be treated according to usual hypertension guidelines, as there is no evidence that hypertension should be treated differently in the presence of COPD. The role of treatment with selective β-blockers is less prominent in recent hypertension guidelines; if these are used in patients with COPD, a selective β_1-blocker should be chosen.

TREATMENT OF COPD IN PATIENTS WITH HYPERTENSION. COPD should be treated as usual, as there is no direct evidence that COPD should be treated differently in the presence of hypertension.

Osteoporosis

Osteoporosis is a major comorbidity in COPD (171, 172), is often underdiagnosed (185), and is associated with poor health status and prognosis. Osteoporosis is more often associated with decreased body mass index (186) and low fat-free mass (187).

Treatment of osteoporosis in patients with COPD. Osteoporosis should be treated according to usual osteoporosis guidelines, as there is no evidence that osteoporosis should be treated differently in the presence of COPD.

Treatment of COPD in patients with osteoporosis. COPD should be treated as usual, as there is no evidence that stable COPD should be treated differently in the presence of osteoporosis. Inhaled triamcinolone was associated with increased loss of bone mass in the Lung Health Study II (188), whereas this was not the case for inhaled budesonide in the EUROSCOP trial (189) or for inhaled fluticasone propionate in the TORCH trial (190). An association between inhaled corticosteroids and fractures has been found in pharmacoepidemiological studies; however, these studies have not fully taken severity of COPD or exacerbations and their treatment into account.

Systemic corticosteroids significantly increase the risk of osteoporosis, and recurrent courses of systemic corticosteroids for COPD exacerbations should be avoided if possible.

Anxiety and Depression

Anxiety and depression are major comorbidities in COPD (191–194), and both are associated with a poor prognosis (193, 195). Both are often associated with younger age, female gender, smoking, lower FEV_1, cough, higher St. George's Respiratory Questionnaire score, and a history of cardiovascular diseases (191, 194).

Treatment of anxiety and depression in patients with COPD. Both disorders should be treated according to usual guidelines, as there is no evidence that anxiety and depression should be treated differently in the presence of COPD.

Treatment of COPD in patients with anxiety and depression. COPD should be treated as usual, as there is no evidence that stable COPD should be treated differently in the presence of anxiety and depression. The potential impact of pulmonary rehabilitation should be stressed, as studies have found that physical exercise has a beneficial effect on depression in general (196).

Lung Cancer

Lung cancer is frequently seen in patients with COPD and has been found to be the most frequent cause of death in patients with mild to moderate COPD (197).

Treatment of lung cancer in patients with COPD. Lung cancer should be treated according to usual lung cancer guidelines, as there is no evidence that lung cancer should be treated differently in the presence of COPD. However, often the reduced lung function of patients with COPD will be a factor limiting surgical intervention for lung cancer.

Treatment of COPD in patients with lung cancer. COPD should be treated as usual, as there is no evidence that stable COPD should be treated differently in the presence of lung cancer.

Infections

Serious infections, especially respiratory infections, are frequently seen in patients with COPD (198).

Treatment of infections in patients with COPD. Macrolide antibiotics increase the serum concentration of theophylline. Apart from this, there is no evidence that infections should be treated differently in the presence of COPD. However, repeat courses of antibiotics for exacerbations may increase the risk for the presence of antibiotic resistant bacterial strains, and more extensive cultures may be warranted.

Treatment of COPD in patients with infection. COPD should be treated as usual, as there is no evidence that stable COPD should be treated differently in the presence of infections. In patients who develop repeated pneumonias while on inhaled corticosteroids, this medication may be stopped to observe whether this medication could be the cause of repeated infections.

Metabolic Syndrome and Diabetes

Studies have shown that the metabolic syndrome and manifest diabetes are more frequent in COPD, and the latter is likely to impact on prognosis (169).

Treatment of diabetes in patients with COPD. Diabetes should be treated according to usual guidelines for diabetes, as there is no evidence that diabetes should be treated differently in the presence of COPD. However, for patients with severe COPD, it is not advised to aim for a body mass index less than 21 kg/m^2.

Treatment of COPD in patients with diabetes. COPD should be treated as usual, as there is no evidence that stable COPD should be treated differently in the presence of diabetes.

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