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

GOLD EXECUTIVE SUMMARY

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ABSTRACT

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 in order to avoid misdiagnosis and to ensure proper evaluation of severity of airflow limitation. The document highlights that the assessment of the COPD patient 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 split COPD patients into 4 categories - A, B, C and D. Non-pharmacologic 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 chapter in the document addresses management of comorbidities as well as COPD in the presence of comorbidities. The revised document also contains a new chapter 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.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem. In 2020, COPD is projected to rank fifth worldwide in term of burden of disease and third in term 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 e.g. 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 ten 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 3 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 towards 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 upon 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 towards 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 include:

1. This document has been considerably shortened in length by limiting Chapter 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. Chapter 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 co-morbidities. 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 under-diagnosis in adults younger than 45 years. The concept of staging has been abandoned as 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 chapter (Chapter 3) on therapeutic approaches has been added. This includes descriptive information on both pharmacologic and non-pharmacologic therapies, and identifying any adverse effects.

6. Management of COPD is presented in three chapters: Management of Stable COPD (Chapter 4); Management of COPD Exacerbations (Chapter 5); and COPD and Comorbidities (Chapter 6), covering both management of comorbidities in patients with COPD and of COPD in patients with comorbidities.

7. In Chapter 4, Management of Stable COPD, recommended approaches to both pharmacologic and non-pharmacologic 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. Chapter 5, Management of Exacerbations, presents a revised definition of a COPD exacerbation.

9. Chapter 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

- *Chronic Obstructive Pulmonary Disease (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

Chronic Obstructive Pulmonary Disease (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 under-recognition and under-diagnosis 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) has 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[10-12] and may be affected by other comorbid chronic conditions (e.g., cardiovascular disease, musculoskeletal impairment, 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. Under-recognition and under-diagnosis of COPD still affect the accuracy of mortality data[5,6] with COPD often listed as a *contributory* cause of death or omitted from the death certificate entirely[7]. 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[8]. 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 twelfth leading cause of Disability-Adjusted Life Year (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[8].

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[9-12].

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 or ETS) 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 ageing, bronchial hyperreactivity and socioeconomic status, among others, are listed in recent reviews and in the full document (www.goldcopd.org).

PATHOLOGY, PATHOGENESIS AND PATHOPHYSIOLOGY[±]

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.

[±] *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.*

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 auto-antigens 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 Air 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 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[41]. Other medical conditions (pneumonia, thrombo-embolism, 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/or 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 postbronchodilator $FEV_1/FVC < 0.70$ 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 COPD patients. 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/or 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 $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and thus of COPD.

The spirometric criterion for airflow limitation remains a post-bronchodilator fixed ratio of $FEV_1/FVC < 0.70$. 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 non-specialist clinician. While post-bronchodilator spirometry 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 disease on 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 COPD patients 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), in order 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; e.g., the Clinical COPD Questionnaire (CCQ), 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 in order to minimize variability. Worsening airflow limitation is associated with an increasing prevalence of exacerbations (see below) and risk of death.

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	$FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4:	Very Severe	$FEV_1 < 30\%$ predicted

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 (2 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

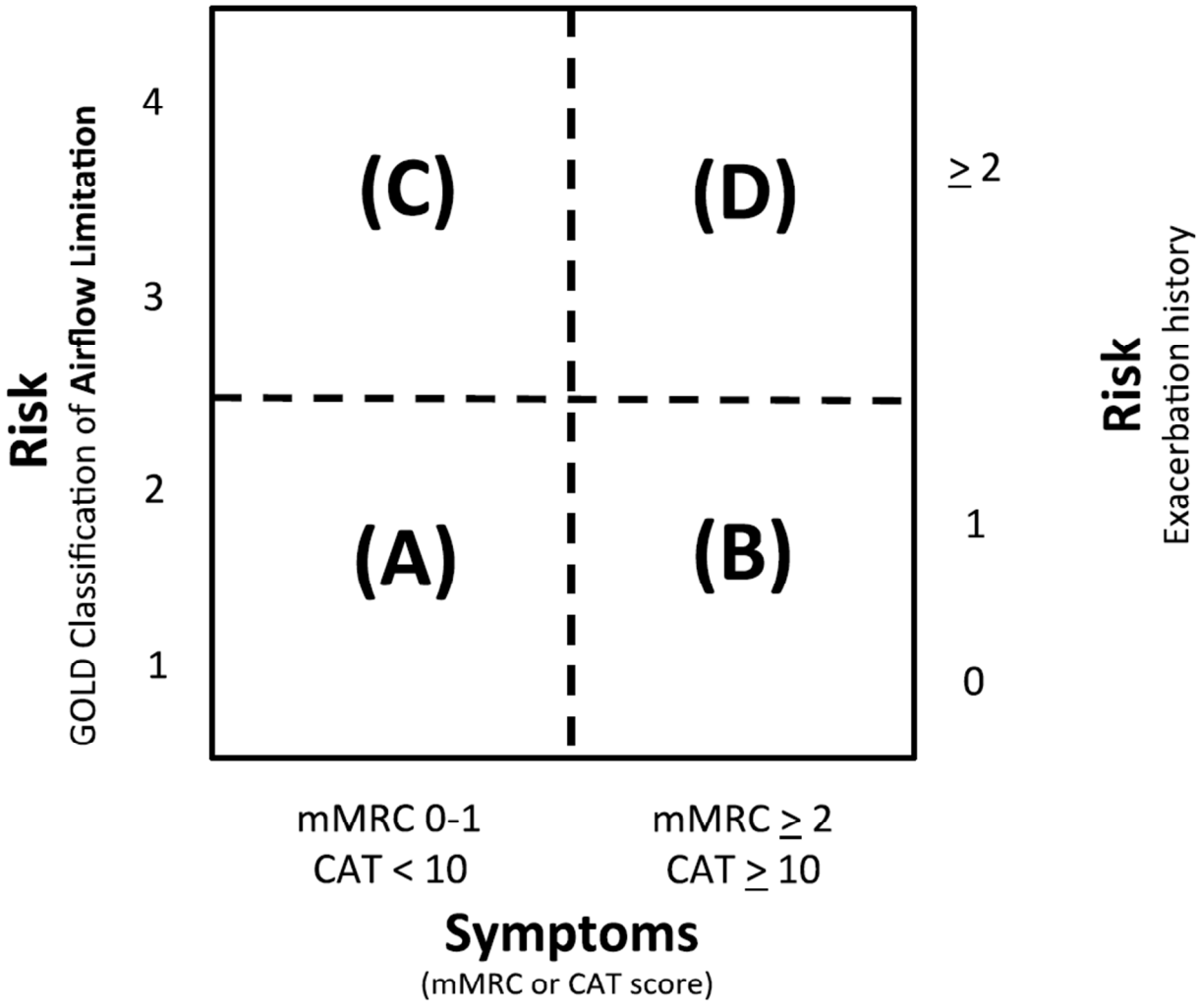
intervention including a short course of antibiotic and/or oral steroids, and severe when exacerbations of respiratory symptoms require hospitalization.

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 ≥ 2 or a CAT score ≥ 10 indicating a high level of symptoms. These cut-offs 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**.

Figure 1. Combined COPD Assessment

*When assessing risk, choose the **highest** risk according to GOLD spirometric grade or exacerbation history*



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 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 1-2 indicate Low Risk, while GOLD 3-4 indicate High Risk); or (2) assess the number of exacerbations the patient has had within the previous 12 months (0 or 1 indicates Low Risk, while 2 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 ≥ 2 or CAT score ≥ 10

Patient Group C – High Risk, Less Symptoms
GOLD 3-4 (Severe or Very Severe airflow limitation)
and/or ≥ 2 exacerbations per year / ≥ 1 hospitalised exacerbation per year *and*
mMRC grade < 2 or CAT score < 10

Patient Group D – High Risk, More Symptoms
GOLD 3-4 (Severe or Very Severe airflow limitation)
and/or ≥ 2 exacerbations per year / ≥ 1 hospitalised exacerbation per year *and*
mMRC grade ≥ 2 or CAT score ≥ 10

This approach, combined with an assessment of potential comorbidities, reflects the complexity of COPD better than the uni-dimensional analysis of airflow limitation previously used for staging the disease and forms the basis of the guide to individualized management provided in Chapter 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. COPD patients 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 < 35% predicted or with clinical signs suggestive of respiratory failure or right heart failure. If peripheral saturation is < 92% arterial blood gases should be assessed[58].

Alpha-1 Antitrypsin Deficiency Screening. The World Health Organization recommends that COPD patients from areas with a particularly high prevalence of alpha-1 antitrypsin deficiency should be screened for this genetic disorder[59]. The typical patient tends to present at a younger age (< 45 years) with lower lobe emphysema. A serum concentration of alpha-1 antitrypsin below 15-20% of the normal value is highly suggestive of homozygous alpha-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[64,65,66].

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 anti-inflammatory drugs and other treatments need to be individualized. Other potential diagnoses are usually easier to distinguish from COPD (**Table 2**).

Table 2. COPD and its Differential Diagnoses	
Diagnosis	**Suggestive Features**
COPD	Onset in mid-life. 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.
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.	

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 COPD patient; 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 chapter 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 COPD patients 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 $beta_2$-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 $FEV_1 < 50\%$ 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 COPD patients.
- 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.

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 COPD patients because they commonly have comorbidities that also need to be carefully identified and treated.

Table 3. Goals for Treatment of Stable COPD

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

} REDUCE SYMPTOMS

and

- Prevent disease progression
- Prevent exacerbations
- Reduce mortality

} REDUCE RISK

IDENTIFY AND REDUCE EXPOSURE TO RISK FACTORS

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.

NON-PHARMACOLOGIC 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 COPD patients 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 COPD patients depend on local policies, availability, and affordability.

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

Table 4. Non-Pharmacologic 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

PHARMACOLOGIC TREATMENT

The classes of medications commonly used in treating COPD are shown in **Table 1** in the online supplement and a detailed description of the effects of these medications is given in Chapter 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.**

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 $beta_2$-agonist prn	Long-acting anticholinergic *or* Long-acting $beta_2$-agonist *or* Short-acting anticholinergic + short-acting $beta_2$-agonist	Theophylline
B	Long-acting anticholinergic *or* Long-acting $beta_2$-agonist	Long-acting anticholinergic and long-acting $beta_2$-agonist	Short-acting anticholinergic and*/or* Short-acting $beta_2$-agonist Theophylline
C	Inhaled corticosteroid + long-acting $beta_2$-agonist *or* Long-acting anticholinergic	Long-acting anticholinergic and long-acting $beta_2$-agonist	Phosphodiesterase-4 inhibitor Short-acting anticholinergic and*/or* Short-acting $beta_2$-agonist Theophylline
D	Inhaled corticosteroid + long-acting $beta_2$-agonist *or* Long-acting anticholinergic	Inhaled corticosteroid and long-acting anticholinergic *or* Inhaled corticosteroid + long-acting $beta_2$-agonist and long-acting anticholinergic *or* Inhaled corticosteroid + long-acting $beta_2$-agonist and phosphodiesterase-4 inhibitor *or* Long-acting anticholinergic and long-acting $beta_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine Short-acting anticholinergic and*/or* Short-acting $beta_2$-agonist Theophylline

*Medications in each box 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 Second Choice columns.

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 $FEV_1 > 80\%$ 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 patients have more significant symptoms but still a low risk of exacerbations. Long-acting bronchodilators are superior to short-acting bronchodilators (taken as needed, or prn) 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. Alternative choices include short-acting bronchodilators and theophylline, the latter of which can be used if inhaled bronchodilators are unavailable or unaffordable.

Group C patients have few symptoms but a high risk of exacerbations. As first choice a combination of inhaled corticosteroid/long-acting beta$_2$-agonist or a long-acting anticholinergic 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 beta$_2$-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 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 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 beta$_2$-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 phosphodiesterase4-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 beta$_2$-agonists and anticholinergics, long-acting formulations are preferred over short-acting formulations (**Evidence A**).
- The combined use of short- or long-acting beta$_2$-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 < 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 beta$_2$-agonists (**Evidence A**).
- The phosphodiesterase-4 inhibitor, roflumilast, may also be used to reduce exacerbations for patients with chronic bronchitis, FEV_1 < 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:

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 COPD Assessment Test (CAT)[87] can be performed every two to three 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. 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. 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 Chapter 6).

Surgery in the COPD Patient

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, COPD patients 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 DL_{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 VO_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 $beta_2$-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 (PaO_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)[106-108 109-111 112]. 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 develop 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 (PaO_2 < 8.0 kPa (60 mmHg) with or without $PaCO_2$ > 6.7 kPa (50 mmHg) 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]. *Hemophilus 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 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)**.**

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

Local resources need to be considered.

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 beta$_2$-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.*

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 beta$_2$-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 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 (PaO_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]. Nebulised 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, e.g., 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 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 COPD patients with exacerbations requiring mechanical ventilation (invasive or noninvasive) indicated that not giving antibiotics was associated with increased mortality and a greater incidence of secondary nosocomial pneumonia[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 30-60 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 intensive care unit (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 ventilation (by oro-tracheal tube or tracheostomy)**.** Respiratory stimulants are not recommended for acute respiratory failure[121].

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 (PaO_2 < 5.3 kPa, 40 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.*

<u>*Noninvasive mechanical ventilation*</u>. Noninvasive mechanical ventilation (NIV) has been studied in several randomized controlled trials in acute respiratory failure, consistently providing success rates of 80-85%[144-147]. NIV improves respiratory acidosis (increases pH and decreases $PaCO_2$), 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[144].

<u>*Invasive mechanical ventilation*</u>. The indications for initiating invasive mechanical ventilation during an exacerbation are shown in **Table 10**, and include failure of an initial trial of NIV[151]. 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 non-invasive ventilation[151].

Table 9. Indications for Noninvasive Mechanical Ventilation[90,146,152,153]

At least one of the following

- Respiratory acidosis (arterial pH ≤ 7.35 and/or $PaCO_2$ ≥ 6.0 kPa, 45 mmHg)
- 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

The use of invasive ventilation in very severe COPD patients is influenced by the likely reversibility of the precipitating event, 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 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[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 following admission for an exacerbation[159]. In the hospital prior to discharge, patients should start long-

acting bronchodilators, either beta$_2$-agonists and/or anticholinergics 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.

Table 11. Checklist of Items to Assess at Time of Discharge from Hospital
• Reinforce smoking cessation measures
• Assurance of effective home maintenance of pharmacotherapy regimen
• Reassessment of inhaler technique
• Education regarding role of maintenance regimen
• Instruction regarding completion of steroid therapy and antibiotics, if prescribed
• Assess need for long-term oxygen therapy
• Assure follow-up visit in 4-6 weeks
• 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
• Reinforce smoking cessation measures
• Ability to cope in usual environment
• Measurement of FEV_1
• Reassessment of inhaler technique
• Understanding of recommended treatment regimen
• Reassess 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

Home visits by a community nurse may permit earlier discharge of patients hospitalized with an exacerbation without 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 utilization[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[469,470] (**Evidence A**). However, the exact criteria for this

approach as opposed to hospital treatment remain uncertain and will vary by health care setting[160,161]. 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 under-diagnosed, 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.

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 since comorbidities may mimic COPD symptoms; e.g., 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 (CVD)

CVD 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 (IHD*).* The prevalence of IHD is increased in COPD, to some extent because of an unfavourable IHD risk profile in COPD patients[173,174]. Yet, it is often under-diagnosed in COPD patients[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 $beta_1$-blockers, which are considered safe in COPD patients[176] although this is based on relatively few short-term studies. The benefits of selective $beta_1$-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 beta-agonists.

Heart Failure (HF). Roughly 30% of patients with stable COPD will have some degree of 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.

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 $beta_1$-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 $beta_1$-blockers is considered safe for heart failure patients who also have COPD[176]. The benefits of selective $beta_1$-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 beta-agonists[183], possibly indicating a need for close follow-up of patients with severe HF who are on this treatment for COPD.

Atrial Fibrillation (AF*).* Atrial fibrillation is the most frequent cardiac arrhythmia and COPD patients 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 beta-blockers are used, $beta_1$-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 $beta_2$-agonists as this can make appropriate heart rate control difficult.

Hypertension: Hypertension is likely to be the most frequently occurring comorbity 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 beta-blockers is less prominent in recent hypertension guidelines; if these are used in patients with COPD, a selective $beta_1$-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 under-diagnosed[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 since 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 pharmaco-epidemiological 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 SGRQ 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-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 COPD patients 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 in order 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 (BMI) 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.

REFERENCES

1. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet 2009;374:733-43.
2. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J 2006;28:523-32.
3. van den Boom G, van Schayck CP, van Mollen MP, et al. Active detection of chronic obstructive pulmonary disease and asthma in the general population. Results and economic consequences of the DIMCA program. Am J Respir Crit Care Med 1998;158:1730-8.
4. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 2007; 370: 741-50. Lancet 2007;370:741-50.
5. Pena VS, Miravitlles M, Gabriel R, et al. Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. Chest 2000;118:981-9.
6. Talamo C, de Oca MM, Halbert R, et al. Diagnostic labeling of COPD in five Latin American cities. Chest 2007;131:60-7.
7. Jensen HH, Godtfredsen N, Lange P, Vestbo J. Potential misclassification of causes of death from COPD in a Danish population study. Eur Respir J 2006;28:781-5.
8. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.
9. Behrendt CE. Mild and moderate-to-severe COPD in non-smokers. Distinct demographic profiles. Chest 2005;128:1239-44.
10. Celli BR, Halbert RJ, Nordyke RJ, Schan B. Airway obstruction in never smokers: results from the Third National Health and Nutrition Examination Survey. Am J Med 2005;118:1364-72.
11. Eisner MD, Anthonisen N, Coultas D, et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:693-718.
12. Lamprecht B, McBurnie MA, Vollmer WM, et al. COPD in never smokers: results from the population-based burden of obstructive lung disease study. Chest 2011;139:752-63.
13. Kohansal R, Martinez-Camblor P, Agusti A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. Am J Respir Crit Care Med 2009;180:3-10.
14. Raad D, Gaddam S, Schunemann HJ, et al. Effects of water-pipe smoking on lung function: a systematic review and meta-analysis. Chest 2011;139:764-74.
15. Tan WC, Lo C, Jong A, et al. Marijuana and chronic obstructive lung disease: a population-based study. CMAJ 2009;180:814-20.
16. WHO Study Group on Tobacco Product Regulation. Water Pipe smoking: health effects, research needs, and recommended actions by regulators. World Health Organization Publication. ISBN 92 4 159385. 2005.
17. Tetrault JM, Crothers K, Moore BA, Mehra R, Concato J, Fiellin DA. Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. Arch Intern Med 2007;167:221-8.
18. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General, Department of Health and Human Services. Washington, DC, US; 2006.

19. Eisner MD, Balmes J, Katz BP, Trupin L, Yelin E, Blanc P. Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. Environ Health Perspect 2005;4:7-15.
20. Dayal HH, Khuder S, Sharrar R, Trieff N. Passive smoking in obstructive respiratory disease in an industrialized urban population. Environ Res 1994;65:161-71.
21. Leuenberger P, Schwartz J, Ackermann-Liebrich U, et al. Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. Am J Respir Crit Care Med 1994;150:1222-8.
22. Holt PG. Immune and inflammatory function in cigarette smokers. Thorax 1987;42:241-9.
23. Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy. Effects on lung function during the first 18 months of life. Am J Respir Crit Care Med 1995;152:977-83.
24. Trupin L, Earnest G, San Pedro M, et al. The occupational burden of chronic obstructive pulmonary disease. Eur Respir J 2003;22:462-9.
25. Matheson MC, Benke G, Raven J, et al. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. Thorax 2005;60:645-51.
26. Hnizdo E, Sullivan PA, Bang KM, Wagner G. Airflow obstruction attributable to work in industry and occupation among U.S. race/ethnic groups: a study of NHANES III data. Am J Ind Med 2004;46:126-35.
27. Boman C, Forsberg B, Sandstrom T. Shedding new light on wood smoke: a risk factor for respiratory health. Eur Respir J 2006;27:446-7.
28. Ezzati M. Indoor air pollution and health in developing countries. Lancet 2005;366:104-6.
29. Mishra V, Dai X, Smith KR, Mika L. Maternal exposure to biomass smoke and reduced birth weight in Zimbabwe. Ann Epidemiol 2004;14:740-7.
30. Oroczo-Levi M, Garcia -Aymerich J, Villar J, Ramirez-Sarmiento A, Anto JM, Gea J. Wood smoke exposure and risk of chronic obstructive pulmonary disease. Eur Respir J 2006;27:542-6.
31. Sezer H, Akkurt I, Guler N, Marakoglu K, Berk S. A case-control study on the effect of exposure to different substances on the development of COPD. Ann Epidemiol 2006;16:59-62.
32. Smith KR, Mehta S, Maeusezahl-Feuz M. Indoor air-pollution from household solid fuel use. In: Ezzati, M., Lopez, A. D., Rodgers, M., Murray, C. J., eds. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Geneva: World Health Organization; 2004.
33. Warwick H, Doig A. Smoke the killer in the kitchen: Indoor air pollution in developing countries. ITDG Publishing, 103-105 Southampton Row, London WC1B HLD, UK 2004:URL: http://www.itdgpublishing.org.uk.
34. Torres-Duque C, Maldonado D, Perez-Padilla R, Ezzati M, Viegi G. Biomass fuels and respiratory diseases: a review of the evidence. Pro Am Thorac Soc 2008;5:577-90.
35. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet 2004;364:709-21.
36. Cosio MG, Saetta M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. N Engl J Med 2009;360:2445-54.
37. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 2004;350:2645-53.

38. Rodriguez-Roisin R, Drakulovic M, Rodriguez DA, Roca J, Barbera JA, Wagner PD. Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. J Appl Physiol 2009;106:1902-8.
39. Peinado VI, Pizarro S, Barbera JA. Pulmonary vascular involvement in COPD. Chest 2008;134:808-14.
40. Parker CM, Voduc N, Aaron SD, Webb KA, O'Donnell DE. Physiological changes during symptom recovery from moderate exacerbations of COPD. Eur Respir J 2005;26:420-8.
41. Barbera JA, Roca J, Ferrer A, et al. Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. Eur Respir J 1997;10:1285-91.
42. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009;33:1165-85.
43. Barr RG, Bluemke DA, Ahmed FS, et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med 2010;362:217-27.
44. Kesten S, Chapman KR. Physician perceptions and management of COPD. Chest 1993;104:254-8.
45. Loveridge B, West P, Kryger MH, Anthonisen NR. Alteration in breathing pattern with progression of chronic obstructive pulmonary disease. Am Rev Respir Dis 1986;134:930-4.
46. Jackson H, Hubbard R. Detecting chronic obstructive pulmonary disease using peak flow rate: cross sectional survey. BMJ 2003;327:653-4.
47. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. Chest 2000;117:398S-401S.
48. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. Eur Respir J Suppl 2003;41:46s-53s.
49. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. Eur Respir J 2007;29:1224-38.
50. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res 2010;11:122.
51. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363:1128-38.
52. Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Ventilatory function and chronic mucus hypersecretion as predictors of death from lung cancer. Am Rev Respir Dis 1990;141:613-7.
53. Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study. Ann Intern Med 1986;105:503-7.
54. Stavem K, Aaser E, Sandvik L, et al. Lung function, smoking and mortality in a 26-year follow-up of healthy middle-aged males. Eur Respir J 2005;25:618-25.
55. Tockman MS, Anthonisen NR, Wright EC, Donithan MG. Airways obstruction and the risk for lung cancer. Ann Intern Med 1987;106:512-8.
56. Soler-Cataluna JJ, Rodriguez-Roisin R. Frequent chronic obstructive pulmonary disease exacerbators: how much real, how much fictitious? COPD 2010;7:276-84.
57. Garcia-Aymerich J, Serra Pons I, Mannino DM, Maas AK, Miller DP, Davis KJ. Lung function impairment, COPD hospitalisations and subsequent mortality. Thorax 2011;66:585-90.
58. Kelly AM, McAlpine R, Kyle E. How accurate are pulse oximeters in patients with acute exacerbations of chronic obstructive airways disease? Respir Med 2001;95:336-40.
59. Alpha-1 Antitrypsin Deficiency: Memorandum from a WHO Meeting. Bulletin of the World Health Organization 1997;75:397-415.

60. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J 2004;23:28-33.
61. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. Am J Respir Crit Care Med 2003;167:544-9.
62. Jones PW. Health status measurement in chronic obstructive pulmonary disease. Thorax 2001;56:880-7.
63. Waschki B KA, Holz O, Muller KC, Meyer T, Watz H, Magnussen H. Physical activity is the strongest predictor of all-cause mortality in patients with chronic obstructive pulmonary disease: a prospective cohort study. Chest 2011.
64. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005-12.
65. Jones RC, Donaldson GC, Chavannes NH, et al. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE Index. Am J Respir Crit Care Med 2009;180:1189-95.
66. Puhan MA, Garcia-Aymerich J, Frey M, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. Lancet 2009;374:704-11.
67. Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. Am J Respir Crit Care Med 1999;160:1248-53.
68. COMBIVENT Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. Chest 1994;105:1411-9.
69. Friedman M, Serby CW, Menjoge SS, Wilson JD, Hilleman DE, Witek TJ, Jr. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. Chest 1999;115:635-41.
70. Appleton S, Poole P, Smith B, Veale A, Lasserson TJ, Chan MM. Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. Cochrane database of systematic reviews 2006;3:CD001104.
71. Barr RG, Bourbeau J, Camargo CA, Ram FS. Inhaled tiotropium for stable chronic obstructive pulmonary disease. Cochrane database of systematic reviews 2005:CD002876.
72. Tashkin DP, Pearle J, Iezzoni D, Varghese ST. Formoterol and tiotropium compared with tiotropium alone for treatment of COPD. COPD 2009;6:17-25.
73. van Noord JA, Aumann JL, Janssens E, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Respir J 2005;26:214-22.
74. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003;361:449-56.
75. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775-89.
76. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 2003;22:912-9.

77. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med 2005;143:317-26.
78. Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003;21:74-81.
79. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008;359:1543-54.
80. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008;177:19-26.
81. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 2009;374:685-94.
82. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet 2009;374:695-703.
83. Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180:741-50.
84. Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2007;146:545-55.
85. Singh D, Brooks J, Hagan G, Cahn A, O'Connor BJ. Superiority of "triple" therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. Thorax 2008;63:592-8.
86. Zheng JP, Kang J, Huang SG, et al. Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. Lancet 2008;371:2013-8.
87. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J 2009;34:648-54.
88. Kessler R, Stahl E, Vogelmeier C, et al. Patient understanding, detection, and experience of COPD exacerbations: an observational, interview-based study. Chest 2006;130:133-42.
89. Mazzone PJ. Preoperative evaluation of the lung cancer resection candidate. Expert Rev Respir Med 2010;4:97-113.
90. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932-46.
91. Schuurmans MM, Diacon AH, Bolliger CT. Functional evaluation before lung resection. Clin Chest Med 2002;23:159-72.
92. Smetana GW. Preoperative pulmonary evaluation. N Engl J Med 1999;340:937-44.
93. Trayner E, Jr., Celli BR. Postoperative pulmonary complications. Med Clin North Am 2001;85:1129-39.
94. Brunelli A, Charloux A, Bolliger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J 2009;34:17-41.

95. Colice GL, Shafazand S, Griffin JP, Keenan R, Bolliger CT. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest 2007;132:161S-77S.
96. Spencer S, Calverley PM, Burge PS, Jones PW. Impact of preventing exacerbations on deterioration of health status in COPD. Eur Respir J 2004;23:698-702.
97. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;161:1608-13.
98. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002;57:847-52.
99. Kanner RE, Anthonisen NR, Connett JE. Lower respiratory illnesses promote FEV(1) decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: results from the lung health study. Am J Respir Crit Care Med 2001;164:358-64.
100. Wouters EF. The burden of COPD in The Netherlands: results from the Confronting COPD survey. Respir Med 2003;97 Suppl C:S51-9.
101. Connors AF, Jr., Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 1996;154:959-67.
102. Gunen H, Hacievliyagil SS, Kosar F, et al. Factors affecting survival of hospitalised patients with COPD. Eur Respir J 2005;26:234-41.
103. Kong GK, Belman MJ, Weingarten S. Reducing length of stay for patients hospitalized with exacerbation of COPD by using a practice guideline. Chest 1997;111:89-94.
104. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA 1995;274:1852-7.
105. Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;169:1298-303.
106. Monso E, Rosell A, Bonet G, et al. Risk factors for lower airway bacterial colonization in chronic bronchitis. Eur Respir J 1999;13:338-42.
107. Pela R, Marchesani F, Agostinelli C, et al. Airways microbial flora in COPD patients in stable clinical conditions and during exacerbations: a bronchoscopic investigation. Monaldi Arch Chest Dis 1998;53:262-7.
108. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med 2008;359:2355-65.
109. Fagon JY, Chastre J, Trouillet JL, et al. Characterization of distal bronchial microflora during acute exacerbation of chronic bronchitis. Use of the protected specimen brush technique in 54 mechanically ventilated patients. Am Rev Respir Dis 1990;142:1004-8.
110. Monso E, Ruiz J, Rosell A, et al. Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. Am J Respir Crit Care Med 1995;152:1316-20.
111. Soler N, Torres A, Ewig S, et al. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. Am J Respir Crit Care Med 1998;157:1498-505.

112. Sethi S, Wrona C, Grant BJ, Murphy TF. Strain-specific immune response to Haemophilus influenzae in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;169:448-53.
113. Ling SH, van Eeden SF. Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2009;4:233-43.
114. Sint T, Donohue JF, Ghio AJ. Ambient air pollution particles and the acute exacerbation of chronic obstructive pulmonary disease. Inhalation toxicology 2008;20:25-9.
115. Peacock JL, Anderson HR, Bremner SA, et al. Outdoor air pollution and respiratory health in patients with COPD. Thorax 2011;66:591-6.
116. Adams S, J. M, Luther M. Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of chronic obstructive pulmonary disease. Chest 2000;117:1345-52.
117. Emerman CL, Connors AF, Lukens TW, Effron D, May ME. Relationship between arterial blood gases and spirometry in acute exacerbations of chronic obstructive pulmonary disease. Ann Emerg Med 1989;18:523-7.
118. Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. Chest 2000;117:1638-45.
119. Martinez FJ, Han MK, Flaherty K, Curtis J. Role of infection and antimicrobial therapy in acute exacerbations of chronic obstructive pulmonary disease. Expert Rev Anti Infect Ther 2006;4:101-24.
120. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med 2008;178:332-8.
121. National Institute for Clinical Excellence (NICE). Chronic obstructive pulmonary disease. Management of chronic obstructive pulmonary disease in adults in primary and secondary care. http://guidanceniceorguk/CG101/Guidance/pdf/English 2010.
122. Turner MO, Patel A, Ginsburg S, FitzGerald JM. Bronchodilator delivery in acute airflow obstruction. A meta-analysis. Arch Intern Med 1997;157:1736-44.
123. Barbera JA, Reyes A, Roca J, Montserrat JM, Wagner PD, Rodriguez-Roisin R. Effect of intravenously administered aminophylline on ventilation/perfusion inequality during recovery from exacerbations of chronic obstructive pulmonary disease. Am Rev Respir Dis 1992;145:1328-33.
124. Emerman CL, Connors AF, Lukens TW, May ME, Effron D. Theophylline concentrations in patients with acute exacerbation of COPD. Am J Emerg Med 1990;8:289-92.
125. Lloberes P, Ramis L, Montserrat JM, et al. Effect of three different bronchodilators during an exacerbation of chronic obstructive pulmonary disease. Eur Respir J 1988;1:536-9.
126. Mahon JL, Laupacis A, Hodder RV, et al. Theophylline for irreversible chronic airflow limitation: a randomized study comparing n of 1 trials to standard practice. Chest 1999;115:38-48.
127. Murciano D, Aubier M, Lecocguic Y, Pariente R. Effects of theophylline on diaphragmatic strength and fatigue in patients with chronic obstructive pulmonary disease. N Engl J Med 1984;311:349-53.
128. Barr RG, Rowe BH, Camargo CA, Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease: meta-analysis of randomised trials. BMJ 2003;327:643.

129. Duffy N, Walker P, Diamantea F, Calverley PM, Davies L. Intravenous aminophylline in patients admitted to hospital with non-acidotic exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Thorax 2005;60:713-7.
130. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Lancet 1999;354:456-60.
131. Maltais F, Ostinelli J, Bourbeau J, et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Am J Respir Crit Care Med 2002;165:698-703.
132. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. N Engl J Med 1999;340:1941-7.
133. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. Am J Respir Crit Care Med 1996;154:407-12.
134. Aaron SD, Vandemheen KL, Hebert P, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. N Engl J Med 2003;348:2618-25.
135. de Jong YP, Uil SM, Grotjohan HP, Postma DS, Kerstjens HA, van den Berg JW. Oral or IV prednisolone in the treatment of COPD exacerbations: a randomized, controlled, double-blind study. Chest 2007;132:1741-7.
136. Gunen H, Hacievliyagil SS, Yetkin O, Gulbas G, Mutlu LC, In E. The role of nebulised budesonide in the treatment of exacerbations of COPD. Eur Respir J 2007;29:660-7.
137. Stallberg B, Selroos O, Vogelmeier C, Andersson E, Ekstrom T, Larsson K. Budesonide/formoterol as effective as prednisolone plus formoterol in acute exacerbations of COPD. A double-blind, randomised, non-inferiority, parallel-group, multicentre study. Respir Res 2009;10:11.
138. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006:CD004403.
139. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. Chest 2008;133:756-66.
140. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet 2004;363:600-7.
141. Nouira S, Marghli S, Belghith M, Besbes L, Elatrous S, Abroug F. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo- controlled trial. Lancet 2001;358:2020-5.
142. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J 2005;26:1138-80.
143. Austin MA, Wills KE, Blizzard L, Walters EH, Wood-Baker R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. BMJ 2010;341:c5462.
144. Consensus conference report. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation. Chest 1999;116:521-34.

145. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 1995;333:817-22.
146. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ 2003;326:185.
147. Meyer TJ, Hill NS. Noninvasive positive pressure ventilation to treat respiratory failure. Ann Intern Med 1994;120:760-70.
148. Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet 1993;341:1555-7.
149. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 1995;151:1799-806.
150. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet 2000;355:1931-5.
151. Conti G, Antonelli M, Navalesi P, et al. Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. Intensive Care Med 2002;28:1701-7.
152. International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 2001;163(1):283-91.
153. Esteban A, Anzueto A, Alia I, et al. How is mechanical ventilation employed in the intensive care unit? An international utilization review. Am J Respir Crit Care Med 2000;161:1450-8.
154. Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002;287:345-55.
155. Wildman MJ, Sanderson C, Groves J, et al. Implications of prognostic pessimism in patients with chronic obstructive pulmonary disease (COPD) or asthma admitted to intensive care in the UK within the COPD and asthma outcome study (CAOS): multicentre observational cohort study. BMJ 2007;335:1132.
156. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:158-64.
157. Mushlin AI, Black ER, Connolly CA, Buonaccorso KM, Eberly SW. The necessary length of hospital stay for chronic pulmonary disease. JAMA 1991;266:80-3.
158. Regueiro CR, Hamel MB, Davis RB, Desbiens N, Connors AF, Jr., Phillips RS. A comparison of generalist and pulmonologist care for patients hospitalized with severe chronic obstructive pulmonary disease: resource intensity, hospital costs, and survival. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. Am J Med 1998;105:366-72.
159. Price LC, Lowe D, Hosker HS, Anstey K, Pearson MG, Roberts CM. UK National COPD Audit 2003: Impact of hospital resources and organisation of care on patient outcome following admission for acute COPD exacerbation. Thorax 2006;61:837-42.
160. Cotton MM, Bucknall CE, Dagg KD, et al. Early discharge for patients with exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Thorax 2000;55:902-6.

161. Hermiz O, Comino E, Marks G, Daffurn K, Wilson S, Harris M. Randomised controlled trial of home based care of patients with chronic obstructive pulmonary disease. BMJ 2002;325:938.
162. Hughes SL, Weaver FM, Giobbie-Hurder A, et al. Effectiveness of team-managed home-based primary care: a randomized multicenter trial. JAMA 2000;284:2877-85.
163. Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995;8:1398-420.
164. Wood-Baker R, McGlone S, Venn A, Walters EH. Written action plans in chronic obstructive pulmonary disease increase appropriate treatment for acute exacerbations. Respirology 2006;11:619-26.
165. Bischoff EW, Hamd DH, Sedeno M, et al. Effects of written action plan adherence on COPD exacerbation recovery. Thorax 2011;66:26-31.
166. Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. Lancet 2009;374:1171-8.
167. Jenkins CR, Jones PW, Calverley PM, et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respir Res 2009;10:59.
168. Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. BMJ 2004;329:1209.
169. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J 2008;32:962-9.
170. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: Role of comorbidities. Eur Respir J 2006;28:1245-57.
171. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest 2005;128:2099-107.
172. Fabbri LM, Luppi F, Beghe B, Rabe KF. Complex chronic comorbidities of COPD. Eur Respir J 2008;31:204-12.
173. Johnston AK, Mannino DM, Hagan GW, Davis KJ, Kiri VA. Relationship between lung function impairment and incidence or recurrence of cardiovascular events in a middle-aged cohort. Thorax 2008;63:599-605.
174. Lange P, Mogelvang R, Marott JL, Vestbo J, Jensen JS. Cardiovascular morbidity in COPD: A study of the general population. COPD 2010;7:5-10.
175. Brekke PH, Omland T, Smith P, Soyseth V. Underdiagnosis of myocardial infarction in COPD - Cardiac Infarction Injury Score (CIIS) in patients hospitalised for COPD exacerbation. Respir Med 2008;102:1243-7.
176. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. Cochrane database of systematic reviews 2005:CD003566.
177. Calverley PM, Anderson JA, Celli B, et al. Cardiovascular events in patients with COPD: TORCH study results. Thorax 2010;65:719-25.
178. Rutten FH, Cramer MJ, Grobbee DE, et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J 2005;26:1887-94.
179. Hawkins NM, Huang Z, Pieper KS, et al. Chronic obstructive pulmonary disease is an independent predictor of death but not atherosclerotic events in patients with myocardial

infarction: analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). Eur J Heart Fail 2009;11:292-8.
180. Iversen KK, Kjaergaard J, Akkan D, et al. Chronic obstructive pulmonary disease in patients admitted with heart failure. J Intern Med 2008;264:361-9.
181. Iversen KK, Kjaergaard J, Akkan D, et al. The prognostic importance of lung function in patients admitted with heart failure. Eur J Heart Fail 2010;12:685-91.
182. Hawkins NM, Jhund PS, Simpson CR, et al. Primary care burden and treatment of patients with heart failure and chronic obstructive pulmonary disease in Scotland. Eur J Heart Fail 2010;12:17-24.
183. Au DH, Udris EM, Fan VS, Curtis JR, McDonell MB, Fihn SD. Risk of mortality and heart failure exacerbations associated with inhaled beta-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. Chest 2003;123:1964-9.
184. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Eur Respir J 2003;21:1012-6.
185. Madsen H, Brixen K, Hallas J. Screening, prevention and treatment of osteoporosis in patients with chronic obstructive pulmonary disease - a population-based database study. Clin Respir J 2010;4:22-9.
186. Bolton CE, Cannings-John R, Edwards PH, et al. What community measurements can be used to predict bone disease in patients with COPD? Respir Med 2008;102:651-7.
187. Bolton CE, Ionescu AA, Shiels KM, et al. Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;170:1286-93.
188. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease: Lung Health Study II. N Engl J Med 2000;343:1902-9.
189. Pauwels RA, Lofdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med 1999;340:1948-53.
190. Ferguson GT, Calverley PM, Anderson JA, et al. Prevalence and progression of osteoporosis in patients with COPD: results from the TOwards a Revolution in COPD Health study. Chest 2009;136:1456-65.
191. Hanania NA, Mullerova H, Locantore NW, et al. Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort. Am J Respir Crit Care Med 2011;183:604-11.
192. Kunik ME, Roundy K, Veazey C, et al. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. Chest 2005;127:1205-11.
193. Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med 2007;167:60-7.
194. Maurer J, Rebbapragada V, Borson S, et al. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. Chest 2008;134:43S-56S.
195. Eisner MD, Blanc PD, Yelin EH, et al. Influence of anxiety on health outcomes in COPD. Thorax 2010;65:229-34.

196. Knubben K, Reischies FM, Adli M, Schlattmann P, Bauer M, Dimeo F. A randomised, controlled study on the effects of a short-term endurance training programme in patients with major depression. Br J Sports Med 2007;41:29-33.
197. Anthonisen NR, Connett JE, Enright PL, Manfreda J. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002;166:333-9.
198. Benfield T, Lange P, Vestbo J. COPD stage and risk of hospitalization for infectious disease. Chest 2008;134:46-53.

Online supplement for

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

GOLD EXECUTIVE SUMMARY

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Chapter 3. THERAPEUTIC OPTIONS

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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 COPD patient; 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.

SMOKING CESSATION

Smoking cessation is the intervention with the greatest capacity to influence the natural history of COPD. Because tobacco dependence is a chronic disease[1], clinicians should recognize that relapse is common and reflects the chronic nature of dependence and addiction, not failure on the part of the clinician or the patient. However, if effective resources and time are dedicated to smoking cessation, 25% long-term quit rates can be achieved[2].

Nicotine Replacement Products. Nicotine replacement therapy in any form (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge) reliably increases long-term smoking abstinence rates[1,3,4] and is significantly more effective than placebo (**Evidence A**). Patients need to be informed about the proper use of these products to optimize efficacy.

Pharmacologic. Varenicline[5], bupropion[6] and nortriptyline have been shown to increase long-term quit rates[3,7,8] (**Evidence A**).

Counseling delivered by physicians and other health professionals significantly increases quit rates over self-initiated strategies[9] (**Evidence A**). Even a brief (3-minute) period of counseling to urge a smoker to quit results in smoking cessation rates of 5-10%[10].

PHARMACOLOGIC THERAPY FOR STABLE COPD

Pharmacologic therapy for COPD is used to reduce 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 conclusively shown to modify the long-term decline in lung function when this was tested as a primary or secondary outcome in clinical trials[2,11-13]. Post- hoc evidence of such an effect with long-acting bronchodilators and/or inhaled corticosteroids[14,15] requires confirmation in specifically designed trials.

The classes of medications commonly used in treating COPD are shown in **Table S1.** The choice within each class depends on the availability and cost of medication and the patient's response. Each treatment regimen needs to be patient-specific as the relationship between severity of symptoms, airflow limitation, and frequency as well as severity of exacerbations will differ between patients.

When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential[16]. 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 problems with coordination and find it hard to use a metered-dose inhaler (MDI). It is essential to ensure that inhaler technique is correct and to re-check this at each visit. Alternative breath-activated or spacer devices are available.

Bronchodilators. Bronchodilator drugs commonly used in treating COPD include $beta_2$-agonists, anticholinergics, and methylxanthines. The choice depends on the availability of the medications and the patient's response. Bronchodilator medications are given on either an as-needed basis or a regular basis to prevent or reduce symptoms[17-20] (**Evidence A**)

Table S1. Formulations and Typical Doses of COPD Medications*					
Drug	**Inhaler (mcg)**	**Solution for Nebulizer (mg/ml)**	**Oral**	**Vials for Injection (mg)**	**Duration of Action (hours)**
Beta$_2$-agonists					
Short-acting					
Fenoterol	100-200 (MDI)	1	0.05% (Syrup)		4-6
Levalbuterol	45-90 (MDI)	0.21, 0.42			6-8
Salbutamol (albuterol)	100, 200 (MDI & DPI)	5	5 mg (Pill), 0.024%(Syrup)	0.1, 0.5	4-6
Terbutaline	400, 500 (DPI)		2.5, 5 mg (Pill)		4-6
Long-acting					
Formoterol	4.5-12 (MDI & DPI)	0.01¶			12
Arformoterol		0.0075			12
Indacaterol	75-300 (DPI)				24
Salmeterol	25-50 (MDI & DPI)				12
Tulobuterol			2 mg (transdermal)		24
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), 5 (SMI)				24
Combination short-acting beta$_2$-agonists plus anticholinergic in one inhaler					
Fenoterol/Ipratropium	200/80 (MDI)	1.25/0.5			6-8
Salbutamol/Ipratropium	75/15 (MDI)	0.75/0.5			6-8
Methylxanthines					
Aminophylline			200-600 mg (Pill)	240	Variable, up to 24
Theophylline (SR)			100-600 mg (Pill)		Variable, up to 24
Inhaled corticosteroids					
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)				
Combination long-acting beta$_2$-agonists plus corticosteroids in one inhaler					
Formoterol/Budesonide	4.5/160 (MDI) 9/320 (DPI)				12
Salmeterol/Fluticasone	50/100, 250, 500 (DPI) 25/50, 125, 250 (MDI)				12
Systemic corticosteroids					
Prednisone			5-60 mg (Pill)		
Methyl-prednisolone			4, 8, 16 mg (Pill)		
Phosphodiesterase-4 inhibitors					
Roflumilast			500 mcg (Pill)		24

MDI=metered dose inhaler; DPI=dry powder inhaler; SMI=smart mist inhaler

*Not all formulations are available in all countries; in some countries, other formulations may be available.

¶Formoterol nebulized solution is based on the unit dose vial containing 20 mcg in a volume of 2.0 ml

Corticosteroids

Inhaled Corticosteroids. The dose-response relationships and long-term safety of inhaled corticosteroids in COPD are not known. Only moderate to high doses have been used in long-term clinical trials. The effects of corticosteroids on pulmonary and systemic inflammation in patients with COPD are controversial, and their role in the management of stable COPD is limited to specific indications. Regular treatment with inhaled corticosteroids improves symptoms, lung function, and quality of life, and reduces the frequency of exacerbations[21] in COPD patients with an $FEV_1 < 60\%$ predicted[22-27] (**Evidence A**). Withdrawal from treatment with inhaled corticosteroids may lead to exacerbations in some patients[28]. Regular treatment with inhaled corticosteroids does not modify the long-term decline of FEV_1 nor mortality in patients with COPD[11-13,23,29,30] (**Evidence A**).

Inhaled corticosteroid use is associated with higher prevalence of oral candidiasis, hoarse voice, and skin bruising[11,12]. Treatment with inhaled corticosteroids is associated with an increased risk of pneumonia[23,29-31].

Combination Inhaled Corticosteroid/Bronchodilator Therapy. An inhaled corticosteroid combined with a long-acting $beta_2$-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate (**Evidence B**) to very severe COPD[22,23,26,27,29,32-34] (**Evidence A**). Combination therapy is associated with an increased risk of pneumonia[35], but no other significant side effect (**Evidence A**). The addition of a long-acting $beta_2$-agonist/inhaled corticosteroid combination to tiotropium improves lung function and quality of life[36,37] and may further reduce exacerbations (**Evidence B**) but more studies of triple therapy are needed[38].

Oral Corticosteroids. Oral corticosteroids have numerous side effects. An important side effect of long-term treatment of COPD with systemic corticosteroids is steroid myopathy[39-41], which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with very severe COPD.

Phosphodiesterase-4 Inhibitors. The phosphodiesterase-4 inhibitor roflumilast has been approved for use in some countries for patients with chronic bronchitis, $FEV_1 < 50$ % of predicted, and a history of exacerbations. In these patients, roflumilast reduces moderate and severe exacerbations treated with corticosteroids by 15-20% [42] (**Evidence A**). Roflumilast is a once daily oral medication with no direct bronchodilator activity, although it has been shown to improve FEV_1 in patients treated with salmeterol or tiotropium[43] [42] (**Evidence A**). There are no comparison or add-on studies of roflumilast

and inhaled corticosteroids. The effects of roflumilast on other patient-related outcomes and remain uncertain[44].

Roflumilast has more adverse effects than inhaled medications for COPD[42-44] including diarrhea, nausea, reduced appetite, abdominal pain, sleep disturbances, and headache. In addition, the patient's weight needs to be monitored as weight loss was observed. Roflumilast should be used with caution in patients with depression. Roflumilast and theophylline should not be given together.

Other Pharmacologic Treatments

Vaccines. Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization[45]) and death in COPD patients[46-48] (**Evidence A**). The strains are adjusted each year for appropriate effectiveness and should be given once each year[49]. Pneumococcal polysaccharide 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[50] (**Evidence B**).

Alpha-1 Antitrypsin Augmentation Therapy. Patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy (**Evidence C**). 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.

Antibiotics. In older studies prophylactic, continuous use of antibiotics was shown to have no effect on the frequency of exacerbations in COPD[51-53], and a study that examined the efficacy of chemoprophylaxis undertaken in winter months over a period of 5 years concluded that there was no benefit[54]. Although recent studies have shown some effects of antibiotics on exacerbation rate[55,56], the role of this treatment is unclear. A large trial of daily azithromycin showed efficacy on exacerbation end-points; however, treatment is not recommended because of an unfavorable balance between benefits and side effects[57]. Thus, the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is currently not indicated[58,59] (**Evidence B**).

Mucolytic (mucokinetic, mucoregulator) and Antioxidant 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[60-62] and the overall benefits seem to be very small (**Evidence D).** There is some evidence that in COPD patients not receiving inhaled corticosteroids, treatment with mucolytics such as carbocysteine and N-acetylcysteine may reduce exacerbations[63,64] (**Evidence B**).

Immunoregulators (immunostimulators, immunomodulators). Studies using an immunoregulator in COPD report a decrease in the severity and frequency of exacerbations[65,66]. However, additional studies to examine the long-term effects of this therapy are required; at present, its regular use cannot be recommended[67].

Vasodilators. The results of previous studies attempting to reduce right ventricular afterload, increase cardiac output, and improve oxygen delivery and tissue oxygenation have been uniformly disappointing. Nitric oxide is contraindicated in stable COPD and use of endothelium-modulating agents used for the treatment of primary pulmonary hypertension is not recommended.

Narcotics (morphine). Oral and parenteral opioids are effective for treating dyspnea in COPD patients with very severe disease. There is insufficient data to conclude whether nebulized opioids are effective[68]. 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[69-73].

Others. No studies have shown effect of nedocromil and leukotriene modifiers in COPD. 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[74]. There is no evidence for the effectiveness of herbal medicines in treating COPD[75] and other alternative healing methods (e.g., acupuncture and homeopathy) have not been adequately tested.

NON-PHARMACOLOGIC THERAPIES

Rehabilitation. The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities[76,77]. Pulmonary rehabilitation has been carefully evaluated in a large number of clinical trials and shown to increase peak workload, peak oxygen consumption, and endurance time[78]. Benefits have been reported from rehabilitation programs conducted in inpatient, outpatient, and home settings[78,79]; considerations of cost and availability most often determine the choice of setting.

The minimum length of an effective rehabilitation program is 6 weeks; the longer the program continues, the more effective the results[80-82]. However, as yet, no effective program has been developed to maintain the effects over time[83]. Many physicians advise patients unable to participate in a structured program to exercise on their own (e.g., walking 20 minutes daily). The benefits of this general advice have not been tested, but because observational studies have indicated significant benefits of physical activity[84,85],

and because physical activity is good for so many other reasons, it is highly reasonable to offer such advice to patients if a formal program is not available.

The components of pulmonary rehabilitation vary widely but a comprehensive program includes exercise training, smoking cessation, 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 post-bronchodilator spirometry
- Assessment of exercise capacity
- Measurement of health status and impact of breathlessness (e.g., CAT and mMRC scales)
- 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 in patients with severe resting hypoxemia[86] (**Evidence B**). Long-term oxygen therapy is indicated for patients who have:

- PaO_2 at or below 7.3 kPa (55 mmHg) or SaO_2 at or below 88%, with or without hypercapnia confirmed twice over a three week period (**Evidence B**); *or*

- PaO_2 between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO_2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%) (**Evidence D**).

A decision about the use of long-term oxygen should be based on the resting PaO_2 or saturation values repeated twice over three weeks in the stable patient. Current data do not support the use of ambulatory oxygen in patient populations that do not meet the above criteria[87].

Ventilatory Support. The combination of Non-invasive ventilation (NIV) with long-term oxygen therapy may be of some use in a selected subset of patients, particularly in

those with pronounced daytime hypercapnia[88] in whom it may improve survival but not quality of life[88]. By contrast, in patients with both COPD and obstructive sleep apnea there are clear benefits from continuous positive airway pressure (CPAP) in both survival and risk of hospital admission[89].

Surgical Treatments

Lung Volume Reduction Surgery (LVRS). LVRS is a surgical procedure in which parts of the lung are resected to reduce hyperinflation[90], making respiratory muscles more effective pressure generators by improving their mechanical efficiency (as measured by length/tension relationship, curvature of the diaphragm, and area of apposition)[91,92]. Compared to medical treatment, LVRS has been demonstrated to result in improved survival (54% vs. 39.7%) in severe emphysema patients with upper-lobe emphysema and low post-rehabilitation exercise capacity[93] (**Evidence A**). LVRS has been demonstrated to result in higher mortality than medical management in severe emphysema patients with an $FEV_1 \leq 20\%$ predicted and either homogeneous emphysema on high resolution computed tomography or a $DL_{CO} \leq 20\%$ predicted[94].

Bronchoscopic Lung Volume Reduction (BLVR). In a post-hoc analysis, BLVR in COPD patients with severe airflow limitation (FEV_1 15-45% predicted), heterogeneous emphysema on CT scan, and hyperinflation (TLC > 100% and RV > 150% predicted) has been demonstrated to result in modest improvements in lung function, exercise tolerance, and symptoms at the cost of more frequent exacerbations of COPD, pneumonia, and hemoptysis after implantation[95]. Additional data are required to define the optimal technique and patient population.

Lung Transplantation. In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity[96,97]. Criteria for referral for lung transplantation include COPD with a BODE index exceeding 5. Recommended criteria for listing include a BODE index of 7-10 and at least one of the following: history of exacerbation associated with acute hypercapnia [$PaCO_2 > 6.7$ kPa (50 mmHg)]; pulmonary hypertension, cor pulmonale, or both despite oxygen therapy; and $FEV_1 < 20\%$ predicted with either $DL_{CO} < 20\%$ predicted or homogenous distribution of emphysema[98] (**Evidence C**).

REFERENCES

1. The tobacco use and dependence clinical practice guideline panel, staff, and consortium representatives. A clinical practice guideline for treating tobacco use and dependence. JAMA 2000;28:3244-54.

2. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. JAMA 1994;272:1497-505.
3. Lancaster T, Stead L, Silagy C, Sowden A. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. BMJ 2000;321:355-8.
4. Tonnesen P, Mikkelsen K, Bremann L. Nurse-conducted smoking cessation in patients with COPD using nicotine sublingual tablets and behavioral support. Chest 2006;130:334-42.
5. Tashkin DP, Rennard S, Hays JT, Ma W, Lawrence D, Lee TC. Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. Chest 2011;139:591-9.
6. Tashkin D, Kanner R, Bailey W, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. Lancet 2001;357:1571-5.
7. Fiore MC, Bailey WC, Cohen SJ. Smoking cessation: information for specialists. Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research and Centers for Disease Control and Prevention; 1996.
8. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 1999;340:685-91.
9. Baillie AJ, Mattick RP, Hall W, Webster P. Meta-analytic review of the efficacy of smoking cessation interventions. Drug and Alcohol Review 1994;13:157-70.
10. Wilson DH, Wakefield MA, Steven ID, Rohrsheim RA, Esterman AJ, Graham NM. "Sick of Smoking": evaluation of a targeted minimal smoking cessation intervention in general practice. Med J Aust 1990;152:518-21.
11. Pauwels RA, Lofdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med 1999;340:1948-53.
12. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297-303.
13. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 1999;353:1819-23.
14. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med 2008;178:332-8.
15. Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. Lancet 2009;374:1171-8.

16. Al-Showair RA, Tarsin WY, Assi KH, Pearson SB, Chrystyn H. Can all patients with COPD use the correct inhalation flow with all inhalers and does training help? Respir Med 2007;101:2395-401.
17. Vathenen AS, Britton JR, Ebden P, Cookson JB, Wharrad HJ, Tattersfield AE. High-dose inhaled albuterol in severe chronic airflow limitation. Am Rev Respir Dis 1988;138:850-5.
18. Gross NJ, Petty TL, Friedman M, Skorodin MS, Silvers GW, Donohue JF. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease. A three-center study. Am Rev Respir Dis 1989;139:1188-91.
19. Chrystyn H, Mulley BA, Peake MD. Dose response relation to oral theophylline in severe chronic obstructive airways disease. BMJ 1988;297:1506-10.
20. Higgins BG, Powell RM, Cooper S, Tattersfield AE. Effect of salbutamol and ipratropium bromide on airway calibre and bronchial reactivity in asthma and chronic bronchitis. Eur Respir J 1991;4:415-20.
21. Spencer S, Calverley PM, Burge PS, Jones PW. Impact of preventing exacerbations on deterioration of health status in COPD. Eur Respir J 2004;23:698-702.
22. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003;361:449-56.
23. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775-89.
24. Calverley PM, Spencer S, Willits L, Burge PS, Jones PW. Withdrawal from treatment as an outcome in the ISOLDE study of COPD. Chest 2003;124:1350-6.
25. Jones PW, Willits LR, Burge PS, Calverley PM. Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. Eur Respir J 2003;21:68-73.
26. Mahler DA, Wire P, Horstman D, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;166:1084-91.
27. Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003;21:74-81.
28. van der Valk P, Monninkhof E, van der Palen J, Zielhuis G, van Herwaarden C. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. Am J Respir Crit Care Med 2002;166:1358-63.
29. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 2008;300:2407-16.
30. Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. Arch Intern Med 2009;169:219-29.
31. Calverley PM, Stockley RA, Seemungal TA, et al. Reported pneumonia in patients with COPD: findings from the INSPIRE study. Chest 2011;139:505-12.
32. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 2003;22:912-9.

33. Hanania NA, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. Chest 2003;124:834-43.
34. Mahler DA. Pulmonary rehabilitation. Chest 1998;113:263S-8S.
35. Crim C, Calverley PM, Anderson JA, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. Eur Respir J 2009;34:641-7.
36. Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180:741-50.
37. Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2007;146:545-55.
38. Karner C, Cates CJ. Combination inhaled steroid and long-acting beta(2)-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. Cochrane database of systematic reviews 2011;3:CD008532.
39. Decramer M, de Bock V, Dom R. Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996;153:1958-64.
40. Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. Am J Respir Crit Care Med 1994;150:11-6.
41. Decramer M, Stas KJ. Corticosteroid-induced myopathy involving respiratory muscles in patients with chronic obstructive pulmonary disease or asthma. Am Rev Respir Dis 1992;146:800-2.
42. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 2009;374:685-94.
43. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet 2009;374:695-703.
44. Rabe KF. Update on roflumilast, a phosphodiesterase 4 inhibitor for the treatment of chronic obstructive pulmonary disease. Br J Pharmacol 2011;163:53-67.
45. Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritrutai W, Charoenratanakul S. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. Chest 2004;125:2011-20.
46. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. N Engl J Med 1994;331:778-84.
47. Wongsurakiat P, Lertakyamanee J, Maranetra KN, Jongriratanakul S, Sangkaew S. Economic evaluation of influenza vaccination in Thai chronic obstructive pulmonary disease patients. J Med Assoc Thai 2003;86:497-508.
48. Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR Morb Mortal Wkly Rep 2009;58 (RR08):1-52.

49. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J 2005;26:1138-80.
50. Alfageme I, Vazquez R, Reyes N, et al. Clinical efficiacy of anti-pneumococcal vaccination in patients with COPD. Thorax 2006;61:189-95.
51. Francis RS, May JR, Spicer CC. Chemotherapy of bronchitis: influence of penicillin and tetracylcline administered daily, or intermittently for exacerbations. BMJ 1961;2:979-85.
52. Francis RS, Spicer CC. Chemotherapy in chronic bronchitis: influence of daily penicillin and teracycline on exacerbations and their cost. A report to the research committee of the British Tuberculosis Assoication by their Chronic Bronchitis subcommittee. BMJ 1960;1:297-303.
53. Fletcher CM, Ball JD, Carstairs LW, et al. Value of chemoprophylaxis and chemotherapy in early chronic bronchitis. A report to the Medical Research Council by their Working Party on trials of chemotherpay in early chronic bronchitis. In: BMJ; 1966:1317-22.
54. Johnston RN, McNeill RS, Smith DH, et al. Five-year winter chemoprophylaxis for chronic bronchitis. BMJ 1969;4:265-9.
55. Seemungal TA, Wilkinson TM, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. Am J Respir Crit Care Med 2008;178:1139-47.
56. Sethi S, Jones PW, Theron MS, et al. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Respir Res 2010;11:10.
57. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365:689-98.
58. Isada CM, Stoller JK. Chronic bronchitis: the role of antibiotics. In: Niederman MS, Sarosi GA, Glassroth J, eds. Respiratory infections: a scientific basis for management. London: WB Saunders; 1994:621-33.
59. Siafakas NM, Wedzicha AJ. Management of acute exacerbation of chronic obstructive pulmonary disease. In: Siafakas NM, ed. Management of chronic obstructive pulmonary disease: Eur Respir Mon; 2006:387-400.
60. Allegra L, Cordaro CI, Grassi C. Prevention of acute exacerbations of chronic obstructive bronchitis with carbocysteine lysine salt monohydrate: a multicenter, double-blind, placebo-controlled trial. Respiration 1996;63:174-80.
61. Guyatt GH, Townsend M, Kazim F, Newhouse MT. A controlled trial of ambroxol in chronic bronchitis. Chest 1987;92:618-20.
62. Petty TL. The National Mucolytic Study. Results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. Chest 1990;97:75-83.
63. Zheng JP, Kang J, Huang SG, et al. Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. Lancet 2008;371:2013-8.
64. Decramer M, Rutten-van Molken M, Dekhuijzen PN, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. Lancet 2005;365:1552-60.

65. Collet JP, Shapiro P, Ernst P, Renzi T, Ducruet T, Robinson A. Effects of an immunostimulating agent on acute exacerbations and hospitalizations in patients with chronic obstructive pulmonary disease. The PARI-IS Study Steering Committee and Research Group. Prevention of Acute Respiratory Infection by an Immunostimulant. Am J Respir Crit Care Med 1997;156:1719-24.
66. Li J, Zheng JP, Yuan JP, Zeng GQ, Zhong NS, Lin CY. Protective effect of a bacterial extract against acute exacerbation in patients with chronic bronchitis accompanied by chronic obstructive pulmonary disease. Chin Med J (Engl) 2004;117:828-34.
67. Anthonisen NR. OM-8BV for COPD. Am J Respir Crit Care Med 1997;156:1713-4.
68. Jennings AL, Davies AN, Higgins JP, Gibbs JS, Broadley KE. A systematic review of the use of opioids in the management of dyspnoea. Thorax 2002;57:939-44.
69. Eiser N, Denman WT, West C, Luce P. Oral diamorphine: lack of effect on dyspnoea and exercise tolerance in the "pink puffer" syndrome. Eur Respir J 1991;4:926-31.
70. Young IH, Daviskas E, Keena VA. Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease. Thorax 1989;44:387-90.
71. Woodcock AA, Gross ER, Gellert A, Shah S, Johnson M, Geddes DM. Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. N Engl J Med 1981;305:1611-6.
72. Rice KL, Kronenberg RS, Hedemark LL, Niewoehner DE. Effects of chronic administration of codeine and promethazine on breathlessness and exercise tolerance in patients with chronic airflow obstruction. Br J Dis Chest 1987;81:287-92.
73. Poole PJ, Veale AG, Black PN. The effect of sustained-release morphine on breathlessness and quality of life in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1877-80.
74. Rennard SI, Fogarty C, Kelsen S, et al. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007;175:926-34.
75. Guo R, Pittler MH, Ernst E. Herbal medicines for the treatment of COPD: a systematic review. Eur Respir J 2006;28:330-8.
76. Nici L, Donner C, Wouters E, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 2006;173:1390-413.
77. Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. Chest 2007;131:4S-42S.
78. Lacasse Y, Brosseau L, Milne S, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2002:CD003793.
79. Maltais F, Bourbeau J, Shapiro S, et al. Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2008;149:869-78.
80. Behnke M, Taube C, Kirsten D, Lehnigk B, Jorres RA, Magnussen H. Home-based exercise is capable of preserving hospital-based improvements in severe chronic obstructive pulmonary disease. Respir Med 2000;94:1184-91.

81. Finnerty JP, Keeping I, Bullough I, Jones J. The effectiveness of outpatient pulmonary rehabilitation in chronic lung disease: a randomized controlled trial. Chest 2001;119:1705-10.
82. Green RH, Singh SJ, Williams J, Morgan MD. A randomised controlled trial of four weeks versus seven weeks of pulmonary rehabilitation in chronic obstructive pulmonary disease. Thorax 2001;56:143-5.
83. Ries AL, Kaplan RM, Myers R, Prewitt LM. Maintenance after pulmonary rehabilitation in chronic lung disease: a randomized trial. Am J Respir Crit Care Med 2003;167:880-8.
84. Esteban C, Quintana JM, Aburto M, et al. Impact of changes in physical activity on health-related quality of life among patients with COPD. Eur Respir J 2010;36:292-300.
85. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax 2006;61:772-8.
86. Stoller JK, Panos RJ, Krachman S, Doherty DE, Make B. Oxygen therapy for patients with COPD: current evidence and the long-term oxygen treatment trial. Chest 2010;138:179-87.
87. Moore RP, Berlowitz DJ, Denehy L, et al. A randomised trial of domiciliary, ambulatory oxygen in patients with COPD and dyspnoea but without resting hypoxaemia. Thorax 2011;66:32-7.
88. McEvoy RD, Pierce RJ, Hillman D, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax 2009;64:561-6.
89. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med 2010;182:325-31.
90. Cooper JD, Trulock EP, Triantafillou AN, et al. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg 1995;109:106-16; discussion 16-9.
91. Criner G, Cordova FC, Leyenson V, et al. Effect of lung volume reduction surgery on diaphragm strength. Am J Respir Crit Care Med 1998;157:1578-85.
92. Martinez FJ, de Oca MM, Whyte RI, Stetz J, Gay SE, Celli BR. Lung-volume reduction improves dyspnea, dynamic hyperinflation, and respiratory muscle function. Am J Respir Crit Care Med 1997;155:1984-90.
93. Naunheim KS, Wood DE, Mohsenifar Z, et al. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg 2006;82:431-43.
94. National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. N Engl J Med 2001;345:1075-83.
95. Sciurba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363:1233-44.
96. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report--2010. J Heart Lung Transplant 2010;29:1104-18.

97. Trulock EP. Lung transplantation. Am J Respir Crit Care Med 1997;155:789-818.
98. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:745-55.