

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report GOLD Executive Summary

Claus F. Vogelmeier^{1*}, Gerard J. Criner^{2*}, Fernando J. Martinez^{3*}, Antonio Anzueto^{4,5}, Peter J. Barnes⁶, Jean Bourbeau⁷, Bartolome R. Celli⁸, Rongchang Chen⁹, Marc Decramer¹⁰, Leonardo M. Fabbri¹¹, Peter Frith¹², David M. G. Halpin¹³, M. Victorina López Varela¹⁴, Masaharu Nishimura¹⁵, Nicolas Roche¹⁶, Roberto Rodriguez-Roisin¹⁷, Don D. Sin¹⁸, Dave Singh¹⁹, Robert Stockley²⁰, Jørgen Vestbo¹⁹, Jadwiga A. Wedzicha⁶, and Alvar Agustí²¹

¹University of Marburg, Member of the German Center for Lung Research (DZL), Marburg, Germany; ²Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania; ³New York-Presbyterian Hospital, Weill Cornell Medical Center, New York, New York; ⁴University of Texas Health Science Center, San Antonio, Texas; ⁵South Texas Veterans Health Care System, San Antonio, Texas; ⁶National Heart and Lung Institute, Imperial College, London, United Kingdom; ⁷McGill University Health Centre, McGill University, Montreal, Quebec, Canada; ⁸Brigham and Women's Hospital, Boston, Massachusetts; ⁹State Key Lab for Respiratory Disease, Guangzhou Institute of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; ¹⁰University of Leuven, Leuven, Belgium; ¹¹University of Modena and Reggio Emilia, Modena, Italy; ¹²Faculty of Medicine, Flinders University, Bedford Park, South Australia, Australia; ¹³Royal Devon and Exeter Hospital, Exeter, United Kingdom; ¹⁴Universidad de la República, Hospital Maciel, Montevideo, Uruguay; ¹⁵Hokkaido University School of Medicine, Sapporo, Japan; ¹⁶Hôpital Cochin (Assistance Publique-Hôpitaux de Paris), University Paris Descartes, Paris, France; ¹⁷Thorax Institute, Hospital Clinic Universitat de Barcelona, Barcelona, Spain; ¹⁸St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; ¹⁹University of Manchester, Manchester, United Kingdom; ²⁰University Hospital, Birmingham, United Kingdom; and ²¹Hospital Clínic, Universitat de Barcelona, Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Barcelona, Spain

ORCID ID: 0000-0002-9798-2527 (C.F.V.).

Abstract

This Executive Summary of the Global Strategy for the Diagnosis, Management, and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 report focuses primarily on the revised and novel parts of the document. The most significant changes include: (1) the assessment of chronic obstructive pulmonary disease has been refined to separate the spirometric assessment from symptom evaluation. ABCD groups are now proposed to be derived exclusively from patient symptoms and their

history of exacerbations; (2) for each of the groups A to D, escalation strategies for pharmacologic treatments are proposed; (3) the concept of deescalation of therapy is introduced in the treatment assessment scheme; (4) nonpharmacologic therapies are comprehensively presented; and (5) the importance of comorbid conditions in managing chronic obstructive pulmonary disease is reviewed.

Keywords: chronic obstructive pulmonary disease; COPD diagnosis; COPD management; COPD prevention

Introduction

This Executive Summary of the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive

Pulmonary Disease (COPD) Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 report is based on peer-reviewed publications to October 2016. Levels of evidence are assigned to

evidence-based recommendations where appropriate. Categories used to grade the levels of evidence are provided in Table E1 in the online supplement.

(Received in original form January 26, 2017; accepted in final form January 27, 2017)

*These authors contributed equally to the article.

Correspondence should be addressed to Claus F. Vogelmeier, M.D., Department of Medicine, Pulmonary and Critical Care Medicine, University of Marburg, Baldingerstrasse, 35043 Marburg, Germany. E-mail: claus.vogelmeier@med.uni-marburg.de

For reprint requests, please contact Diane Gern at dgern@thoracic.org or 212-315-6441.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 195, Iss 5, pp 557–582, Mar 1, 2017

Copyright © 2017 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201701-0218PP on January 27, 2017

Internet address: www.atsjournals.org

<p>Contents</p> <p>Introduction</p> <p>Definition and Factors That Influence Chronic Obstructive Pulmonary Disease</p> <p>Development and Progression</p> <p> Key Points</p> <p> Definition and Pathogenesis</p> <p> Factors That Influence Disease Development and Progression</p> <p>Diagnosis and Initial Assessment</p> <p> Key Points</p> <p> Diagnosis</p> <p> Symptoms</p> <p> Medical History</p> <p> Assessment</p> <p> Additional Investigations</p> <p>Prevention and Maintenance</p> <p> Therapy</p> <p> Key Points</p> <p> Smoking Cessation</p> <p> Vaccinations</p> <p> Pharmacologic Therapy for Stable COPD</p>	<p>Rehabilitation, Education, and Self-Management</p> <p> Pulmonary Rehabilitation</p> <p> Education, Self-Management, and Integrative Care</p> <p>Supportive, Palliative, End-of-Life, and Hospice Care</p> <p> Symptom Control and Palliative Care</p> <p> End-of-Life and Hospice Care</p> <p>Other Treatments</p> <p> Oxygen Therapy and Ventilatory Support</p> <p>Interventional Therapy</p> <p> Surgical Interventions</p> <p> Bronchoscopic Interventions to Reduce Hyperinflation in Severe Emphysema</p> <p>Management of Stable COPD</p> <p> Key Points</p> <p> Identify and Reduce Exposure to Risk Factors</p>	<p>Treatment of Stable COPD</p> <p> Pharmacologic Treatment</p> <p> Nonpharmacologic Treatment</p> <p>Monitoring and Follow-up</p> <p> Key Points</p> <p> Management of Exacerbations</p> <p>Treatment Options</p> <p> Treatment Setting</p> <p> Pharmacologic Treatment</p> <p> Respiratory Support</p> <p> Hospital Discharge and Follow-up</p> <p> Prevention of Exacerbations</p> <p>COPD and Comorbidities</p> <p> Key Points</p> <p> Cardiovascular Disease</p> <p> Osteoporosis</p> <p> Anxiety and Depression</p> <p> COPD and Lung Cancer</p> <p> Metabolic Syndrome and Diabetes</p> <p> Gastroesophageal Reflux</p> <p> Bronchiectasis</p> <p> OSA</p>
--	--	---

Definition and Factors That Influence Chronic Obstructive Pulmonary Disease Development and Progression

Key Points:

- Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases.
- Dyspnea, cough, and/or sputum production are the most frequent symptoms; symptoms are commonly underreported by patients.
- Tobacco smoking is the main risk exposure for COPD, but environmental exposures like biomass fuel exposure and air pollution may contribute. Besides exposures, host factors (genetic abnormalities, abnormal lung development, and accelerated aging)

predispose individuals to develop COPD.

- COPD may be punctuated by acute worsening of respiratory symptoms, called exacerbations.
- In most patients, COPD is associated with significant concomitant chronic diseases, which increase morbidity and mortality.

Definition and Pathogenesis

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases.

The chronic airflow limitation that characterizes COPD is caused by a mixture of small airway disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Chronic inflammation causes structural changes, small airway narrowing, and destruction of

lung parenchyma. A loss of small airways may contribute to airflow limitation and mucociliary dysfunction, a characteristic feature of the disease.

Chronic respiratory symptoms may precede the development of airflow limitation and be associated with acute respiratory events (1). Chronic respiratory symptoms may exist in individuals with normal spirometry (1, 2), and a significant number of smokers without airflow limitation have structural evidence of lung disease manifested by the presence of emphysema, airway wall thickening, and gas trapping (1, 2).

Factors That Influence Disease Development and Progression

Although cigarette smoking is the most well-studied COPD risk factor, epidemiologic studies demonstrate that nonsmokers may also develop chronic airflow limitation (3). Compared with smokers with COPD, never smokers with chronic airflow limitation have fewer symptoms, milder disease, and a lower burden of systemic inflammation (4). Never smokers with chronic airflow limitation do not have an increased risk of lung cancer or cardiovascular comorbidities; however, they have an

increased risk of pneumonia and mortality from respiratory failure (4).

Processes occurring during gestation, birth, and exposures during childhood and adolescence affect lung growth (5, 6). Reduced maximal attained lung function (as measured by spirometry) may identify individuals at increased risk for COPD (2, 7). Factors in early life termed “childhood disadvantage factors” are as important as heavy smoking in predicting lung function in adult life (8). An examination of three different longitudinal cohorts found that approximately 50% of patients developed COPD owing to an accelerated decline in FEV₁; the other 50% developed COPD owing to abnormal lung growth and development.

Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV₁, and a greater COPD mortality rate than nonsmokers (9). Other types of tobacco (e.g., pipe, cigar, water pipe) (10–12) and marijuana (13) are also risk factors for COPD. Passive exposure to cigarette smoke, also known as environmental tobacco smoke, may also contribute to respiratory symptoms and COPD (14) by increasing the lung’s total burden of inhaled particles and gases. Smoking during pregnancy may pose a risk for the fetus by affecting *in utero* lung growth and development and possibly priming the immune system (15).

Occupational exposures, including organic and inorganic dusts, chemical agents, and fumes, are underappreciated risk factors for COPD development (16, 17).

Wood, animal dung, crop residues, and coal, typically burned in open fires or poorly functioning stoves, may lead to indoor air pollution (18). Indoor pollution from biomass cooking and heating in poorly ventilated dwellings is a risk for COPD (19–21).

Asthma may be a risk for the development of chronic airflow limitation and COPD (22).

Airway hyperresponsiveness can exist without a clinical diagnosis of asthma and is an independent predictor of COPD and respiratory mortality in population studies (23, 24). It may indicate a risk for excessive lung function decline in mild COPD (25).

A history of severe childhood respiratory infection is associated with reduced lung

function and increased respiratory symptoms in adulthood (26). HIV infection accelerates the onset of smoking-related emphysema and COPD (27); tuberculosis has also been identified as a risk for COPD as well as a potential comorbidity (28–30).

Diagnosis and Initial Assessment

Key Points:

- COPD should be considered in any patient with dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors.
- Spirometry is required to make the diagnosis; a post-bronchodilator FEV₁/FVC less than 0.70 confirms the presence of persistent airflow limitation.
- The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient’s health status, and the risk of future events (such as exacerbations, hospital admissions, or death) to guide therapy.
- Concomitant chronic diseases occur frequently in patients with COPD and should be treated because they can independently affect mortality and hospitalizations.

Diagnosis

COPD should be considered in any patient with dyspnea, chronic cough, or sputum production, and/or a history of exposure to risk factors for the disease (Figure 1 and Table 1). Spirometry is required to make the diagnosis in this clinical context (31); a post-bronchodilator FEV₁/FVC less than 0.70 confirms the presence of persistent airflow limitation and identifies the presence of COPD in patients with appropriate symptoms and predisposing risks.

Symptoms

Chronic and progressive dyspnea is the most characteristic symptom of COPD.

Dyspnea. Dyspnea is a major cause of disability and anxiety in COPD (32). The terms used to describe dyspnea vary individually and culturally (33).

Cough. Chronic cough is often the first symptom of COPD and is frequently discounted by the patient as a consequence of smoking and/or environmental exposures.

Sputum production. Regular sputum production for 3 months or more in 2 consecutive years is the classic definition of chronic bronchitis (34), an arbitrary definition that does not reflect the range of sputum production reported in COPD. Patients producing large volumes of sputum may have underlying bronchiectasis.

Wheezing and chest tightness. Wheezing and chest tightness may vary between days and throughout a single day.

Additional features in severe disease. Fatigue, weight loss, and anorexia are common in patients with more severe forms of COPD (35, 36).

Medical History

A detailed medical history of any patient who is known, or suspected, to have COPD should include:

- Exposure to risk factors, such as smoking and occupational or environmental exposures.
- Past medical history, including asthma, allergy, sinusitis, or nasal polyps; respiratory infections in childhood; other chronic respiratory and nonrespiratory diseases.
- Family history of COPD or other chronic respiratory diseases.
- Pattern of symptom development: age of onset, type of symptom, more frequent or prolonged “winter colds,” and social restriction.
- History of exacerbations or previous hospitalizations for a respiratory disorder.
- Presence of comorbidities, such as heart disease, osteoporosis, musculoskeletal disorders, and malignancies.
- Impact of disease on patient’s life, including limitation of activity, missed work and economic impact, and feelings of depression or anxiety.
- Social and family support available to the patient.
- Possibilities for reducing risk factors, especially smoking cessation.

Physical examination. Although important for general health, a physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation/hyperinflation are usually not identifiable until significantly impaired lung function is present (37, 38).

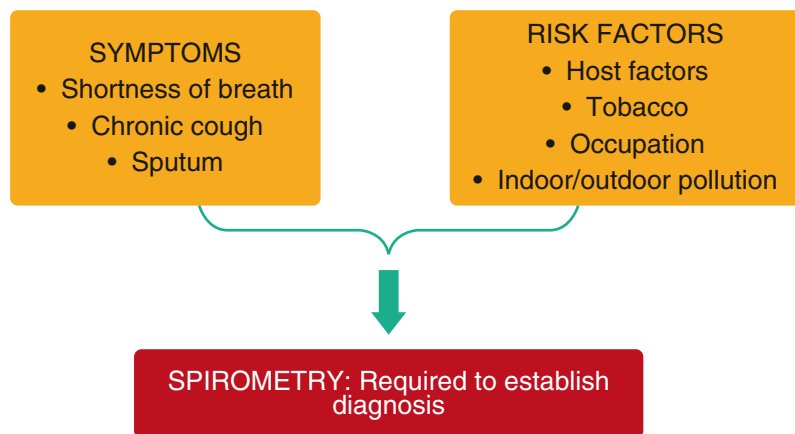


Figure 1. Pathways to the diagnosis of chronic obstructive pulmonary disease.

Spirometry. Spirometry is the most reproducible and objective measurement of airflow limitation. It is a noninvasive and readily available test. Good-quality spirometry is possible in any healthcare setting; all healthcare workers who care for patients with COPD should have access to spirometry.

A post-bronchodilator fixed ratio of FEV₁/FVC less than 0.70 is the spirometric criterion for airflow limitation. This criterion is simple and independent of reference values and has been used in numerous clinical trials. However, it may result in more frequent diagnosis of COPD in the elderly (39, 40) and less frequent diagnosis in adults younger than 45 years

(40), especially in mild disease, compared with a cutoff based on the lower limit of normal (LLN) values for FEV₁/FVC. Several limitations occur with using LLN as the diagnostic criterion for spirometric obstruction: (1) LLN values are dependent on the choice of reference equations that use post-bronchodilator FEV₁, (2) there are no longitudinal studies that validate using the LLN, and (3) studies using LLN in populations where smoking is not the major cause of COPD are lacking.

Normal spirometry may be defined by a new approach from the Global Lung Initiative (GLI) (41, 42). Using GLI equations, z scores were calculated for FEV₁, FVC, and FEV₁/FVC and compared

with fixed ratio data. The findings suggest that among adults with GLI-defined normal spirometry, the use of a fixed ratio may misclassify individuals as having respiratory impairment. These findings await additional study in other cohorts.

The risk of misdiagnosis and overtreatment using the fixed ratio as a diagnostic criterion is limited because spirometry is only one parameter used to establish the clinical diagnosis of COPD. GOLD favors using the fixed ratio over LLN because diagnostic simplicity and consistency are crucial for the busy clinician.

Assessing the degree of reversibility of airflow limitation (e.g., measuring FEV₁ before and after bronchodilator or corticosteroids) to make therapeutic decisions is not recommended (43) because it does not aid the diagnosis of COPD, differentiate COPD from asthma, or predict the long-term response to treatment (44).

In asymptomatic individuals without exposures to tobacco or other noxious stimuli, screening spirometry is not indicated. However, in those with symptoms and/or risk factors (e.g., >20 pack-years of smoking or recurrent chest infections), the diagnostic yield for COPD is relatively high and spirometry should be considered (45, 46). GOLD advocates active case finding (45, 47) (i.e., performing spirometry in patients with symptoms and/or risk factors) but not routine screening spirometry in asymptomatic individuals without COPD risk factors.

Table 1. Key Indicators for Considering a Diagnosis of Chronic Obstructive Pulmonary Disease

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

Dyspnea that is	Progressive over time Characteristically worse with exercise Persistent
Chronic cough	May be intermittent and may be unproductive Recurrent wheeze
Chronic sputum production	With any pattern
Recurrent lower respiratory tract infections	
History of risk factors	Host factors (such as genetic factors, congenital/developmental abnormalities, etc.) Tobacco smoke Smoke from home cooking and heating fuels Occupational dusts, vapors, fumes, gases and other chemicals
Family history of COPD and/or childhood factors	For example, low birthweight, childhood respiratory infections

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

Assessment

The goals of COPD assessment to guide therapy are (1) to determine the level of airflow limitation, (2) to define its impact on the patient’s health status, and (3) to identify the risk of future events (such as exacerbations, hospital admissions, or death).

To achieve these goals, COPD assessment must consider separately the following aspects of the disease:

- Presence and severity of the spirometric abnormality
- Current nature and magnitude of symptoms
- History/future risk of exacerbations
- Presence of comorbidities

Classification of severity of airflow limitation. Spirometry should be performed after administration of an adequate dose of at least one short-acting inhaled bronchodilator to minimize variability.

The role of spirometry for the diagnosis, assessment, and follow-up of COPD is summarized in Table 2.

Assessment of Symptoms. COPD was previously viewed as a disease largely characterized by breathlessness. A simple measure of breathlessness, such as the modified British Medical Research Council (mMRC) Questionnaire (48), was considered adequate for assessment of symptoms (49–51). However, COPD impacts patients well beyond dyspnea (52). For this reason, a comprehensive assessment of symptoms is recommended. The most comprehensive disease-specific health status questionnaires include the Chronic Respiratory Questionnaire (53) and St. George’s Respiratory Questionnaire (SGRQ) (54). These are too complex to use in clinical practice, but shorter measures, such as the COPD Assessment Test (CAT™), are suitable.

Choice of Thresholds. SGRQ scores less than 25 are uncommon in patients with COPD (55), and scores greater than or equal to 25 are very uncommon in healthy persons (56, 57). The equivalent cutoff point for the CAT is 10 (58). An mMRC threshold of greater than or equal to 2 is used to separate “less breathlessness” from “more breathlessness.”

Assessment of Exacerbation Risk. The best predictor of frequent exacerbations (defined as two or more exacerbations per year) is a history of earlier treated events (59). Hospitalization for a COPD exacerbation has a poor prognosis and an increased risk of death (60).

BLOOD EOSINOPHIL COUNT. *Post hoc* analysis of two clinical trials in patients with COPD with an exacerbation history showed that higher blood eosinophil counts may predict increased exacerbation rates in patients treated with long-acting β-agonists (LABAs) (without inhaled corticosteroids [ICSs]) (61, 62). The treatment effect of ICS/LABA versus LABA on exacerbations was greater in patients with higher blood eosinophil counts. These findings suggest that blood eosinophil counts (1) are a biomarker of exacerbation risk in patients with a history of exacerbations, and (2) can predict the effects of ICSs on exacerbation prevention. Prospective trials are required to validate the use of blood eosinophil counts to predict ICS effects, to determine a cutoff threshold for blood eosinophils that predicts exacerbation risk, and to clarify blood eosinophil cutoff values that could be used in clinical practice.

Table 2. Role of Spirometry

- Diagnosis
- Assessment of severity of airflow obstruction (for prognosis)
- Follow-up assessment
 - Therapeutic decisions
 - Pharmacologic in selected circumstances (e.g., discrepancy between spirometry and level of symptoms)
 - Consider alternative diagnoses when symptoms are disproportionate to degree of airflow obstruction
 - Nonpharmacologic (e.g., interventional procedures)
 - Identification of rapid decline

Assessment of Concomitant Chronic Diseases (Comorbidities). Patients with COPD often have important concomitant chronic illnesses as COPD represents an important component of multimorbidity, particularly in the elderly (60, 63–65).

Revised Combined COPD Assessment. The “ABCD” assessment tool of the 2011 GOLD Report was a major step forward from the simple spirometric grading system of earlier GOLD reports because it incorporated patient-reported outcomes and highlighted the importance of exacerbation prevention in COPD management. However, there were important limitations. ABCD assessment performed no better than spirometric grades for mortality prediction or other important health outcomes (66–68). Moreover, group D outcomes were modified by two parameters: lung function and/or exacerbation history, which caused

confusion (69). To address these concerns, the 2017 GOLD Report provides a refinement of the ABCD assessment that separates spirometric grades from ABCD groupings. For some therapy recommendations, especially pharmacologic treatments, ABCD groups are derived exclusively from patient symptoms and their exacerbation history. However, spirometry, in conjunction with patient symptoms and exacerbation history, remains vital for the diagnosis, prognostication, and consideration of other important therapeutic approaches, especially nonpharmacologic therapies. This new approach to assessment is illustrated in Figure 2.

In the refined assessment scheme, patients should undergo spirometry to determine the severity of airflow limitation (i.e., spirometric grade). They should also undergo assessment of either dyspnea using

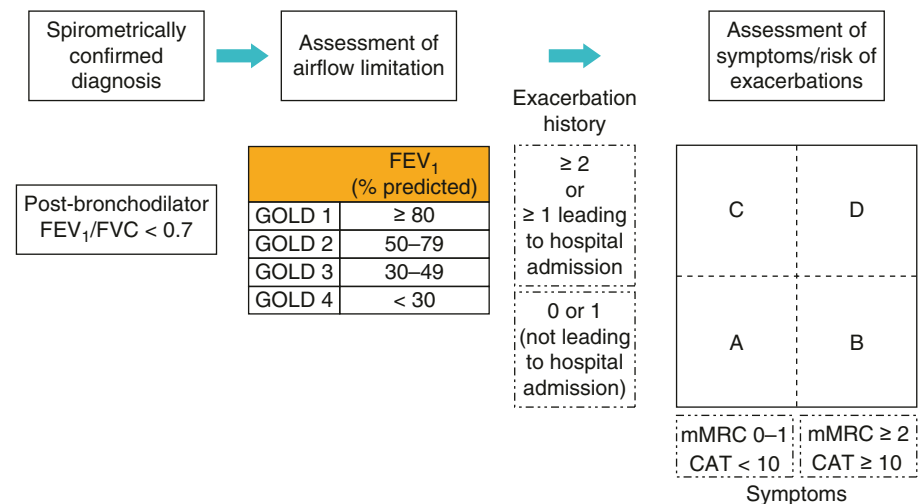


Figure 2. The refined ABCD assessment tool. CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified British Medical Research Council questionnaire.

mMRC or symptoms using CAT. Finally, their history of exacerbations (including prior hospitalizations) should be recorded.

The number provides information regarding severity of airflow limitation (spirometric grades 1 to 4), whereas the letter (groups A to D) provides information regarding symptom burden and risk of exacerbation. FEV₁ is a very important parameter at the population level in the prediction of important clinical outcomes, such as mortality and hospitalizations, or prompting consideration for nonpharmacologic therapies, such as lung reduction or lung transplantation. However, at the individual patient level, FEV₁ loses precision and thus cannot be used alone to determine all therapeutic options. Furthermore, in some circumstances, such as during hospitalization or urgent presentation to the clinic or emergency room, the ability to assess patients on the basis of symptoms and exacerbation history, independent of the spirometric value, allows clinicians to initiate a treatment plan on the basis of the revised ABCD scheme. This approach acknowledges the limitations of FEV₁ in making treatment decisions for individualized patient care and highlights the importance of patient symptoms and exacerbation risks in guiding therapies in COPD. The separation of airflow limitation from clinical parameters makes it clearer what is being evaluated and ranked. This should facilitate more precise treatment recommendations on the basis of parameters that are driving the patient's symptoms at any given time.

EXAMPLE. Consider two patients—both patients with FEV₁ less than 30% predicted, CAT scores of 18, one with no exacerbations in the past year and the other with three exacerbations in the past year. Both would have been labeled GOLD D in the prior classification scheme. However, with the new proposed scheme, the subject with three exacerbations in the past year would be labeled GOLD grade 4, group D. Individual decisions on pharmacotherapeutic approaches would use the recommendations based on the ABCD assessment to treat the patient's major problem at this time (i.e., persistent exacerbations). The other patient, who has had no exacerbations, would be classified as GOLD grade 4, group B. In such patients—besides pharmacotherapy and rehabilitation—lung reduction, lung transplantation, or bullectomy may be

important therapeutic considerations, given their symptom burden and level of spirometric limitation.

Alpha-1 Antitrypsin Deficiency. The World Health Organization recommends that all patients with a diagnosis of COPD be screened once for alpha-1 antitrypsin deficiency (70). A low concentration (<20% of normal) is suggestive of homozygous deficiency. Family members should be screened and together with the patient referred to specialist centers for advice and management.

Additional Investigations

To rule out other concomitant disease contributing to respiratory symptoms, or in cases where patients do not respond to the treatment plan as expected, additional testing may be required. Thoracic imaging (chest X-ray, chest computed tomography [CT]), assessment of lung volumes and/or diffusion capacity, oximetry and arterial blood gas measurement, and exercise testing and assessment of physical activity should be considered.

COMPOSITE SCORES. The BODE (Body mass index, Obstruction, Dyspnea, and Exercise) method gives a composite score that is a better predictor of subsequent survival than any single component (71). Simpler alternatives that do not include exercise testing need validation to confirm suitability for routine clinical use (72, 73).

DIFFERENTIAL DIAGNOSES. In some patients, features of asthma and COPD may coexist. The terms asthma-COPD overlap syndrome (ACOS) or asthma-COPD overlap (ACO) acknowledge the overlap of these two common disorders causing chronic airflow limitation rather than designating it a distinct syndrome. Most other potential differential diagnoses are easier to distinguish from COPD.

OTHER CONSIDERATIONS. Some patients without evidence of airflow limitation have evidence of structural lung disease on chest imaging (emphysema, gas trapping, airway wall thickening). Such patients may report exacerbations of respiratory symptoms or even require treatment with respiratory medications on a chronic basis. Whether these patients have acute or chronic bronchitis, a persistent form of asthma, or an earlier presentation of what will become COPD as it is currently defined is unclear and requires further study.

Prevention and Maintenance Therapy

Key Points:

- Smoking cessation is key. Pharmacotherapy and nicotine replacement increase long-term smoking abstinence rates.
- The effectiveness and safety of e-cigarettes as a smoking cessation aid is uncertain.
- Pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.
- Each pharmacologic treatment regimen should be individualized and guided by the severity of symptoms, risk of exacerbations, side effects, comorbidities, drug availability and cost, and the patient's response, preference, and ability to use various drug delivery devices.
- Inhaler technique needs to be assessed regularly.
- Influenza and pneumococcal vaccinations decrease the incidence of lower respiratory tract infections.
- Pulmonary rehabilitation improves symptoms, quality of life, and physical and emotional participation in everyday activities.
- In patients with severe resting chronic hypoxemia, long-term oxygen therapy improves survival.
- In patients with stable COPD and resting or exercise-induced moderate desaturation, long-term oxygen treatment should not be prescribed routinely; however, individual patient factors should be considered.
- In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long-term noninvasive ventilation may decrease mortality and prevent rehospitalization.
- In select patients with advanced emphysema refractory to optimized medical care, surgical or bronchoscopic interventional treatments may be beneficial.
- Palliative approaches are effective in controlling symptoms in advanced COPD.

Smoking Cessation

Smoking cessation influences the natural history of COPD. If effective resources and time are dedicated to smoking cessation, long-term quit success rates of up to 25% can be achieved (74).

Nicotine replacement products.

Nicotine replacement therapy increases long-term smoking abstinence rates (75–77) and is more effective than placebo. E-cigarettes are increasingly used as a form of nicotine replacement therapy, although their efficacy remains controversial (78–82).

Pharmacologic products. Varenicline (83), bupropion (84), and nortriptyline (85) increase long-term quit rates (85) but should be used as part of an interventional program rather than as a sole intervention.

Smoking cessation programs. A five-step program for intervention (75) provides a framework to guide healthcare providers to help patients stop smoking (75, 77, 86). Counseling delivered by health professionals significantly increases quit rates over self-initiated strategies (87). The combination of pharmacotherapy and behavioral support increases smoking cessation rates (88).

Vaccinations

Influenza vaccine and pneumococcal vaccines.

Influenza vaccination reduces serious illness (89), death (90–93), the risk of ischemic heart disease (94), and the total number of exacerbations (90). Vaccines containing either killed or live inactivated viruses are recommended (95) as they are more effective in elderly patients with COPD (96).

The pneumococcal vaccinations pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23) are recommended for all patients 65 years of age and older (Table E2).

Pharmacologic Therapy for Stable COPD

Overview of medications. Pharmacologic therapy for COPD reduces symptoms and the frequency and severity of exacerbations and improves exercise tolerance and health status. No existing medication modifies the long-term decline in lung function (97–101). The classes of medications used to treat COPD are shown in Table E3. The choice within each class depends on the availability and cost of medication and

favorable clinical response balanced against side effects. Each treatment regimen needs to be individualized as the relationship between severity of symptoms, airflow limitation, and severity of exacerbations varies between patients.

Bronchodilators. Bronchodilators increase FEV₁, reduce dynamic hyperinflation at rest and during exercise (102, 103), and improve exercise performance. Bronchodilator medications are usually given on a regular basis to prevent or reduce symptoms. Toxicity is dose related.

β₂-AGONISTS. β₂-agonists, including short-acting β₂-agonist (SABA) and LABA agents, relax airway smooth muscle. Stimulation of β₂-adrenergic receptors can produce resting sinus tachycardia and precipitate cardiac rhythm disturbances in susceptible patients. Exaggerated somatic tremor occurs in some patients treated with higher doses of β₂-agonists.

ANTIMUSCARINIC DRUGS.

Ipratropium, a short-acting muscarinic antagonist, provides small benefits over SABAs in terms of lung function, health status, and requirement for oral steroids (104). Long-acting muscarinic antagonist (LAMA) treatment improves symptoms and health status (105, 106), improves the effectiveness of pulmonary rehabilitation (107, 108), and reduces exacerbations and related hospitalizations (107). Clinical trials

have shown a greater effect on exacerbation rates for LAMA treatment (tiotropium) versus LABA treatment (109, 110). An unexpected small increase in cardiovascular events was reported in patients with COPD regularly treated with ipratropium bromide (111, 112). A large trial reported no difference in mortality, cardiovascular morbidity, or exacerbation rates when using tiotropium as a dry-powder inhaler compared with a mist delivered by the Respimat inhaler (113).

METHYLXANTHINES. Theophylline exerts a modest bronchodilator effect in stable COPD (114) and improves FEV₁ and breathlessness when added to salmeterol (115, 116). There is limited and contradictory evidence regarding the effect of low-dose theophylline on exacerbation rates (117, 118). Toxicity is dose related, which is a problem as most of the benefit occurs when near-toxic doses are given (114, 119).

Combination bronchodilator therapy.

Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation, with a lower risk of side effects compared with increasing the dose of a single bronchodilator (Table 3) (120). There are numerous combinations of LABAs and LAMAs in a single inhaler available (Table E3). These combinations improve lung function compared with placebo (120) and have a greater impact on patient-reported

Table 3. Bronchodilators in Stable Chronic Obstructive Pulmonary Disease

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms (**Evidence A**).
- Regular and as-needed use of SABA or SAMA improves FEV₁ and symptoms (**Evidence A**).
- Combinations of SABA and SAMA are superior to either medication alone in improving FEV₁ and symptoms (**Evidence A**).
- LABAs and LAMAs significantly improve lung function, dyspnea, and health status and reduce exacerbation rates (**Evidence A**).
- LAMAs have a greater effect on exacerbation reduction compared with LABAs (**Evidence A**) and decrease hospitalizations (**Evidence B**).
- Combination treatment with LABA and LAMA increases FEV₁ and reduces symptoms compared with monotherapy (**Evidence A**).
- Combination treatment with LABA and LAMA reduces exacerbations compared with monotherapy (**Evidence B**) or ICS/LABA (**Evidence B**).
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance (**Evidence B**).
- Theophylline exerts a small bronchodilator effect in stable COPD (**Evidence A**) that is associated with modest symptomatic benefits (**Evidence B**).

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β-agonist; SAMA = short-acting muscarinic antagonist.

outcomes than monotherapies (121–124). LABA/LAMA combination improves symptoms and health status in patients with COPD (125), is more effective than long-acting bronchodilator monotherapy for preventing exacerbations (126), and decreases exacerbations to a greater extent than ICS/LABA combination (127).

Antiinflammatory agents.

Exacerbations represent the main clinically relevant end point used for the efficacy assessment of antiinflammatory drugs (Table 4).

ICSs. In patients with moderate to very severe COPD and exacerbations, an ICS combined with an LABA is more effective than either component alone in improving lung function and health status and reducing exacerbations (128, 129).

However, survival is not affected by combination therapy (130, 131).

ICS use has a higher prevalence of oral candidiasis, hoarse voice, skin bruising, and pneumonia (132). Patients at higher risk of pneumonia include those who currently smoke, are aged 55 years or older, have a history of prior exacerbations or pneumonia, have a body mass index (BMI) less than 25 kg/m², or have a poor MRC dyspnea grade and/or severe airflow limitation (133).

Results from randomized controlled trials (RCTs) have yielded variable results regarding the risk of decreased bone density and fractures with ICS treatment (99, 134–137). Observational studies suggest that ICS treatment could be associated with increased risks of diabetes/poor control of

diabetes (138), cataracts (139), and mycobacterial infection (140), including tuberculosis (141, 142).

ICS WITHDRAWAL. Withdrawal studies provide equivocal results regarding the consequences of withdrawal on lung function, symptoms, and exacerbations (143–147).

Triple inhaled therapy. Combination of LABA plus LAMA plus ICS (triple therapy) may improve lung function and patient-reported outcomes (148–151) and reduce exacerbation risk (149, 152–154). However, one RCT failed to demonstrate any benefit of adding an ICS to LABA plus LAMA on exacerbations (155). More evidence is needed to compare the benefits of triple therapy (LABA/LAMA/ICS) to LABA/LAMA.

Oral glucocorticoids. Oral glucocorticoids have no role in the chronic daily treatment of COPD because of a lack of benefit balanced against a high rate of systemic complications.

Phosphodiesterase-4 inhibitors.

Roflumilast reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations (156). Phosphodiesterase-4 inhibitors have more adverse effects than inhaled medications for COPD (157). The most frequent are diarrhea, nausea, reduced appetite, weight loss, abdominal pain, sleep disturbance, and headache. Roflumilast should be avoided in underweight patients and used with caution in patients with depression.

Antibiotics. Azithromycin (250 mg/d or 500 mg three times per wk) or erythromycin (500 mg two times per d) for 1 year reduces the risk of exacerbations in patients prone to exacerbations (158–160). Azithromycin use showed a reduced exacerbation rate in former smokers only and was associated with an increased incidence of bacterial resistance and impaired hearing tests (160). Pulse moxifloxacin therapy in patients with chronic bronchitis and frequent exacerbations does not reduce exacerbation rate (161).

Mucolytic (mucokinetics, mucoregulators) and antioxidant agents (N-acetylcysteine, carbocysteine). Regular treatment with mucolytics, such as carbocysteine and N-acetylcysteine, may reduce exacerbations and modestly improve health status in patients not receiving ICSs (162, 163).

Table 4. Antiinflammatory Therapy in Stable Chronic Obstructive Pulmonary Disease

ICSs

- An ICS combined with an LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD (**Evidence A**).
- Regular treatment with ICSs increases the risk of pneumonia, especially in those with severe disease (**Evidence A**).
- Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms, and health status (**Evidence A**) and reduces exacerbations (**Evidence B**) compared with ICS/LABA or LAMA monotherapy.

Oral glucocorticoids

- Long-term use of oral glucocorticoids has numerous side effects (**Evidence A**) with no evidence of benefits (**Evidence C**).

PDE4 inhibitors

- In patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations:
 - A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations (**Evidence A**).
 - A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations (**Evidence B**).

Antibiotics

- Long-term azithromycin and erythromycin therapy reduces exacerbations over 1 year (**Evidence A**).
- Treatment with azithromycin is associated with an increased incidence of bacterial resistance (**Evidence A**) and hearing test impairment (**Evidence B**).

Mucolytics/antioxidants

- Regular use of NAC and carbocysteine reduces the risk of exacerbations in select populations (**Evidence B**).

Other antiinflammatory agents

- Simvastatin does not prevent exacerbations in patients with COPD at increased risk of exacerbations and without indications for statin therapy (**Evidence A**). However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications (**Evidence C**).
- Leukotriene modifiers have not been tested adequately in patients with COPD.

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β -agonist; LAMA = long-acting muscarinic antagonist; NAC = N-acetylcysteine; PDE4 = phosphodiesterase 4.

Other drugs with antiinflammatory potential. Although RCTs suggest that immunoregulators decrease the severity and frequency of exacerbations (164, 165), the long-term effects of this therapy are unknown. Nedocromil and leukotriene modifiers have not been adequately tested in COPD (166). There was no evidence of benefit, and some evidence of harm, after treatment with an anti-tumor necrosis factor- α antibody (infliximab) in moderate to severe COPD (167). Simvastatin did not prevent exacerbations in patients with COPD who had no metabolic or cardiovascular indication for statin treatment (168). An association between statin use and improved outcomes has been reported in observational studies of patients with COPD who received them for cardiovascular and metabolic indications (169). There is no evidence that vitamin D supplementation reduces exacerbations in unselected patients (170).

Issues related to inhaled delivery.

Observational studies have identified a significant relationship between poor inhaler use and symptom control in COPD (171). Determinants of poor inhaler technique include older age, use of multiple devices, and lack of previous education on inhaler technique (172). Education improves inhalation technique in some but not all patients (172), especially when the “teach-back” approach is implemented (173).

Other pharmacologic treatments for COPD are summarized in Table E4.

ALPHA-1 ANTITRYPSIN AUGMENTATION THERAPY. Observational studies suggest a reduction in spirometric progression in alpha-1 antitrypsin deficiency patients treated with augmentation therapy versus patients who are not treated (174). Studies using sensitive parameters of emphysema progression determined by CT scans provide evidence for an effect on preserving lung tissue compared with placebo (175–177).

ANTITUSSIVES. The role of antitussives in patients with COPD is inconclusive (178).

VASODILATORS. Available studies report worsening gas exchange (179) with little improvement in exercise capacity or health status in patients with COPD (180, 181).

Rehabilitation, Education, and Self-Management

Pulmonary Rehabilitation

Pulmonary rehabilitation is a comprehensive intervention based on thorough patient

assessment followed by patient-tailored therapies (e.g., exercise training, education, and self-management interventions aimed at behavior changes to improve physical and psychological condition and promote adherence to health-enhancing behaviors in patients with COPD) (182). The benefits of pulmonary rehabilitation are considerable (Table E5). Pulmonary rehabilitation can reduce readmissions and mortality in patients after a recent exacerbation (≤ 4 wk from prior hospitalization) (183). Initiating pulmonary rehabilitation before hospital discharge, however, may compromise survival (184).

Pulmonary rehabilitation represents integrated patient management that includes a range of healthcare professionals (185) and sites, including hospital inpatient and outpatient settings and/or the patient's home (182).

Education, Self-Management, and Integrative Care

Education. Smoking cessation, correct use of inhaler devices, early recognition of exacerbation, decision-making, when to seek help, surgical interventions, and the consideration of advance directives are examples of educational topics.

Self-management. Self-management interventions that use written negotiated action plans for worsening symptoms may lead to less respiratory-related hospitalization and all-cause hospitalizations and improved health status (186). The health benefits of COPD self-management programs may be negated by increased mortality (187, 188). Generalization to real life remains difficult.

Integrated care programs. Integrated care programs improve several clinical outcomes, although not mortality (189). However, a large multicenter study within an existing well-organized system of care did not confirm this (190). Delivering integrated interventions by telemedicine provided no significant benefit (191).

Supportive, Palliative, End-of-Life, and Hospice Care

Symptom Control and Palliative Care

The goal of palliative care is to prevent and relieve suffering and to improve quality of life for patients and their families, regardless of the stage of disease or the need for other therapies (192). Palliation efforts should be

focused on the relief of dyspnea, pain, anxiety, depression, fatigue, and poor nutrition.

End-of-Life and Hospice Care

End-of-life care discussions should include patients and their families (193). Advance care planning can reduce anxiety for patients and their families; ensure that care is consistent with their wishes; and avoid unnecessary, unwanted, and costly invasive therapies (194, 195). Table E6 summarizes the approach to palliation, end-of-life, and hospice care.

Other Treatments

Oxygen Therapy and Ventilatory Support

Oxygen therapy. The long-term administration of oxygen (> 15 h/d) to patients with chronic respiratory failure increases survival in patients with severe resting hypoxemia (196). Long-term oxygen therapy does not lengthen time to death or first hospitalization or provide sustained benefit for any of the measured outcomes in patients with stable COPD and resting or exercise-induced moderate arterial oxygen desaturation (197).

Ventilatory support. Whether to use noninvasive positive pressure ventilation chronically at home to treat patients with acute-on-chronic respiratory failure after hospitalization remains undetermined. Retrospective studies have provided inconclusive data (198, 199). RCTs have yielded conflicting data on the use of home noninvasive positive pressure ventilation on survival and rehospitalization in chronic hypercapnic COPD (200–203). In patients with both COPD and obstructive sleep apnea (OSA), continuous positive airway pressure improves survival and avoids hospitalization (Table E7) (204).

Interventional Therapy

Surgical Interventions

Lung volume reduction surgery. An RCT confirmed that patients with COPD with upper-lobe emphysema and low postrehabilitation exercise capacity experienced improved survival when treated with lung volume reduction surgery (LVRS) compared with medical treatment (205). In patients with high postpulmonary rehabilitation exercise capacity, no difference in survival was noted after LVRS, although

health status and exercise capacity improved. LVRS has been demonstrated to result in higher mortality than medical management in patients with severe emphysema with an FEV₁ less than or equal to 20% predicted and either homogeneous emphysema in high-resolution CT (HRCT) or diffusing capacity of the lung for carbon monoxide of less than or equal to 20% predicted (206).

Bullectomy. In selected patients with relatively preserved underlying lung, bullectomy is associated with decreased dyspnea and improved lung function and exercise tolerance (207).

Lung transplantation. In selected patients, lung transplantation has been shown to improve health status and functional capacity but not to prolong survival (207–209). Bilateral lung transplantation has been reported to have longer survival than single lung transplantation in patients with COPD, especially those younger than 60 years of age (210).

Bronchoscopic Interventions to Reduce Hyperinflation in Severe Emphysema

Less-invasive bronchoscopic approaches to lung reduction have been developed (211). Prospective studies have shown that the use of bronchial stents is not effective (212), whereas use of lung sealant caused significant morbidity and mortality (213). An RCT of endobronchial valve placement showed statistically significant improvements in FEV₁ and 6-minute-walk distance compared with control therapy at 6 months postintervention (214), but the magnitude of the observed improvements was not clinically meaningful. Subsequently, efficacy of the same endobronchial valve has been studied in patients with heterogeneous (215) or heterogeneous and homogenous emphysema (216), with mixed outcomes.

Two multicenter trials that examined nitinol coils implanted into the lung compared with usual care reported increases in 6-minute-walk distance with coil treatment compared with control and smaller improvements in FEV₁ and quality of life measured by SGRQ (217, 218).

Additional data are needed to define the optimal patient population to receive a specific bronchoscopic lung volume technique and to compare the long-term durability of improvements in functional or physiological performance to LVRS relative to side effects (218).

Key points for interventional therapy in stable COPD are summarized in Table E8.

Management of Stable COPD

Key Points:

- The management strategy for stable COPD should be based on individualized symptom assessment and future risk of exacerbations.
- All individuals who smoke should be supported to quit.
- The main treatment goals are reduction of symptoms and future risk of exacerbations.
- Management strategies are not limited to pharmacologic treatments and should be complemented by appropriate nonpharmacologic interventions.

Effective COPD management should be based on an individualized assessment to reduce both current symptoms and future risk of exacerbations (Figure E1).

We propose personalization of initiating and escalating/deescalating treatments on the basis of the level of symptoms and an individual's risk of exacerbations. These recommendations are partially based on evidence generated in RCTs. These recommendations are intended to support clinician decision-making.

Identify and Reduce Exposure to Risk Factors

Cigarette smoking is the most commonly encountered and easily identifiable risk factor for COPD; smoking cessation should be continually encouraged for current

smokers. Reduction of total personal exposure to occupational dusts, fumes, and gases, and to indoor and outdoor air pollutants, should be addressed.

Treatment of Stable COPD

Pharmacologic Treatment

Pharmacologic therapies can reduce symptoms and the risk and severity of exacerbations and improve health status and exercise tolerance. The choice within each class depends on the availability of medication and the patient's response and preference (Tables 5–7).

Pharmacologic treatment algorithms. A proposed model for the initiation and then subsequent escalation and/or deescalation of pharmacologic management according to the individualized assessment of symptoms and exacerbation risk is shown in Figure 3. In past GOLD Reports, recommendations were only given for initial therapy. However, many patients with COPD are already receiving treatment and return with persistent symptoms after initial therapy or, less commonly, with resolution of some symptoms that may subsequently require less therapy. Therefore, we now suggest escalation and deescalation strategies. The recommendations are based on available efficacy and safety data. We acknowledge that treatment escalation has not been systematically tested; trials of deescalation are also limited and only include ICSs. There is a lack of direct evidence supporting the therapeutic recommendations for patients in groups C and D. These recommendations will be reevaluated as additional data become available.

GROUP A. All group A patients should be offered a bronchodilator to reduce breathlessness. This can be either a short- or a long-acting bronchodilator, depending on the individual patient's preference. The bronchodilator should

Table 5. Key Points for the Use of Bronchodilators

- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea (**Evidence A**).
- Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator, treatment should be escalated to two (**Evidence A**).
- Inhaled bronchodilators are recommended over oral bronchodilators (**Evidence A**).
- Theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable (**Evidence B**).

Definition of abbreviations: LABA = long-acting β -agonist; LAMA = long-acting muscarinic antagonist.

Table 6. Key Points for the Use of Antiinflammatory Agents

- Long-term monotherapy with ICSs is not recommended (**Evidence A**).
- Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators (**Evidence A**).
- Long-term therapy with oral corticosteroids is not recommended (**Evidence A**).
- In patients with exacerbations despite LABA/ICS or LABA/LAMA/ICS, chronic bronchitis, and severe to very severe airflow obstruction, the addition of a PDE4 inhibitor can be considered (**Evidence B**).
- In former smokers with exacerbations despite appropriate therapy, macrolides can be considered (**Evidence B**).
- Statin therapy is not recommended for prevention of exacerbations (**Evidence A**).
- Antioxidant mucolytics are recommended only in selected patients (**Evidence A**).

Definition of abbreviations: ICS = inhaled corticosteroid; LABA = long-acting β -agonist; LAMA = long-acting muscarinic antagonist; PDE4 = phosphodiesterase 4.

be continued if symptomatic benefit is noted.

GROUP B. Initial therapy should be a long-acting bronchodilator. Long-acting bronchodilators are superior to short-acting bronchodilators taken intermittently (104, 219). There is no evidence to recommend one class of long-acting bronchodilators over another for symptom relief; the choice should depend on individual patient response.

For patients with persistent breathlessness on monotherapy (220), the use of two bronchodilators is recommended. For patients with severe breathlessness, initial therapy with two bronchodilators may be considered.

GROUP C. Initial therapy should be a single long-acting bronchodilator. In two head-to-head comparisons (110, 111), the LAMA tested superior to the LABA regarding exacerbation prevention; therefore, we recommend initiating a LAMA in this group.

Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LABA/LAMA) or using a combination of an LABA and an ICS. As ICSs increase the risk for developing pneumonia, our primary choice is LABA/LAMA.

GROUP D. We recommend initiating an LABA/LAMA combination because:

- In studies with patient-reported outcomes as the primary endpoint, LABA/LAMA combinations showed superior results compared with a single bronchodilator.
- LABA/LAMA combination was superior to LABA/ICS combination in preventing exacerbations and improving other patient-reported outcomes in group D patients.
- Group D patients are at higher risk for pneumonia when receiving ICS treatment (111, 133).

If a single bronchodilator is initially chosen, an LAMA is preferred for exacerbation prevention on the basis of comparison to LABAs.

LABA/ICS may be the first choice for initial therapy in some patients. These patients may have a history and/or findings suggestive of ACO and/or high blood eosinophil counts.

In patients who develop additional exacerbations on LABA/LAMA therapy, we suggest two alternative pathways:

- Escalation to LABA/LAMA/ICS.
- Switch to LABA/ICS. If LABA/ICS therapy does not positively impact exacerbations/symptoms, an LAMA can be added.

If patients treated with LABA/LAMA/ICS still have exacerbations, the following options may be considered:

- Add roflumilast. This may be considered in patients with an FEV₁ less than 50% predicted and chronic bronchitis (221), particularly if they experienced at least one hospitalization for an exacerbation in the previous year (222).
- Add a macrolide in former smokers. The possibility of developing resistant organisms should be factored into the decision-making.
- Stopping ICS. This recommendation is supported by data that show an elevated risk of adverse effects (including pneumonia) and no significant harm from ICS withdrawal.

Nonpharmacologic Treatment

Education and self-management. An individual patient’s evaluation and risk assessment (e.g., exacerbations, patient’s needs, preferences, and personal goals) should aid the design of personalized self-management.

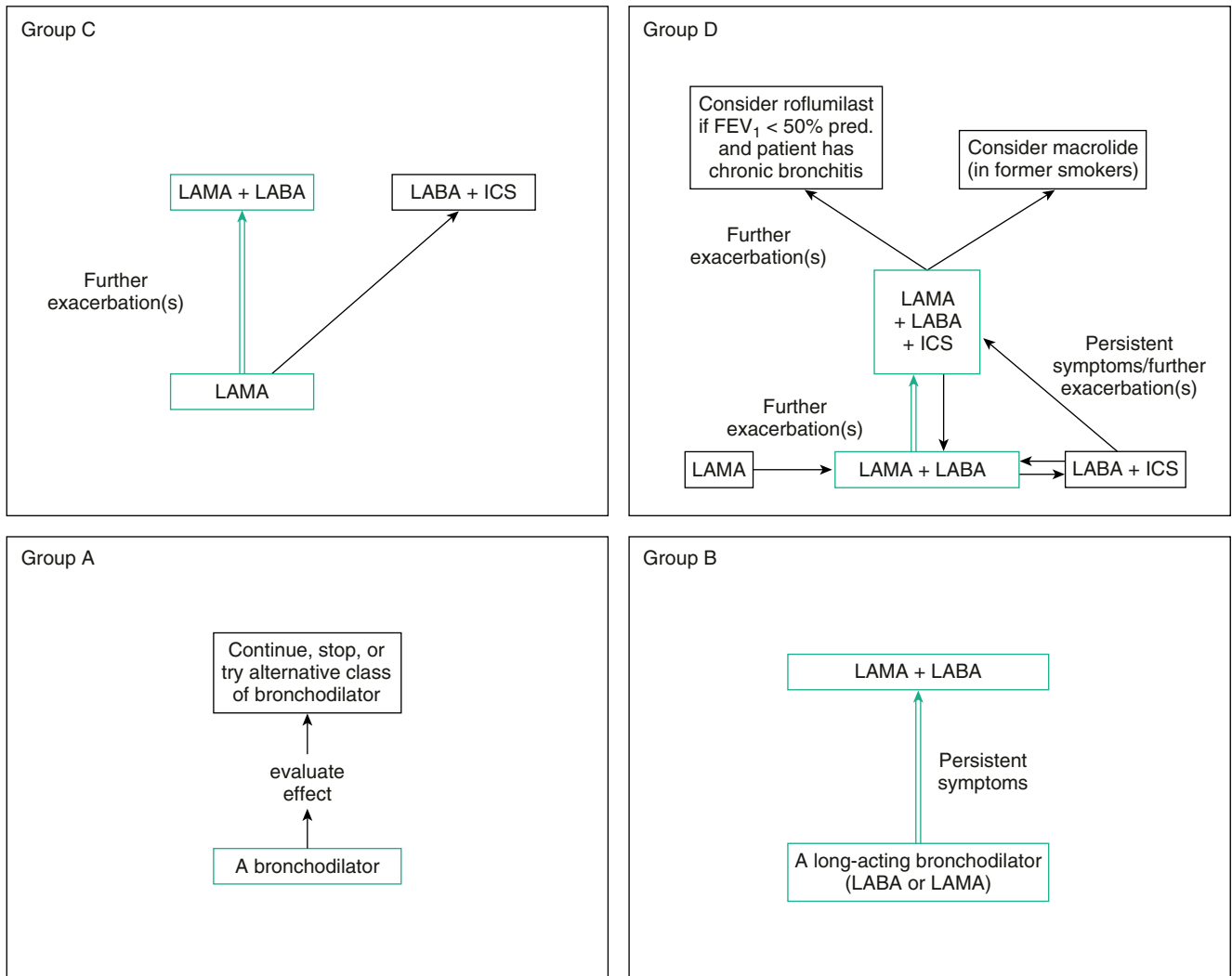
Pulmonary rehabilitation programs. Patients with high symptom burden and risk of exacerbations (groups B, C, and D), should take part in a full rehabilitation program that considers the individual’s characteristics and comorbidities (182, 187, 223).

Exercise training. A combination of constant load or interval training with strength training provides better outcomes than either method alone (224). Adding strength training to aerobic training is effective in improving strength but does not improve health status or exercise tolerance (225). Upper extremity exercise training

Table 7. Key Points for the Use of Other Pharmacologic Treatments

- Patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy (**Evidence B**).
- Antitussives cannot be recommended (**Evidence C**).
- Drugs approved for primary pulmonary hypertension are not recommended for patients with pulmonary hypertension secondary to COPD (**Evidence B**).
- Low-dose long-acting oral and parenteral opioids may be considered for treating dyspnea in patients with COPD with severe disease (**Evidence B**).

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.



Preferred treatment = →

In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted.

Figure 3. Pharmacologic treatment algorithms by Global Initiative for Chronic Obstructive Lung Disease grade. Green boxes and arrows indicate preferred treatment pathways. ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist.

improves arm strength and endurance and improves capacity for upper extremity activities (226).

Self-management education. An educational program should include smoking cessation, basic information about COPD, aspects of medical treatment (respiratory medications and inhalation devices), strategies to minimize dyspnea, advice about when to seek help, and possibly a discussion of advance directives and end-of-life issues.

End-of-life and palliative care. Patients should be informed that should they become critically ill, they or their family members may need to decide whether a course of intensive care is

likely to achieve their personal goals of care. Simple, structured conversations about these possible scenarios should be discussed while patients are in their stable state (227).

Nutritional support. For malnourished patients with COPD, nutritional supplementation is recommended.

Vaccination. Influenza vaccination is recommended for all patients with COPD. The pneumococcal vaccinations PCV13 and PPSV23 are recommended for all patients older than 65 years of age. PPSV23 is also recommended for younger patients with COPD with significant comorbid conditions, including chronic heart or lung disease (228).

Oxygen therapy. Long-term oxygen therapy is indicated for stable patients who have:

- PaO₂ at or below 7.3 kPa (55 mm Hg) or SaO₂ at or below 88%, with or without hypercapnia, confirmed twice over a 3-week period; or
- PaO₂ between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg), or SaO₂ of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%).

Ventilatory support. Noninvasive ventilation (NIV) is occasionally used in patients with stable very severe COPD.

NIV may be considered in a selected group of patients, particularly those with pronounced daytime hypercapnia and recent hospitalization, although contradictory evidence exists regarding its effectiveness (229). In patients with both COPD and OSA, continuous positive airway pressure is indicated (204).

Interventional bronchoscopy and surgery.

- In selected patients with heterogeneous or homogenous emphysema and significant hyperinflation refractory to optimized medical care, surgical or bronchoscopic modes of lung volume reduction (e.g., endobronchial one-way valves or lung coils) may be considered (230).
- In selected patients with a large bulla, surgical bullectomy may be considered.
- In selected patients with very severe COPD and without relevant contraindications, lung transplantation may be considered.

Choosing bronchoscopic lung reduction or LVRS to treat hyperinflation in a patient with emphysema depends on a number of factors, including: the extent and pattern of emphysema identified on HRCT, the presence of interlobar collateral ventilation measured by fissure integrity on HRCT or physiological assessment (endoscopic balloon occlusion and flow assessment), local proficiency in the

performance of the procedures, and patient and provider preferences. An algorithm depicting the various interventions on the basis of radiological and physiological features is shown in Figure 4.

Criteria for referral for lung transplantation include COPD with progressive disease, not a candidate for endoscopic or surgical lung volume reduction, BODE index of 5 to 6, P_{CO2} greater than 50 mm Hg or 6.6 kPa and/or Pa_{O2} less than 60 mm Hg or 8 kPa, and FEV₁ less than 25% predicted (231). Recommended criteria for listing include one of the following: BODE index greater than 7, FEV₁ less than 15 to 20% predicted, three or more severe exacerbations during the preceding year, one severe exacerbation with acute hypercapnic respiratory failure, or moderate to severe pulmonary hypertension (231, 232).

Key points for the use of nonpharmacologic treatments are summarized in Table E9.

Monitoring and Follow-up

Routine follow-up of patients with COPD is essential. Symptoms, exacerbations, and objective measures of airflow limitation should be monitored to determine when to modify management and to identify any

complications and/or comorbidities that may develop. To adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current therapeutic regimen. Symptoms that indicate worsening or development of another comorbid condition should be evaluated and treated.

Key Points:

- An exacerbation of COPD is an acute worsening of respiratory symptoms that results in additional therapy.
- Exacerbations can be precipitated by several factors. The most common causes are respiratory tract infections.
- The goal for treatment of exacerbations is to minimize the negative impact of the current exacerbation and to prevent subsequent events.
- Short-acting inhaled β₂-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation.
- Maintenance therapy with long-acting bronchodilators should be initiated as soon as possible before hospital discharge.
- Systemic corticosteroids improve lung function (FEV₁) and oxygenation and shorten recovery time and hospitalization duration.
- Antibiotics, when indicated, shorten recovery time and reduce the risk of early relapse, treatment failure, and hospitalization duration.
- Methylxanthines are not recommended owing to side effects.
- NIV should be the first mode of ventilation used to treat acute respiratory failure.
- After an exacerbation, appropriate measures for exacerbation prevention should be initiated.

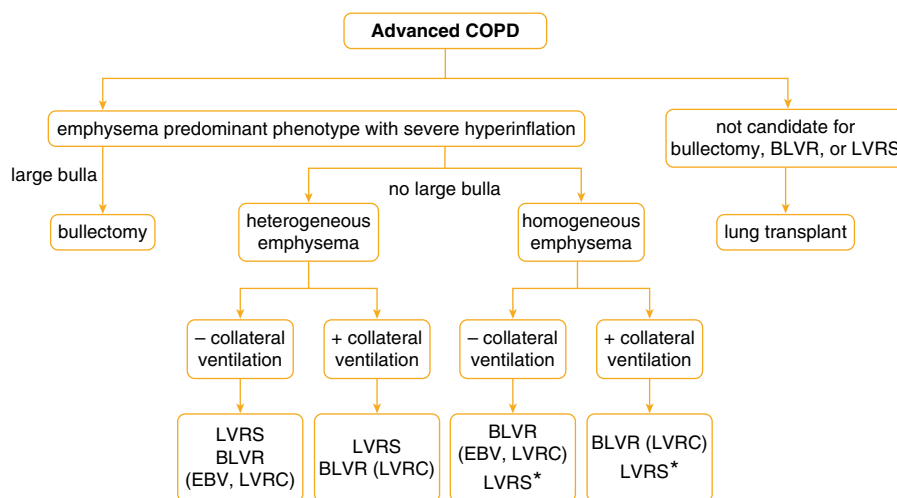


Figure 4. Interventional bronchoscopic and surgical treatments for chronic obstructive pulmonary disease (COPD). Overview of various therapies used to treat patients with COPD and emphysema worldwide. Note that all therapies are not approved for clinical care in all countries. In addition, the effects of BLVR on survival or other long term outcomes or comparison to LVRS are unknown. BLVR = bronchoscopic lung volume reduction; EBV = endobronchial valve; LVRC = lung volume reduction coil; LVRS = lung volume reduction surgery. *At some but not all centers.

Management of Exacerbations

Exacerbations are important events in the management of COPD because they negatively impact health status, rates of hospitalization and readmission, and disease progression (233, 234). COPD exacerbations

are complex events usually associated with increased airway inflammation, increased mucus production, and marked gas trapping. Increased dyspnea is the key symptom of an exacerbation. Other symptoms include increased sputum purulence and volume, together with increased cough and wheeze (235). As comorbidities are common in patients with COPD, exacerbations must be differentiated from acute coronary syndrome, worsening congestive heart failure, pulmonary embolism, and pneumonia.

COPD exacerbations are classified as:

- Mild (treated with short-acting bronchodilators only),
- Moderate (treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids), or
- Severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may be associated with acute respiratory failure.

Exacerbations are mainly triggered by respiratory viral infections, although bacterial infections and environmental factors may also initiate and/or amplify these events (236).

Exacerbations can be associated with increased sputum production and, if purulent, increased bacteria may be found in the sputum (235, 237, 238). Some evidence supports the concept that eosinophils are increased in the airways, lung, and blood in a significant proportion of patients with COPD. Exacerbations associated with an increase in sputum or blood eosinophils may be more responsive to systemic steroids (239), although more prospective data are needed (239).

Symptoms usually last between 7 to 10 days during an exacerbation, but some events may last longer. At 8 weeks, 20% of patients have not recovered to their preexacerbation state (240). COPD exacerbations increase susceptibility to additional events (59, 241).

Patients with COPD susceptible to frequent exacerbations (defined as two or more exacerbations per year) have worse health status and morbidity than patients with less-frequent exacerbations (234). Other factors associated with an increased risk of acute exacerbations and/or severity of exacerbations include an increase in the ratio of the pulmonary artery to aorta cross-sectional dimension (i.e., ratio > 1) (242), a greater percentage of emphysema or airway wall thickness (243) measured by

chest CT imaging, and the presence of chronic bronchitis (244, 245).

Treatment Options

Treatment Setting

The goals of exacerbation treatment are to minimize the negative impact of the current exacerbation and to prevent the development of subsequent events (246). Depending on the severity of an exacerbation and/or the severity of the underlying disease, an exacerbation can be managed in either the outpatient or inpatient setting. More than 80% of exacerbations are managed on an outpatient basis with bronchodilators, corticosteroids, and antibiotics (59, 247, 248).

The indications for hospitalization during a COPD exacerbation are shown in Table E10. When patients with a COPD exacerbation come to the emergency department, they should be given supplemental oxygen and assessed to determine whether the exacerbation is life threatening and requires consideration for NIV and intensive care unit or respiratory unit hospitalization.

Long-term prognosis after hospitalization for COPD exacerbation is poor; the 5-year mortality rate is about 50% (249). Factors associated with poor outcomes include older age, lower BMI, comorbidities (e.g., cardiovascular disease or lung cancer), previous hospitalizations for COPD exacerbations, clinical severity of the index exacerbation, and need for long-term oxygen therapy at discharge (250, 251). Patients with a higher prevalence and severity of respiratory symptoms, poorer quality of life,

worse lung function, lower exercise capacity, lower lung density, and thickened bronchial walls on CT scan are at increased mortality risk after an acute exacerbation (252).

Key points for the management of all exacerbations are given in Table 8.

Pharmacologic Treatment

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

Bronchodilators. Short-acting inhaled β_2 -agonists, with or without short-acting anticholinergics, are the initial bronchodilators recommended for acute treatment of exacerbations (253, 254). There are no significant differences in FEV₁ when using metered dose inhalers (with or without a spacer device) or nebulizers to deliver the agent (255), although the latter may be an easier delivery method for sicker patients. Intravenous methylxanthines are not recommended owing to side effects (256, 257).

Glucocorticoids. Systemic glucocorticoids in COPD exacerbations shorten recovery time and improve FEV₁. They also improve oxygenation (258–261), the risk of early relapse, treatment failure (262), and the length of hospitalization (258, 260, 263). A dose of 40 mg prednisone per day for 5 days is recommended (264). Therapy with oral prednisolone is equally effective to intravenous administration (265). Glucocorticoids may be less efficacious to treat exacerbations in patients with lower blood eosinophil levels (59, 239, 266).

Table 8. Key Points for the Management of Exacerbations

-
- Short-acting inhaled β_2 -agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation (**Evidence C**).
 - Systemic corticosteroids improve lung function (FEV₁) and oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not be more than 5–7 d (**Evidence A**).
 - Antibiotics, when indicated, can shorten recovery time and reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be 5–7 d (**Evidence B**).
 - Methylxanthines are not recommended owing to increased side effect profiles (**Evidence B**).
 - NIV should be the first mode of ventilation used in patients with COPD with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation, decreases hospitalization duration, and improves survival (**Evidence A**).
-

Definition of abbreviation: COPD = chronic obstructive pulmonary disease; NIV = noninvasive ventilation.

Antibiotics. The use of antibiotics in exacerbations remains controversial (267–269). Evidence supports the use of antibiotics in patients with exacerbations and increased sputum purulence (268, 269). One review reported that antibiotics reduce the risk of short-term mortality by 77%, treatment failure by 53%, and sputum purulence by 44% (270). Procalcitonin-guided antibiotic treatment may reduce antibiotic exposure and side effects with the same clinical efficacy (271, 272). A study in patients with exacerbations requiring mechanical ventilation (invasive or noninvasive) reported increased mortality and a higher incidence of secondary nosocomial pneumonia when antibiotics were not given (273). Antibiotics should be given to patients with acute exacerbations who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive) (235, 236). The recommended length of antibiotic therapy is 5 to 7 days (274).

Antibiotic choice should be based on the local bacterial resistance pattern. Usual initial empirical treatment is an aminopenicillin with clavulanic acid, a macrolide, or a tetracycline. In patients with frequent exacerbations, severe airflow limitation (275, 276), and/or exacerbations requiring mechanical ventilation (277), cultures from sputum or other materials from the lung should be performed to identify the presence of resistant pathogens. Administration route depends on the patient's ability to eat and the pharmacokinetics of the antibiotic.

Respiratory Support

Oxygen therapy. Supplemental oxygen should be titrated to improve hypoxemia, with a target saturation of 88 to 92% (278). Once oxygen is started, blood gases should be checked to ensure satisfactory oxygenation without carbon dioxide retention and/or worsening acidosis.

Ventilatory support. Some patients require admission to the intensive care unit. Admission of patients with severe exacerbations to intermediate or special respiratory care units may be appropriate if

adequate personnel skills and equipment exist to manage acute respiratory failure.

NIV. NIV is preferred over invasive ventilation as the initial mode of ventilation to treat acute respiratory failure in patients hospitalized for acute exacerbations of COPD. NIV has been studied in RCTs showing a success rate of 80 to 85% (279–283). Mortality and intubation rates are reduced by NIV (279, 284–286).

Invasive mechanical ventilation. The indication for initiating invasive mechanical ventilation during an exacerbation includes failure of an initial trial of NIV (287). In patients who fail NIV as initial therapy and receive invasive ventilation as subsequent rescue therapy, morbidity, hospital length of stay, and mortality are greater (282).

Hospital Discharge and Follow-up

Lack of spirometric assessment and arterial blood gas analysis has been associated with rehospitalization and mortality (288). Mortality relates to patient age, the presence of acidotic respiratory failure, the need for ventilatory support, and comorbidities, including anxiety and depression (289).

The introduction of care bundles at hospital discharge to include education, optimization of medication, supervision and correction of inhaler technique, assessment and optimal management of comorbidities, early rehabilitation, telemonitoring, and continued patient contact have been investigated (290). There are insufficient data that they influence readmission rates, short-term mortality (288, 289, 291, 292), or cost-effectiveness (289).

Early follow-up (<30 d) after discharge should be undertaken when possible and has been related to fewer exacerbation-related readmissions (184, 293). Early follow-up permits a careful review of discharge therapy and an opportunity to make changes in therapy. Patients not attending early follow-up have increased 90-day mortality.

Additional follow-up at 3 months is recommended to ensure return to a stable state and review of patient's symptoms, lung function (by spirometry), and, when possible, the assessment of prognosis using multiple scoring systems such as BODE (293, 294). An assessment of the presence and management of comorbidities should also be undertaken (Table E11) (295).

Prevention of Exacerbations

After an acute exacerbation, measures for prevention of further exacerbations should be initiated (Table E12).

COPD and Comorbidities

Key Points:

- COPD often coexists with other diseases (comorbidities) that may significantly impact patient outcomes.
- The presence of comorbidities should not alter COPD treatment, and comorbidities should be treated per usual standards regardless of the presence of COPD.
- When COPD is part of a multimorbidity care plan, attention should be directed to ensure simplicity of treatment and minimize polypharmacy.

COPD often coexists with other diseases (comorbidities) that may have a significant impact on prognosis (63, 296–302). Some of these arise independently of COPD, whereas others may be causally related, either with shared risk factors or by one disease increasing the risk or compounding the severity of the other (303). Management of the patient with COPD must include identification and treatment of its comorbidities; the most common in COPD are outlined below.

Cardiovascular Disease

Heart failure. The prevalence of systolic or diastolic heart failure in patients with COPD ranges from 20 to 70% (304). Unrecognized heart failure may mimic or accompany acute exacerbations of COPD; 40% of patients with COPD who are mechanically ventilated because of hypercapnic respiratory failure have evidence of left ventricular dysfunction (305, 306). Treatment with β_1 -blockers improves survival in chronic heart failure and is recommended. Selective β_1 -blockers should be used (307).

Ischemic heart disease. There is an increased risk of myocardial damage in patients with concomitant ischemic

heart disease who have an acute exacerbation of COPD. Patients who demonstrate abnormal cardiac troponins are at an increased risk of adverse outcomes, including short-term (30 d) and long-term mortality (308).

Arrhythmias. Cardiac arrhythmias are common in COPD and vice versa. Atrial fibrillation is frequent and directly associated with FEV₁. Bronchodilators have been previously described as potentially proarrhythmic agents (309, 310); however, evidence suggests an overall acceptable safety profile for LABAs (311), anticholinergic drugs, and ICSs (101, 113, 133, 248, 312–316).

Peripheral vascular disease. In a large cohort of patients with COPD of all degrees of severity, 8.8% were diagnosed with peripheral artery disease (PAD), which was higher than the prevalence of 1.8% in control subjects without COPD (317). Patients with COPD with PAD reported a worse functional capacity and worse health status than those without PAD.

Hypertension. Hypertension is likely to be the most frequently occurring comorbidity in COPD and may have implications for prognosis (303, 318).

Osteoporosis

Osteoporosis is often associated with emphysema (319, 320), decreased BMI

(321), and low fat-free mass (322). Low bone mineral density and fractures are common in patients with COPD even after adjustment for steroid use, age, pack-years of smoking, current smoking, and exacerbations (323, 324). An association between inhaled corticosteroids and fractures has been found in pharmacoepidemiological studies. Systemic corticosteroids significantly increase the risk of osteoporosis.

Anxiety and Depression

Anxiety and depression are both associated with a poor prognosis (325, 326).

COPD and Lung Cancer

The association between emphysema and lung cancer is stronger than between airflow limitation and lung cancer (327–329). Increased age and greater smoking history further increase risk (330). Two studies of low-dose chest CT screening report improved survival in subjects aged 55 to 74 years, current smokers, or those who quit within the previous 15 years, with a smoking history of at least 30 pack-years (331, 332). Low-dose chest CT is now recommended in the United States for patients meeting these demographics; however, this is not a worldwide practice.

Metabolic Syndrome and Diabetes

Metabolic syndrome and diabetes are more frequent in COPD, and the latter is likely to affect prognosis (297). The prevalence of metabolic syndrome has been estimated to be more than 30% (333).

Gastroesophageal Reflux

Gastroesophageal reflux is an independent risk factor for exacerbations and is associated with worse health status (59, 334, 335).

Bronchiectasis

Bronchiectasis is associated with longer exacerbations (336) and increased mortality (295).

OSA

Patients with “overlap syndrome” (COPD and OSA) have a worse prognosis than patients with COPD or OSA alone. Patients with OSA and COPD with apneic events have more profound hypoxemia and more cardiac arrhythmias (337) and are more likely to develop daytime pulmonary hypertension (338, 339) than patients with just OSA or COPD alone. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

- Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA, Kanner RE, *et al.*; SPIROMICS Research Group. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med* 2016; 374:1811–1821.
- Regan EA, Lynch DA, Curran-Everett D, Curtis JL, Austin JH, Grenier PA, Kauczor HU, Bailey WC, DeMeo DL, Casaburi RH, *et al.*; Genetic Epidemiology of COPD (COPDGene) Investigators. Clinical and radiologic disease in smokers with normal spirometry. *JAMA Intern Med* 2015;175:1539–1549.
- Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, Studnicka M, Bateman E, Anto JM, Burney P, *et al.*; BOLD Collaborative Research Group. COPD in never smokers: results from the population-based burden of obstructive lung disease study. *Chest* 2011;139:752–763.
- Thomsen M, Nordestgaard BG, Vestbo J, Lange P. Characteristics and outcomes of chronic obstructive pulmonary disease in never smokers in Denmark: a prospective population study. *Lancet Respir Med* 2013; 1:543–550.
- Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 1991;303:671–675.
- Todisco T, de Benedictis FM, Iannacci L, Baglioni S, Eslami A, Todisco E, Dottorini M. Mild prematurity and respiratory functions. *Eur J Pediatr* 1993;152:55–58.
- Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007; 370:758–764.
- Lawlor DA, Ebrahim S, Davey Smith G. Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis. *Thorax* 2005;60: 851–858.
- Kohansal R, Martinez-Cambor P, Agustí 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.
- Raad D, Gaddam S, Schunemann HJ, Irani J, Abou Jaoude P, Honeine R, Akl EA. Effects of water-pipe smoking on lung function: a systematic review and meta-analysis. *Chest* 2011;139:764–774.
- She J, Yang P, Wang Y, Qin X, Fan J, Wang Y, Gao G, Luo G, Ma K, Li B, *et al.* Chinese water-pipe smoking and the risk of COPD. *Chest* 2014;146:924–931.
- Günen H, Tarraf H, Nemati A, Al Ghobain M, Al Mutairi S, Aoun Bacha Z. Waterpipe tobacco smoking. *Tuberk Toraks* 2016;64: 94–96.
- Tan WC, Lo C, Jong A, Xing L, Fitzgerald MJ, Vollmer WM, Buist SA, Sin DD; Vancouver Burden of Obstructive Lung Disease (BOLD) Research Group. Marijuana and chronic obstructive lung disease: a population-based study. *CMAJ* 2009;180:814–820.
- Yin P, Jiang CQ, Cheng KK, Lam TH, Lam KH, Miller MR, Zhang WS, Thomas GN, Adab P. Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. *Lancet* 2007;370:751–757.

15. 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;152:977–983.
16. Paulin LM, Diette GB, Blanc PD, Putcha N, Eisner MD, Kanner RE, Belli AJ, Christenson S, Tashkin DP, Han M, *et al.*; SPIROMICS Research Group. Occupational exposures are associated with worse morbidity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015;191:557–565.
17. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, Romieu I, Silverman EK, Balmes JR; Committee on Nonsmoking COPD, Environmental and Occupational Health Assembly. 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.
18. Orozco-Levi M, Garcia-Aymerich J, Villar J, Ramirez-Sarmiento A, Antó JM, Gea J. Wood smoke exposure and risk of chronic obstructive pulmonary disease. *Eur Respir J* 2006;27:542–546.
19. Gan WQ, FitzGerald JM, Carlsen C, Sadatsafavi M, Brauer M. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. *Am J Respir Crit Care Med* 2013;187:721–727.
20. Ezzati M. Indoor air pollution and health in developing countries. *Lancet* 2005;366:104–106.
21. Zhou Y, Zou Y, Li X, Chen S, Zhao Z, He F, Zou W, Luo Q, Li W, Pan Y, *et al.* Lung function and incidence of chronic obstructive pulmonary disease after improved cooking fuels and kitchen ventilation: a 9-year prospective cohort study. *Plos Med* 2014;11:e1001621.
22. Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004;126:59–65.
23. Rijcken B, Schouten JP, Weiss ST, Speizer FE, van der Lende R. The relationship of nonspecific bronchial responsiveness to respiratory symptoms in a random population sample. *Am Rev Respir Dis* 1987;136:62–68.
24. Hoppers JJ, Postma DS, Rijcken B, Weiss ST, Schouten JP. Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. *Lancet* 2000;356:1313–1317.
25. Tashkin DP, Altose MD, Connett JE, Kanner RE, Lee WW, Wise RA; The Lung Health Study Research Group. Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;153:1802–1811.
26. de Marco R, Accordini S, Marcon A, Cerveri I, Antó JM, Gislason T, Heinrich J, Janson C, Jarvis D, Kuenzli N, *et al.*; European Community Respiratory Health Survey (ECRHS). Risk factors for chronic obstructive pulmonary disease in a European cohort of young adults. *Am J Respir Crit Care Med* 2011;183:891–897.
27. Drummond MB, Kirk GD. HIV-associated obstructive lung diseases: insights and implications for the clinician. *Lancet Respir Med* 2014;2:583–592.
28. Menezes AM, Hallal PC, Perez-Padilla R, Jardim JR, Muiño A, Lopez MV, Valdivia G, Montes de Oca M, Talamo C, Pertuze J, *et al.*; Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) Team. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. *Eur Respir J* 2007;30:1180–1185.
29. Jordan TS, Spencer EM, Davies P. Tuberculosis, bronchiectasis and chronic airflow obstruction. *Respirology* 2010;15:623–628.
30. Byrne AL, Marais BJ, Mitnick CD, Lecca L, Marks GB. Tuberculosis and chronic respiratory disease: a systematic review. *Int J Infect Dis* 2015;32:138–146.
31. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, Menezes AM, Sullivan SD, Lee TA, Weiss KB, *et al.*; BOLD Collaborative Research Group. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007;370:741–750.
32. Miravittles M, Worth H, Soler Cataluña JJ, Price D, De Benedetto F, Roche N, Godtfredsen NS, van der Molen T, Löfdahl CG, Padullés L, *et al.* Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. *Respir Res* 2014;15:122.
33. Elliott MW, Adams L, Cockcroft A, MacRae KD, Murphy K, Guz A. The language of breathlessness: use of verbal descriptors by patients with cardiopulmonary disease. *Am Rev Respir Dis* 1991;144:826–832.
34. Medical Research Council Committee on the Aetiology of Chronic Bronchitis. Definition and classification of chronic bronchitis for clinical and epidemiological purposes: a report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis. *Lancet* 1965;1:775–779.
35. von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. *J Cachexia Sarcopenia Muscle* 2010;1:1–5.
36. Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993;147:1151–1156.
37. Holleman DR Jr, Simel DL. Does the clinical examination predict airflow limitation? *JAMA* 1995;273:313–319.
38. Kesten S, Chapman KR. Physician perceptions and management of COPD. *Chest* 1993;104:254–258.
39. van Dijk W, Tan W, Li P, Guo B, Li S, Benedetti A, Bourbeau J; CanCOLD Study Group. Clinical relevance of fixed ratio vs lower limit of normal of FEV1/FVC in COPD: patient-reported outcomes from the CanCOLD cohort. *Ann Fam Med* 2015;13:41–48.
40. Güder G, Brenner S, Angermann CE, Ertl G, Held M, Sachs AP, Lammers JW, Zanen P, Hoes AW, Störk S, *et al.* GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study. *Respir Res* 2012;13:13.
41. Vaz Fragoso CA, McAvay G, Van Ness PH, Casaburi R, Jensen RL, MacIntyre N, Gill TM, Yaggi HK, Concato J. Phenotype of normal spirometry in an aging population. *Am J Respir Crit Care Med* 2015;192:817–825.
42. Vaz Fragoso CA, McAvay G, Van Ness PH, Casaburi R, Jensen RL, MacIntyre N, Yaggi HK, Gill TM, Concato J. Phenotype of spirometric impairment in an aging population. *Am J Respir Crit Care Med* 2016;193:727–735.
43. Albert P, Agusti A, Edwards L, Tal-Singer R, Yates J, Bakke P, Celli BR, Coxson HO, Crim C, Lomas DA, *et al.* Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. *Thorax* 2012;67:701–708.
44. Hansen JE, Porszasz J. Counterpoint: is an increase in FEV₁ and/or FVC \geq 12% of control and \geq 200 mL the best way to assess positive bronchodilator response? No. *Chest* 2014;146:538–541.
45. Hill K, Goldstein RS, Guyatt GH, Blouin M, Tan WC, Davis LL, Heels-Ansdell DM, Erak M, Bragaglia PJ, Tamari IE, *et al.* Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. *CMAJ* 2010;182:673–678.
46. López Varela MV, Montes de Oca M, Rey A, Casas A, Stirbulov R, Di Boscio V; PUMA Team. Development of a simple screening tool for opportunistic COPD case finding in primary care in Latin America: the PUMA study. *Respirology* 2016;21:1227–1234.
47. Dirven JA, Tange HJ, Muris JW, van Haaren KM, Vink G, van Schayck OC. Early detection of COPD in general practice: implementation, workload and socioeconomic status. A mixed methods observational study. *Prim Care Respir J* 2013;22:338–343.
48. Fletcher CM. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). *BMJ* 1960;2:1662.
49. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581–586.
50. Sundh J, Janson C, Lisspers K, Stållberg B, Montgomery S. The Dyspnoea, Obstruction, Smoking, Exacerbation (DOSE) index is predictive of mortality in COPD. *Prim Care Respir J* 2012;21:295–301.
51. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002;121:1434–1440.

52. Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001;56:880–887.
53. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;42:773–778.
54. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145:1321–1327.
55. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, MacNee W, Miller BE, Rennard S, Silverman EK, et al.; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) investigators. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010;11:122.
56. Nishimura K, Mitsuma S, Kobayashi A, Yanagida M, Nakayasu K, Hasegawa Y, Jones PW. COPD and disease-specific health status in a working population. *Respir Res* 2013;14:61.
57. Miravittles M, Soriano JB, García-Río F, Muñoz L, Duran-Tauleria E, Sanchez G, Sobradillo V, Ancochea J. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. *Thorax* 2009;64:863–868.
58. Jones PW, Tabberer M, Chen WH. Creating scenarios of the impact of COPD and their relationship to COPD Assessment Test (CAT™) scores. *BMC Pulm Med* 2011;11:42.
59. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, Miller B, Lomas DA, Agusti A, Macnee W, et al.; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;363:1128–1138.
60. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005;60:925–931.
61. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015;3:435–442.
62. Siddiqui SH, Guasconi A, Vestbo J, Jones P, Agusti A, Paggiaro P, Wedzicha JA, Singh D. Blood eosinophils: a biomarker of response to extrafine beclomethasone/formoterol in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015;192:523–525.
63. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005;128:2099–2107.
64. National Institute for Health and Care Excellence. Multimorbidity: clinical assessment and management, in press. 2016 [accessed 2016 Aug 1]. Available from: <https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0704/documents>
65. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Buijzeel PL, Rutten EP, Op 't Roodt J, Wouters EF, Franssen FM. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;187:728–735.
66. Soriano JB, Lamprecht B, Ramirez AS, Martinez-Cambor P, Kaiser B, Alfageme I, Almagro P, Casanova C, Esteban C, Soler-Cataluña JJ, et al. Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data. *Lancet Respir Med* 2015;3:443–450.
67. Goossens LM, Leimer I, Metzendorf N, Becker K, Rutten-van Mölken MP. Does the 2013 GOLD classification improve the ability to predict lung function decline, exacerbations and mortality: a post-hoc analysis of the 4-year UPLIFT trial. *BMC Pulm Med* 2014;14:163.
68. Kim J, Yoon HI, Oh YM, Lim SY, Lee JH, Kim TH, Lee SY, Lee JH, Lee SD, Lee CH. Lung function decline rates according to GOLD group in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2015;10:1819–1827.
69. Han MK, Muellerova H, Curran-Everett D, Dransfield MT, Washko GR, Regan EA, Bowler RP, Beaty TH, Hokanson JE, Lynch DA, et al. GOLD 2011 disease severity classification in COPDGen: a prospective cohort study. *Lancet Respir Med* 2013;1:43–50.
70. Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. *Bull World Health Organ* 1997;75:397–415.
71. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005–1012.
72. Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, Wedzicha JA, Price D, Hyland ME. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE Index. *Am J Respir Crit Care Med* 2009;180:1189–1195.
73. Puhan MA, Garcia-Aymerich J, Frey M, ter Riet G, Antó JM, Agustí AG, Gómez FP, Rodríguez-Roisin R, Moons KG, Kessels AG, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet* 2009;374:704–711.
74. van Eerd EA, van der Meer RM, van Schayck OC, Kotz D. Smoking cessation for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2016;8:CD010744.
75. A clinical practice guideline for treating tobacco use and dependence: a US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. *JAMA* 2000;283:3244–3254.
76. van der Meer RM, Wagena EJ, Ostelo RW, Jacobs JE, van Schayck CP. Smoking cessation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2003;2:CD002999.
77. Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med* 2008;35:158–176.
78. McNeill A, Brose LS, Calder R, Hitchman SC. E-cigarettes: an evidence update. A report commissioned by Public Health England. London: Public Health England; 2015.
79. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst Rev* 2014;12:CD010216.
80. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation: authors' reply. *Lancet Respir Med* 2016;4:e26–e27.
81. Malas M, van der Tempel J, Schwartz R, Minichiello A, Lightfoot C, Noormohamed A, Andrews J, Zawertailo L, Ferrence R. Electronic cigarettes for smoking cessation: a systematic review. *Nicotine Tob Res* 2016;18:1926–1936.
82. Beard E, West R, Michie S, Brown J. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends. *BMJ* 2016;354:i4645.
83. 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;139:591–599.
84. Tashkin D, Kanner R, Bailey W, Buist S, Anderson P, Nides M, Gonzales D, Dozier G, Patel MK, Jamerson B. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001;357:1571–1575.
85. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev* 2013;5:CD009329.
86. Glynn T, Manley M. How to help your patients stop smoking: a National Cancer Institute manual for physicians. NIH Publication No. 90-3064. Bethesda, MD: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute; 1990.
87. Stead LF, Buitrago D, Preciado N, Sanchez G, Hartmann-Boyce J, Lancaster T. Physician advice for smoking cessation. *Cochrane Database Syst Rev* 2013;5:CD000165.
88. Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev* 2016;3:CD008286.

89. 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: 2011–2020.
90. Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;1:CD002733.
91. 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.
92. 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: 778–784.
93. Fiore AE, Shay DK, Broder K, Iskander JK, Uyekti TM, Mootrey G, Bresee JS, Cox NJ; Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR Recomm Rep* 2009;58:1–52.
94. Huang CL, Nguyen PA, Kuo PL, Iqbal U, Hsu YH, Jian WS. Influenza vaccination and reduction in risk of ischemic heart disease among chronic obstructive pulmonary elderly. *Comput Methods Programs Biomed* 2013;111:507–511.
95. Edwards KM, Dupont WD, Westrich MK, Plummer WD Jr, Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. *J Infect Dis* 1994;169:68–76.
96. Hak E, van Essen GA, Buskens E, Stalman W, de Melker RA. Is immunising all patients with chronic lung disease in the community against influenza cost effective? Evidence from a general practice based clinical prospective cohort study in Utrecht, The Netherlands. *J Epidemiol Community Health* 1998; 52:120–125.
97. 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: 1297–1303.
98. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA Jr, Enright PL, Kanner RE, O'Hara P, *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;272:1497–1505.
99. Pauwels RA, Löfdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, Ohlsson SV; European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *N Engl J Med* 1999;340: 1948–1953.
100. Vestbo J, Sørensen 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;353:1819–1823.
101. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543–1554.
102. O'Donnell DE, Flüge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, Make B, Magnussen H. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;23: 832–840.
103. O'Donnell DE, Sciruba F, Celli B, Mahler DA, Webb KA, Kalberg CJ, Knobil K. Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. *Chest* 2006;130: 647–656.
104. Appleton S, Jones T, Poole P, Pilotto L, Adams R, Lasserson TJ, Smith B, Muhammad J. Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;3:CD006101.
105. Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014; 7:CD009285.
106. Melani AS. Long-acting muscarinic antagonists. *Expert Rev Clin Pharmacol* 2015;8:479–501.
107. Kesten S, Casaburi R, Kukafka D, Cooper CB. Improvement in self-reported exercise participation with the combination of tiotropium and rehabilitative exercise training in COPD patients. *Int J Chron Obstruct Pulmon Dis* 2008;3:127–136.
108. Casaburi R, Kukafka D, Cooper CB, Witek TJ Jr, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest* 2005;127:809–817.
109. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Mölken MP, Beeh KM, Rabe KF, Fabbri LM; POET-COPD Investigators. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011;364:1093–1103.
110. Decramer ML, Chapman KR, Dahl R, Frith P, Devouassoux G, Fritscher C, Cameron R, Shoaib M, Lawrence D, Young D, *et al.*; INVIGORATE investigators. Once-daily inhaled tiotropium versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. *Lancet Respir Med* 2013;1:524–533.
111. Anthonisen NR, Connett JE, Enright PL, Manfreda J; Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med* 2002;166: 333–339.
112. Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium—the FDA's conclusions. *N Engl J Med* 2010;363:1097–1099.
113. Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B, Dusser D, Joseph E, Kattenbeck S, Koenen-Bergmann M, *et al.*; TIOSPIR Investigators. Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med* 2013;369:1491–1501.
114. Ram FS, Jones PW, Castro AA, De Brito JA, Atallah AN, Lacasse Y, Mazzini R, Goldstein R, Cendon S. Oral theophylline for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002; 4:CD003902.
115. ZuWallack RL, Mahler DA, Reilly D, Church N, Emmett A, Rickard K, Knobil K. Salmeterol plus theophylline combination therapy in the treatment of COPD. *Chest* 2001;119:1661–1670.
116. Zacarias EC, Castro AA, Cendon S. Effect of theophylline associated with short-acting or long-acting inhaled beta2-agonists in patients with stable chronic obstructive pulmonary disease: a systematic review. *J Bras Pneumol* 2007;33:152–160.
117. Cosío BG, Shafiek H, Iglesias A, Yanez A, Córdova R, Palou A, Rodríguez-Roisin R, Peces-Barba G, Pascual S, Gea J, *et al.* Oral low-dose theophylline on top of inhaled fluticasone-salmeterol does not reduce exacerbations in patients with severe COPD: a pilot clinical trial. *Chest* 2016;150:123–130.
118. Zhou Y, Wang X, Zeng X, Qiu R, Xie J, Liu S, Zheng J, Zhong N, Ran P. Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year. *Respirology* 2006; 11:603–610.
119. McKay SE, Howie CA, Thomson AH, Whiting B, Addis GJ. Value of theophylline treatment in patients handicapped by chronic obstructive lung disease. *Thorax* 1993;48:227–232.
120. Cazzola M, Molimard M. The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. *Pulm Pharmacol Ther* 2010;23:257–267.
121. van der Molen T, Cazzola M. Beyond lung function in COPD management: effectiveness of LABA/LAMA combination therapy on patient-centred outcomes. *Prim Care Respir J* 2012; 21:101–108.
122. Mahler DA, Decramer M, D'Urzo A, Worth H, White T, Alagappan VK, Chen H, Gallagher N, Kulich K, Banerji D. Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study. *Eur Respir J* 2014;43:1599–1609.
123. Singh D, Ferguson GT, Bolitschek J, Grönke L, Hallmann C, Bennett N, Abrahams R, Schmidt O, Bjermer L. Tiotropium + olodaterol shows clinically meaningful improvements in quality of life. *Respir Med* 2015;109:1312–1319.

124. Bateman ED, Chapman KR, Singh D, D'Urzo AD, Molins E, Leselbaum A, Gil EG. Acclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). *Respir Res* 2015;16:92.
125. Mahler DA, Kerwin E, Ayers T, FowlerTaylor A, Maitra S, Thach C, Lloyd M, Patalano F, Banerji D. FLIGHT1 and FLIGHT2: efficacy and safety of QVA149 (indacaterol/glycopyrrolate) versus its monocomponents and placebo in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015;192:1068–1079.
126. Wedzicha JA, Decramer M, Ficker JH, Niewoehner DE, Sandström T, Taylor AF, D'Andrea P, Arrasate C, Chen H, Banerji D. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med* 2013;1:199–209.
127. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, Thach C, Fogel R, Patalano F, Vogelmeier CF; FLAME Investigators. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med* 2016;374:2222–2234.
128. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;9:CD006829.
129. Nannini LJ, Poole P, Milan SJ, Kesterton A. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013;8:CD006826.
130. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775–789.
131. Vestbo J, Anderson JA, Brook RD, Calverley PM, Celli BR, Crim C, Martinez F, Yates J, Newby DE; SUMMIT Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016;387:1817–1826.
132. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;7:CD002991.
133. Crim C, Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, Vestbo J, Wachtel A, Martinez FJ, Barnhart F, et al. Pneumonia risk with inhaled fluticasone furoate and vilanterol compared with vilanterol alone in patients with COPD. *Ann Am Thorac Soc* 2015;12:27–34.
134. Johann O, Pauwels R, Löfdahl CG, Laitinen LA, Postma DS, Pride NB, Ohlsson SV. Bone mineral density in patients with chronic obstructive pulmonary disease treated with budesonide Turbuhaler. *Eur Respir J* 2002;19:1058–1063.
135. Ferguson GT, Calverley PM, Anderson JA, Jenkins CR, Jones PW, Willits LR, Yates JC, Vestbo J, Celli B. Prevalence and progression of osteoporosis in patients with COPD: results from the TOWARDS a Revolution in COPD Health study. *Chest* 2009;136:1456–1465.
136. Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, Vestbo J, Wachtel A, Martinez FJ, Barnhart F, Sanford L, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med* 2013;1:210–223.
137. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. *Thorax* 2011;66:699–708.
138. Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. *Am J Med* 2010;123:1001–1006.
139. Wang JJ, Rochtchina E, Tan AG, Cumming RG, Leeder SR, Mitchell P. Use of inhaled and oral corticosteroids and the long-term risk of cataract. *Ophthalmology* 2009;116:652–657.
140. Andréjak C, Nielsen R, Thomsen VO, Duhaut P, Sørensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. *Thorax* 2013;68:256–262.
141. Dong YH, Chang CH, Lin Wu FL, Shen LJ, Calverley PM, Löfdahl CG, Lai MS, Mahler DA. Use of inhaled corticosteroids in patients with COPD and the risk of TB and influenza: a systematic review and meta-analysis of randomized controlled trials. *Chest* 2014;145:1286–1297.
142. Lee CH, Kim K, Hyun MK, Jang EJ, Lee NR, Yim JJ. Use of inhaled corticosteroids and the risk of tuberculosis. *Thorax* 2013;68:1105–1113.
143. Nadeem NJ, Taylor SJ, Eldridge SM. Withdrawal of inhaled corticosteroids in individuals with COPD—a systematic review and comment on trial methodology. *Respir Res* 2011;12:107.
144. van der Valk P, Monnikhof 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;166:1358–1363.
145. Wouters EF, Postma DS, Fokkens B, Hop WC, Prins J, Kuipers AF, Pasma HR, Hensing CA, Creutzberg EC; COSMIC (COPD and Seretide: a Multi-Center Intervention and Characterization) Study Group. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. *Thorax* 2005;60:480–487.
146. Kunz LI, Postma DS, Klooster K, Lapperre TS, Vonk JM, Sont JK, Kerstjens HA, Snoeck-Stroband JB, Hiemstra PS, Sterk PJ; GLUCOLD Study Group. Relapse in FEV1 decline after steroid withdrawal in COPD. *Chest* 2015;148:389–396.
147. Magnussen H, Disse B, Rodriguez-Roisin R, Kirsten A, Watz H, Tetzlaff K, Towse L, Finnigan H, Dahl R, Decramer M, et al.; WISDOM Investigators. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med* 2014;371:1285–1294.
148. Welte T, Miravittles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, Kessler R. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;180:741–750.
149. 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;63:592–598.
150. Jung KS, Park HY, Park SY, Kim SK, Kim YK, Shim JJ, Moon HS, Lee KH, Yoo JH, Lee SD; Korean Academy of Tuberculosis and Respiratory Diseases study group; Korea Chronic Obstructive Pulmonary Disease study group. Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study. *Respir Med* 2012;106:382–389.
151. Hanania NA, Crater GD, Morris AN, Emmett AH, O'Dell DM, Niewoehner DE. Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. *Respir Med* 2012;106:91–101.
152. Frith PA, Thompson PJ, Ratnavadivel R, Chang CL, Bremner P, Day P, Frenzel C, Kurstjens N; Glisten Study Group. Glycopyrronium once-daily significantly improves lung function and health status when combined with salmeterol/fluticasone in patients with COPD: the GLISTEN study, a randomised controlled trial. *Thorax* 2015;70:519–527.
153. Siler TM, Kerwin E, Singletary K, Brooks J, Church A. Efficacy and safety of umeclidinium added to fluticasone propionate/salmeterol in patients with COPD: results of two randomized, double-blind studies. *COPD* 2016;13:1–10.
154. Singh D, Papi A, Corradi M, Pavlišová I, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Vestbo J. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2 -agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016;388:963–973.

155. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, Balter M, O'Donnell D, McIvor A, Sharma S, *et al.*; Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007;146:545–555.
156. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ; M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 2009;374:685–694.
157. Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013;11:CD002309.
158. 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;178:1139–1147.
159. Uzun S, Djamin RS, Kluytmans JA, Mulder PG, van't Veer NE, Ermens AA, Pelle AJ, Hoogsteden HC, Aerts JG, van der Eerden MM. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2014;2:361–368.
160. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, Curtis JL, Dransfield MT, Han MK, Lazarus SC, *et al.*; COPD Clinical Research Network. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011;365:689–698.
161. Sethi S, Jones PW, Theron MS, Miravittles M, Rubinstein E, Wedzicha JA, Wilson R; PULSE Study group. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Respir Res* 2010;11:10.
162. Cazzola M, Calzetta L, Page C, Jardim J, Chuchalin AG, Rogliani P, Matera MG. Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. *Eur Respir Rev* 2015;24:451–461.
163. Poole P, Chong J, Cates CJ. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015;7:CD001287.
164. 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;156:1719–1724.
165. 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;117:828–834.
166. Lee JH, Kim HJ, Kim YH. The Effectiveness of anti-leukotriene agents in patients with COPD: a systemic review and meta-analysis. *Lung* 2015;193:477–486.
167. Rennard SI, Fogarty C, Kelsen S, Long W, Ramsdell J, Allison J, Mahler D, Saadeh C, Siler T, Snell P, *et al.*; COPD Investigators. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:926–934.
168. Criner GJ, Connett JE, Aaron SD, Albert RK, Bailey WC, Casaburi R, Cooper JA Jr, Curtis JL, Dransfield MT, Han MK, *et al.*; COPD Clinical Research Network; Canadian Institutes of Health Research. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med* 2014;370:2201–2210.
169. Ingebrigtsen TS, Marott JL, Nordestgaard BG, Lange P, Hallas J, Vestbo J. Statin use and exacerbations in individuals with chronic obstructive pulmonary disease. *Thorax* 2015;70:33–40.
170. Lehouck A, Mathieu C, Caremans C, Baeke F, Verhaegen J, Van Eldere J, Decallonne B, Bouillon R, Decramer M, Janssens W. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2012;156:105–114.
171. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, Serra M, Scichilone N, Sestini P, Aliani M, *et al.*; Gruppo Educazionale Associazione Italiana Pneumologi Ospedalieri. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med* 2011;105:930–938.
172. Rootmensen GN, van Keimpema AR, Jansen HM, de Haan RJ. Predictors of incorrect inhalation technique in patients with asthma or COPD: a study using a validated videotaped scoring method. *J Aerosol Med Pulm Drug Deliv* 2010;23:323–328.
173. Dantic DE. A critical review of the effectiveness of “teach-back” technique in teaching COPD patients self-management using respiratory inhalers. *Health Educ J* 2014;73:41–50.
174. Chapman KR, Stockley RA, Dawkins C, Wilkes MM, Navickis RJ. Augmentation therapy for alpha1 antitrypsin deficiency: a meta-analysis. *COPD* 2009;6:177–184.
175. Chapman KR, Burdon JG, Piitulainen E, Sandhaus RA, Seersholm N, Stocks JM, Stoel BC, Huang L, Yao Z, Edelman JM, *et al.*; RAPID Trial Study Group. Intravenous augmentation treatment and lung density in severe α 1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;386:360–368.
176. Dirksen A, Dijkman JH, Madsen F, Stoel B, Hutchison DC, Ulrik CS, Skovgaard LT, Kok-Jensen A, Rudolphus A, Seersholm N, *et al.* A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999;160:1468–1472.
177. Dirksen A, Piitulainen E, Parr DG, Deng C, Wencker M, Shaker SB, Stockley RA. Exploring the role of CT densitometry: a randomised study of augmentation therapy in alpha1-antitrypsin deficiency. *Eur Respir J* 2009;33:1345–1353.
178. Schildmann EK, Rémi C, Bausewein C. Levodropropizine in the management of cough associated with cancer or nonmalignant chronic disease—a systematic review. *J Pain Palliat Care Pharmacother* 2011;25:209–218.
179. Barberà JA, Roger N, Roca J, Rovira I, Higenbottam TW, Rodriguez-Roisin R. Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease. *Lancet* 1996;347:436–440.
180. Blanco I, Santos S, Gea J, Güell R, Torres F, Gimeno-Santos E, Rodriguez DA, Vilaró J, Gómez B, Roca J, *et al.* Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial. *Eur Respir J* 2013;42:982–992.
181. Goudie AR, Lipworth BJ, Hopkinson PJ, Wei L, Struthers AD. Tadalafil in patients with chronic obstructive pulmonary disease: a randomised, double-blind, parallel-group, placebo-controlled trial. *Lancet Respir Med* 2014;2:293–300.
182. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, *et al.*; ATS/ERS Task Force on Pulmonary Rehabilitation. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188:e13–e64.
183. Puhan MA, Gimeno-Santos E, Scharplatz M, Troosters T, Walters EH, Steurer J. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011;10:CD005305.
184. Greening NJ, Williams JE, Hussain SF, Harvey-Dunstan TC, Bankart MJ, Chaplin EJ, Vincent EE, Chimera R, Morgan MD, Singh SJ, *et al.* An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. *BMJ* 2014;349:g4315.
185. Vogiatzis I, Rochester CL, Spruit MA, Troosters T, Cline EM; American Thoracic Society/European Respiratory Society Task Force on Policy in Pulmonary Rehabilitation. Increasing implementation and delivery of pulmonary rehabilitation: key messages from the new ATS/ERS policy statement. *Eur Respir J* 2016;47:1336–1341.
186. Zwerink M, Brusse-Keizer M, van der Valk PD, Zielhuis GA, Monninkhof EM, van der Palen J, Frith PA, Effing T. Self management for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014;3:CD002990.

187. Fan VS, Gaziano JM, Lew R, Bourbeau J, Adams SG, Leatherman S, Thwin SS, Huang GD, Robbins R, Sriram PS, *et al.* A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations: a randomized, controlled trial. *Ann Intern Med* 2012;156:673–683.
188. Peytremann-Bridevaux I, Taffe P, Burnand B, Bridevaux PO, Puhon MA. Mortality of patients with COPD participating in chronic disease management programmes: a happy end? *Thorax* 2014;69:865–866.
189. Kruis AL, Smidt N, Assendelft WJ, Gussekloo J, Boland MR, Rutten-van Mölken M, Chavannes NH. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013;10:CD009437.
190. Kruis AL, Boland MR, Assendelft WJ, Gussekloo J, Tsiachristas A, Stijnen T, Blom C, Sont JK, Rutten-van Mölken MP, Chavannes NH. Effectiveness of integrated disease management for primary care chronic obstructive pulmonary disease patients: results of cluster randomised trial. *BMJ* 2014;349:g5392.
191. Cartwright M, Hirani SP, Rixon L, Beynon M, Doll H, Bower P, Bardsley M, Steventon A, Knapp M, Henderson C, *et al.*; Whole Systems Demonstrator Evaluation Team. Effect of telehealth on quality of life and psychological outcomes over 12 months (Whole Systems Demonstrator telehealth questionnaire study): nested study of patient reported outcomes in a pragmatic, cluster randomised controlled trial. *BMJ* 2013;346:f653.
192. American Academy of Hospice and Palliative Medicine; Center to Advance Palliative Care; Hospice and Palliative Nurses Association; Last Acts Partnership; National Hospice and Palliative Care Organization. National Consensus Project for Quality Palliative Care: Clinical Practice Guidelines for quality palliative care, executive summary. *J Palliat Med* 2004;7:611–627.
193. Halpin DMG, Seamark DA, Seamark CJ. Palliative and end-of-life care for patients with respiratory diseases. *Eur Respir Monograph* 2009;43:327–353.
194. Weber C, Stinemann J, Herrmann FR, Pautex S, Janssens JP. Can early introduction of specialized palliative care limit intensive care, emergency and hospital admissions in patients with severe and very severe COPD? A randomized study. *BMC Palliat Care* 2014;13:47.
195. Ek K, Andershed B, Sahlberg-Blom E, Ternstedt BM. “The unpredictable death”-The last year of life for patients with advanced COPD: relatives’ stories. *Palliat Support Care* 2015;13:1213–1222.
196. Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;4:CD001744.
197. Albert RK, Au DH, Blackford AL, Casaburi R, Cooper JA Jr, Criner GJ, Diaz P, Fuhlbrigge AL, Gay SE, Kanner RE, *et al.*; Long-Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med* 2016;375:1617–1627.
198. Galli JA, Krahnke JS, James Mamary A, Shenoy K, Zhao H, Criner GJ. Home non-invasive ventilation use following acute hypercapnic respiratory failure in COPD. *Respir Med* 2014;108:722–728.
199. Coughlin S, Liang WE, Parthasarathy S. Retrospective assessment of home ventilation to reduce rehospitalization in chronic obstructive pulmonary disease. *J Clin Sleep Med* 2015;11:663–670.
200. Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, Ambrosino N; Rehabilitation and Chronic Care Study Group, Italian Association of Hospital Pulmonologists (AIPO). The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002;20:529–538.
201. Köhlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, Karg O, Laier-Groeneveld G, Nava S, Schönhofer B, *et al.* Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014;2:698–705.
202. Struik FM, Sprooten RT, Kerstjens HA, Bladder G, Zijnen M, Asin J, Cobben NA, Vonk JM, Wijkstra PJ. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax* 2014;69:826–834.
203. Casanova C, Celli BR, Tost L, Soriano E, Abreu J, Velasco V, Santolaria F. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. *Chest* 2000;118:1582–1590.
204. 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;182:325–331.
205. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, Weinmann G, Wood DE; National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059–2073.
206. National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med* 2001;345:1075–1083.
207. Marchetti N, Criner GJ. Surgical approaches to treating emphysema: lung volume reduction surgery, bullectomy, and lung transplantation. *Semin Respir Crit Care Med* 2015;36:592–608.
208. Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, Kirk R, Rahmel AO, Stehlik J, Hertz MI; International Society of Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. *J Heart Lung Transplant* 2012;31:1073–1086.
209. Stavem K, Bjørtuft Ø, Borgan Ø, Geiran O, Boe J. Lung transplantation in patients with chronic obstructive pulmonary disease in a national cohort is without obvious survival benefit. *J Heart Lung Transplant* 2006;25:75–84.
210. Thabut G, Christie JD, Ravaut P, Castier Y, Brugière O, Fournier M, Mal H, Lesèche G, Porcher R. Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: a retrospective analysis of registry data. *Lancet* 2008;371:744–751.
211. Criner GJ, Cordova F, Sternberg AL, Martinez FJ. The National Emphysema Treatment Trial (NETT) Part II: lessons learned about lung volume reduction surgery. *Am J Respir Crit Care Med* 2011;184:881–893.
212. Shah PL, Slebos DJ, Cardoso PF, Cetti E, Voelker K, Levine B, Russell ME, Goldin J, Brown M, Cooper JD, *et al.*; EASE trial study group. Bronchoscopic lung-volume reduction with Exhale Airway Stents for Emphysema (EASE trial): randomised, sham-controlled, multicentre trial. *Lancet* 2011;378:997–1005.
213. Come CE, Kramer MR, Dransfield MT, Abu-Hijleh M, Berkowitz D, Bezzi M, Bhatt SP, Boyd MB, Cases E, Chen AC, *et al.* A randomised trial of lung sealant versus medical therapy for advanced emphysema. *Eur Respir J* 2015;46:651–662.
214. Sciruba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH, Kovitz KL, Chiacchierini RP, Goldin J, McLennan G; VENT Study Research Group. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med* 2010;363:1233–1244.
215. Davey C, Zoumot Z, Jordan S, Carr DH, Polkey MI, Shah PL, Hopkinson NS. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HiFi trial): study design and rationale. *Thorax* 2015;70:288–290.
216. Klooster K, ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ. Endobronchial valves for emphysema without interlobar collateral ventilation. *N Engl J Med* 2015;373:2325–2335.
217. Deslée G, Mal H, Dutau H, Bourdin A, Vergnon JM, Pison C, Kessler R, Jounieaux V, Thiberville L, Leroy S, *et al.*; REVOLENS Study Group. Lung volume reduction coil treatment vs usual care in patients with severe emphysema: the REVOLENS Randomized Clinical Trial. *JAMA* 2016;315:175–184.
218. Sciruba FC, Criner GJ, Strange C, Shah PL, Michaud G, Connolly TA, Deslée G, Tillis WP, Delage A, Marquette CH, *et al.*; RENEW Study Research Group. Effect of endobronchial coils vs usual care on exercise tolerance in patients with severe emphysema: the RENEW randomized clinical trial. *JAMA* 2016;315:2178–2189.

219. Barr RG, Bourbeau J, Camargo CA, Ram FS. Inhaled tiotropium for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;2:CD002876.
220. Kanner C, Cates CJ. Long-acting beta(2)-agonist in addition to tiotropium versus either tiotropium or long-acting beta(2)-agonist alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;4:CD008989.
221. Martinez FJ, Calverley PM, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. *Lancet* 2015;385:857–866.
222. Martinez FJ, Rabe KF, Sethi S, Pizzichini E, Mclvor A, Anzueto A, Alagappan VK, Siddiqui S, Rekeda L, Miller CJ, et al. Effect of roflumilast and inhaled corticosteroid/long-acting β_2 -agonist on chronic obstructive pulmonary disease exacerbations (RE(2) SPOND): a randomized clinical trial. *Am J Respir Crit Care Med* 2016;194:559–567.
223. Garvey C, Bayles MP, Hamm LF, Hill K, Holland A, Limberg TM, Spruit MA. Pulmonary rehabilitation exercise prescription in chronic obstructive pulmonary disease: review of selected guidelines: an official statement from the American Association of Cardiovascular and Pulmonary Rehabilitation. *J Cardiopulm Rehabil Prev* 2016;36:75–83.
224. Ortega F, Toral J, Cejudo P, Villagomez R, Sánchez H, Castillo J, Montemayor T. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;166:669–674.
225. Bernard S, Whittom F, Leblanc P, Jobin J, Belleau R, Bérubé C, Carrier G, Maltais F. Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159:896–901.
226. Velloso M, do Nascimento NH, Gazzotti MR, Jardim JR. Evaluation of effects of shoulder girdle training on strength and performance of activities of daily living in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2013;8:187–192.
227. Au DH, Udris EM, Engelberg RA, Diehr PH, Bryson CL, Reinke LF, Curtis JR. A randomized trial to improve communication about end-of-life care among patients with COPD. *Chest* 2012;141:726–735.
228. Tomczyk S, Bennett NM, Stoecker C, Gierke R, Moore MR, Whitney CG, Hadler S, Pilishvili T; Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥ 65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2014;63:822–825.
229. Struik FM, Lacasse Y, Goldstein RS, Kerstjens HA, Wijkstra PJ. Nocturnal noninvasive positive pressure ventilation in stable COPD: a systematic review and individual patient data meta-analysis. *Respir Med* 2014;108:329–337.
230. Tiong LU, Davies R, Gibson PG, Hensley MJ, Hepworth R, Lasserson TJ, Smith B. Lung volume reduction surgery for diffuse emphysema. *Cochrane Database Syst Rev* 2006;4:CD001001.
231. Weill D, Bendon C, Corris PA, Dark JH, Davis RD, Keshavjee S, Lederer DJ, Mulligan MJ, Patterson GA, Singer LG, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2015;34:1–15.
232. The International Society for Heart and Lung Transplantation. Slide sets: overall lung transplantation statistics; 2015 [accessed 2016 Sept 18]. Available from: https://www.ishlt.org/downloadables/slides/2015/lung_adult.pptx
233. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet* 2007;370:786–796.
234. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1418–1422.
235. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196–204.
236. Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A, Schaberg T, Torres A, van der Heijden G, Verheij TJ; European Respiratory Society; European Society of Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005;26:1138–1180.
237. White AJ, Gompertz S, Stockton RA. Chronic obstructive pulmonary disease. 6: The aetiology of exacerbations of chronic obstructive pulmonary disease. *Thorax* 2003;58:73–80.
238. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, Fabbri LM, Johnston SL. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006;173:1114–1121.
239. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, Lomas DA, Barer MR, Johnston SL, Pavord ID, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012;186:48–55.
240. 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;161:1608–1613.
241. Hurst JR, Donaldson GC, Quint JK, Goldring JJ, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;179:369–374.
242. Wells JM, Washko GR, Han MK, Abbas N, Nath H, Mamy AJ, Regan E, Bailey WC, Martinez FJ, Westfall E, et al.; COPDGene Investigators; ECLIPSE Study Investigators. Pulmonary arterial enlargement and acute exacerbations of COPD. *N Engl J Med* 2012;367:913–921.
243. Han MK, Kazerooni EA, Lynch DA, Liu LX, Murray S, Curtis JL, Criner GJ, Kim V, Bowler RP, Hanania NA, et al.; COPDGene Investigators. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. *Radiology* 2011;261:274–282.
244. Kim V, Han MK, Vance GB, Make BJ, Newell JD, Hokanson JE, Hersh CP, Stinson D, Silverman EK, Criner GJ; COPDGene Investigators. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. *Chest* 2011;140:626–633.
245. Burgel PR, Nesme-Meyer P, Chanez P, Caillaud D, Carré P, Perez T, Roche N; Initiatives Bronchopneumopathie Chronique Obstructive Scientific Committee. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. *Chest* 2009;135:975–982.
246. 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;4:101–124.
247. Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, Vestbo J, Knobil K, Yates JC, Calverley PM. 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;178:332–338.
248. Tashkin DP, Celli B, Decramer M, Liu D, Burkhart D, Cassino C, Kesten S. Bronchodilator responsiveness in patients with COPD. *Eur Respir J* 2008;31:742–750.
249. Hoogendoorn M, Hoogenveen RT, Rutten-van Mölken MP, Vestbo J, Feenstra TL. Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. *Eur Respir J* 2011;37:508–515.
250. Piquet J, Chavaillon JM, David P, Martin F, Blanchon F, Roche N; French College of General Hospital Respiratory Physicians (CPHG). High-risk patients following hospitalisation for an acute exacerbation of COPD. *Eur Respir J* 2013;42:946–955.
251. Singanayagam A, Schembri S, Chalmers JD. Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2013;10:81–89.
252. Garcia-Aymerich J, Serra Pons I, Mannino DM, Maas AK, Miller DP, Davis KJ. Lung function impairment, COPD hospitalisations and subsequent mortality. *Thorax* 2011;66:585–590.

253. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 2010 [accessed 2017 Feb 8]. <https://www.nice.org.uk/guidance/CG101>
254. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–946.
255. Turner MO, Patel A, Ginsburg S, FitzGerald JM. Bronchodilator delivery in acute airflow obstruction: a meta-analysis. *Arch Intern Med* 1997;157:1736–1744.
256. Barr RG, Rowe BH, Camargo CA Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease: meta-analysis of randomised trials. *BMJ* 2003;327:643.
257. 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;60:713–717.
258. 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;354:456–460.
259. Maltais F, Ostinelli J, Bourbeau J, Tonnel AB, Jacquemet N, Haddon J, Rouleau M, Boukhana M, Martinot JB, Duroux P. 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.
260. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, Anderson P, Morgan NA; Department of Veterans Affairs Cooperative Study Group. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1999;340:1941–1947.
261. 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;154:407–412.
262. Alía I, de la Cal MA, Esteban A, Abella A, Ferrer R, Molina FJ, Torres A, Gordo F, Elizalde JJ, de Pablo R, *et al*. Efficacy of corticosteroid therapy in patients with an acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support. *Arch Intern Med* 2011;171:1939–1946.
263. Aaron SD, Vandemheen KL, Hebert P, Dales R, Stiell IG, Ahuja J, Dickinson G, Brison R, Rowe BH, Dreyer J, *et al*. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med* 2003;348:2618–2625.
264. Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, Duerring U, Henzen C, Leibbrandt Y, Maier S, *et al*. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA* 2013;309:2223–2231.
265. 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;132:1741–1747.
266. Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, McCormick M, Haldar K, Keadze T, Duvoix A, *et al*. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011;184:662–671.
267. Vollenweider DJ, Jarrett H, Steurer-Stey CA, Garcia-Aymerich J, Puhon MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;12:CD010257.
268. Miravittles M, Kruesmann F, Haverstock D, Perroncel R, Choudhri SH, Arvis P. Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis. *Eur Respir J* 2012;39:1354–1360.
269. 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;117:1638–1645.
270. 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;2:CD004403.
271. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, Neidert S, Fricker T, Blum C, Schild U, *et al*.; ProHOSP Study Group. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 2009;302:1059–1066.
272. Schuetz P, Müller B, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, *et al*. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev* 2012;9:CD007498.
273. Noura 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;358:2020–2025.
274. Masterton RG, Burley CJ. Randomized, double-blind study comparing 5- and 7-day regimens of oral levofloxacin in patients with acute exacerbation of chronic bronchitis. *Int J Antimicrob Agents* 2001;18:503–512.
275. Adams SG, Melo J, Luther M, Anzueto A. Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. *Chest* 2000;117:1345–1352.
276. Miravittles M, Espinosa C, Fernández-Laso E, Martos JA, Maldonado JA, Gallego M; Study Group of Bacterial Infection in COPD. Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. *Chest* 1999;116:40–46.
277. Soler N, Torres A, Ewig S, Gonzalez J, Celis R, El-Ebiary M, Hernandez C, Rodriguez-Roisin R. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 1998;157:1498–1505.
278. 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.
279. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, Simonneau G, Benito S, Gasparetto A, Lemaire F, *et al*. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995;333:817–822.
280. 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.
281. Meyer TJ, Hill NS. Noninvasive positive pressure ventilation to treat respiratory failure. *Ann Intern Med* 1994;120:760–770.
282. Chandra D, Stamm JA, Taylor B, Ramos RM, Satterwhite L, Krishnan JA, Mannino D, Sciurba FC, Holguin F. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998–2008. *Am J Respir Crit Care Med* 2012;185:152–159.
283. Consensus development conference committee. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation—a consensus conference report. *Chest* 1999;116:521–534.
284. Bott J, Carroll MP, Conway JH, Keilty SE, Ward EM, Brown AM, Paul EA, Elliott MW, Godfrey RC, Wedzicha JA, *et al*. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993;341:1555–1557.
285. 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;151:1799–1806.
286. 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;355:1931–1935.
287. Conti G, Antonelli M, Navalesi P, Rocco M, Bui M, Spadetta G, Meduri GU. 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;28:1701–1707.
288. Jennings JH, Thavarajah K, Mendez MP, Eichenhorn M, Kvale P, Yessayan L. Predischarge bundle for patients with acute exacerbations of COPD to reduce readmissions and ED visits: a randomized controlled trial. *Chest* 2015;147:1227–1234.
 289. Singh G, Zhang W, Kuo YF, Sharma G. Association of psychological disorders with 30-day readmission rates in patients with COPD. *Chest* 2016;149:905–915.
 290. Ringbæk T, Green A, Laursen LC, Frausing E, Brøndum E, Ulrik CS. Effect of tele health care on exacerbations and hospital admissions in patients with chronic obstructive pulmonary disease: a randomized clinical trial. *Int J Chron Obstruct Pulmon Dis* 2015;10:1801–1808.
 291. Hartl S, Lopez-Campos JL, Pozo-Rodríguez F, Castro-Acosta A, Studnicka M, Kaiser B, Roberts CM. Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. *Eur Respir J* 2016;47:113–121.
 292. Jordan RE, Majothi S, Heneghan NR, Blissett DB, Riley RD, Sitch AJ, Price MJ, Bates EJ, Turner AM, Bayliss S, et al. Supported self-management for patients with moderate to severe chronic obstructive pulmonary disease (COPD): an evidence synthesis and economic analysis. *Health Technol Assess* 2015;19:1–516.
 293. Gavish R, Levy A, Dekel OK, Karp E, Maimon N. The association between hospital readmission and pulmonologist follow-up visits in patients with COPD. *Chest* 2015;148:375–381.
 294. Oga T, Tsukino M, Hajiro T, Ikeda A, Nishimura K. Predictive properties of different multidimensional staging systems in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2011;6:521–526.
 295. Martínez-García MA, de la Rosa Carrillo D, Soler-Cataluña JJ, Donat-Sanz Y, Serra PC, Lerma MA, Ballestin J, Sánchez IV, Selma Ferrer MJ, Dafo AR, et al. Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;187:823–831.
 296. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009;33:1165–1185.
 297. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008;32:962–969.
 298. Sin DD, Anthonisen NR, Soriano JB, Agustí AG. Mortality in COPD: role of comorbidities. *Eur Respir J* 2006;28:1245–1257.
 299. Iversen KK, Kjaergaard J, Akkan D, Kober L, Torp-Pedersen C, Hassager C, Vestbo J, Kjoller E; ECHOS Lung Function Study Group. The prognostic importance of lung function in patients admitted with heart failure. *Eur J Heart Fail* 2010;12:685–691.
 300. Almagro P, Soriano JB, Cabrera FJ, Boixeda R, Alonso-Ortiz MB, Barreiro B, Diez-Manglano J, Murio C, Heredia JL; Working Group on COPD, Spanish Society of Internal Medicine. Short- and medium-term prognosis in patients hospitalized for COPD exacerbation: the CODEX index. *Chest* 2014;145:972–980.
 301. Miller J, Edwards LD, Agustí A, Bakke P, Calverley PM, Celli B, Coxson HO, Crim C, Lomas DA, Miller BE, et al.; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. *Respir Med* 2013;107:1376–1384.
 302. Campo G, Napoli N, Serenelli C, Tebaldi M, Ferrari R. Impact of a recent hospitalization on treatment and prognosis of ST-segment elevation myocardial infarction. *Int J Cardiol* 2013;167:296–297.
 303. Fabbri LM, Luppi F, Beghé B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J* 2008;31:204–212.
 304. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. *Transl Res* 2013;162:237–251.
 305. Matamis D, Tsagourias M, Papathanasiou A, Sineffaki H, Lepida D, Galiatsou E, Nakos G. Targeting occult heart failure in intensive care unit patients with acute chronic obstructive pulmonary disease exacerbation: effect on outcome and quality of life. *J Crit Care* 2014;29:315.e7–315.e14.
 306. MacDonald MI, Shafuddin E, King PT, Chang CL, Bardin PG, Hancox RJ. Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. *Lancet Respir Med* 2016;4:138–148.
 307. Lipworth B, Wedzicha J, Devereux G, Vestbo J, Dransfield MT. Beta-blockers in COPD: time for reappraisal. *Eur Respir J* 2016;48:880–888.
 308. Hoiseeth AD, Neukamm A, Karlsson BD, Omland T, Brekke PH, Søyseth V. Elevated high-sensitivity cardiac troponin T is associated with increased mortality after acute exacerbation of chronic obstructive pulmonary disease. *Thorax* 2011;66:775–781.
 309. Singh S, Loke YK, Enright P, Furberg CD. Pro-arrhythmic and pro-ischaemic effects of inhaled anticholinergic medications. *Thorax* 2013;68:114–116.
 310. Wilchesky M, Ernst P, Brophy JM, Platt RW, Suissa S. Bronchodilator use and the risk of arrhythmia in COPD: part 2: reassessment in the larger Quebec cohort. *Chest* 2012;142:305–311.
 311. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004;125:2309–2321.
 312. Tashkin DP, Fabbri LM. Long-acting beta-agonists in the management of chronic obstructive pulmonary disease: current and future agents. *Respir Res* 2010;11:149.
 313. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, Anderson J, Maden C; Trial of Inhaled STeroids ANd long-acting beta2 agonists study group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;361:449–456.
 314. Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, Peterson S, Olsson H. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003;21:74–81.
 315. 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;22:912–919.
 316. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Crim C, Willits LR, Yates JC, Vestbo J; TORCH Investigators. Cardiovascular events in patients with COPD: TORCH study results. *Thorax* 2010;65:719–725.
 317. Houben-Wilke S, Jörres RA, Bals R, Franssen FM, Gläser S, Holle R, Karch A, Koch A, Magnussen H, Obst A, et al. Peripheral artery disease and its clinical relevance in patients with COPD in the Systemic Consequences-Comorbidities Network study. *Am J Respir Crit Care Med* 2017;195:189–197.
 318. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, Zulueta J, Cabrera C, Zagaceta J, Hunninghake G, et al.; BODE Collaborative Group. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186:155–161.
 319. Bon J, Fuhrman CR, Weissfeld JL, Duncan SR, Branch RA, Chang CC, Zhang Y, Leader JK, Gur D, Greenspan SL, et al. Radiographic emphysema predicts low bone mineral density in a tobacco-exposed cohort. *Am J Respir Crit Care Med* 2011;183:885–890.
 320. McAllister DA, Maclay JD, Mills NL, Mair G, Miller J, Anderson D, Newby DE, Murchison JT, Macnee W. Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;176:1208–1214.
 321. Bolton CE, Cannings-John R, Edwards PH, Ionescu AA, Evans WD, Pettit RJ, Faulkner TA, Stone MD, Shale DJ. What community measurements can be used to predict bone disease in patients with COPD? *Respir Med* 2008;102:651–657.
 322. Bolton CE, Ionescu AA, Shiels KM, Pettit RJ, Edwards PH, Stone MD, Nixon LS, Evans WD, Griffiths TL, Shale DJ. Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170:1286–1293.
 323. Jaramillo JD, Wilson C, Stinson DS, Lynch DA, Bowler RP, Lutz S, Bon JM, Arnold B, McDonald ML, Washko GR, et al.; COPD Gene Investigators. Reduced bone density and vertebral fractures in smokers: men and COPD patients at increased risk. *Ann Am Thorac Soc* 2015;12:648–656.

324. Jaramillo J, Wilson C, Stinson D, *et al*. Erratum: reduced bone density and vertebral fractures in smokers: men and COPD patients at increased risk. *Ann Am Thorac Soc* 2015;12:1112.
325. 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;167:60–67.
326. Eisner MD, Blanc PD, Yelin EH, Katz PP, Sanchez G, Iribarren C, Omachi TA. Influence of anxiety on health outcomes in COPD. *Thorax* 2010;65:229–234.
327. de Torres JP, Bastarrika G, Wisnivesky JP, Alcaide AB, Campo A, Seijo LM, Pueyo JC, Villanueva A, Lozano MD, Montes U, *et al*. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. *Chest* 2007; 132:1932–1938.
328. Wilson DO, Leader JK, Fuhrman CR, Reilly JJ, Sciruba FC, Weissfeld JL. Quantitative computed tomography analysis, airflow obstruction, and lung cancer in the Pittsburgh Lung Screening Study. *J Thorac Oncol* 2011;6:1200–1205.
329. Wilson DO, Weissfeld JL, Balkan A, Schragin JG, Fuhrman CR, Fisher SN, Wilson J, Leader JK, Siegfried JM, Shapiro SD, *et al*. Association of radiographic emphysema and airflow obstruction with lung cancer. *Am J Respir Crit Care Med* 2008; 178:738–744.
330. de-Torres JP, Wilson DO, Sanchez-Salcedo P, Weissfeld JL, Berto J, Campo A, Alcaide AB, Garcia-Granero M, Celli BR, Zulueta JJ. Lung cancer in patients with chronic obstructive pulmonary disease: development and validation of the COPD Lung Cancer Screening Score. *Am J Respir Crit Care Med* 2015;191: 285–291.
331. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
332. Infante M, Cavuto S, Lutman FR, Passera E, Chiarenza M, Chiesa G, Brambilla G, Angeli E, Aranzulla G, Chiti A, *et al*.; DANTE Study Group. Long-term follow-up results of the DANTE trial, a randomized study of lung cancer screening with spiral computed tomography. *Am J Respir Crit Care Med* 2015;191: 1166–1175.
333. Cebon Lipovec N, Beijers RJ, van den Borst B, Doehner W, Lainscak M, Schols AM. The prevalence of metabolic syndrome in chronic obstructive pulmonary disease: a systematic review. *COPD* 2016; 13:399–406.
334. Martinez CH, Okajima Y, Murray S, Washko GR, Martinez FJ, Silverman EK, Lee JH, Regan EA, Crapo JD, Curtis JL, *et al*.; COPDGene Investigators. Impact of self-reported gastroesophageal reflux disease in subjects from COPDGene cohort. *Respir Res* 2014;15:62.
335. Ingebrigtsen TS, Marott JL, Vestbo J, Nordestgaard BG, Hallas J, Lange P. Gastro-esophageal reflux disease and exacerbations in chronic obstructive pulmonary disease. *Respirology* 2015;20: 101–107.
336. Patel IS, Vlahos I, Wilkinson TM, Lloyd-Owen SJ, Donaldson GC, Wilks M, Reznik RH, Wedzicha JA. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170:400–407.
337. Shepard JW Jr, Garrison MW, Grither DA, Evans R, Schweitzer PK. Relationship of ventricular ectopy to nocturnal oxygen desaturation in patients with chronic obstructive pulmonary disease. *Am J Med* 1985;78:28–34.
338. Bradley TD, Rutherford R, Grossman RF, Lue F, Zamel N, Moldofsky H, Phillipson EA. Role of daytime hypoxemia in the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. *Am Rev Respir Dis* 1985;131:835–839.
339. Weitzenblum E, Krieger J, Apprill M, Vallée E, Ehrhart M, Ratomaharo J, Oswald M, Kurtz D. Daytime pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Am Rev Respir Dis* 1988;138:345–349.