REVIEW ARTICLE

Jeffrey M. Drazen, M.D., *Editor*

Update on Clinical Aspects of Chronic Obstructive Pulmonary Disease

Bartolomé R. Celli, M.D., and Jadwiga A. Wedzicha, M.D.

From the Pulmonary and Critical Care Division, Brigham and Women's Hospital, and Harvard Medical School — both in Boston (B.R.C.); and the National Heart and Lung Institute, Imperial College London, London (J.A.W.). Address reprint requests to Dr. Celli at 31 River Glen Rd., Wellesley, MA 02481, or at bcelli@copdnet.org.

N Engl J Med 2019;381:1257-66.
DOI: 10.1056/NEJMra1900500

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide; COPD led to 3.2 million deaths in 2017, a toll expected to reach 4.4 million yearly by 2040.[1,2] With a worldwide prevalence of 10.1%, COPD afflicts many people in low-income, middle-income, and wealthy countries (Fig. 1), and years of life lost prematurely increased 13.2% between 2007 and 2017.[1] Although COPD has traditionally been considered a disease that affects men, in some countries, the prevalence and associated mortality are higher among women than among men. In this review, we update the clinical face of COPD, concentrating on the pulmonary aspects of the disease, which also affects many other organ systems. The pathogenesis of COPD is discussed in a companion article by Agustí and Hogg in this issue of the *Journal*,[3] and the review of muco-obstructive lung diseases in a recent issue of the *Journal*[4] complements this article.

Definition

COPD is an umbrella term for various clinical entities with multiple causes resulting in airflow limitation that is not fully reversible.[3,5-7] Hence, COPD is better defined as a clinical syndrome characterized by chronic respiratory symptoms, structural pulmonary abnormalities (airways disease, emphysema, or both), lung-function impairment (primarily airflow limitation that is poorly reversible), or any combination of these.[8] Patients with COPD are at a higher risk than patients without COPD for the development of coexisting conditions that are associated with poor outcomes, including death.[9,10]

Taxonomy

As described in the companion article on the pathogenesis of COPD, a period of environment–gene interaction precedes spirometric airflow limitation.[3] In persons without obstruction who are exposed to cigarette smoking,[3,4] the presence of cough, sputum, and dyspnea and the detection of a low diffusing capacity of the lung for carbon monoxide (DLco) are associated with an increase in the risk of COPD.[11-13] Similarly, in persons without obstruction who have a baseline value for forced expiratory volume in 1 second (FEV_1) at the low end of the normal range, a reduction in FEV_1 that exceeds 40 ml per year (normal rate of loss after the third decade of life, <25 ml per year) over an 18-month period is associated with an increase by a factor of 36 in the risk that COPD will develop in the next 5 years.[14] Patients in this "silent" stage constitute a group that can be labeled as having "pre-COPD," with the term "COPD" reserved for patients with spirometric airflow

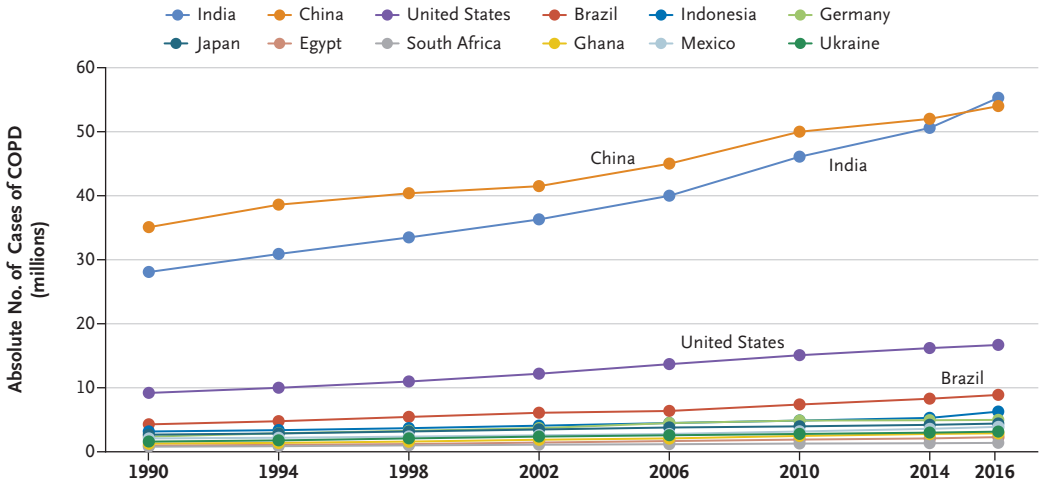

Figure 1. Prevalence of Chronic Obstructive Pulmonary Disease (COPD) in Selected Countries, 1990–2016.

COPD is currently the third leading cause of death and an important cause of complications worldwide. Although COPD is a substantial problem everywhere, China and India account for more than 50% of all cases of COPD in the world. Data are from the Global Burden of Disease (www.healthdata.org/gbd).

limitation[8,15] (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

COPD remains underdiagnosed, primarily because it usually is considered to be a disease of the elderly. The disorder should be recognized at an earlier age because earlier interventions, such as smoking cessation, can normalize lung-function decline.[16] In addition, improved air quality in some cities is associated with better lung function in children living in those communities,[17] and among patients with COPD who are treated with bronchodilators, those younger than 50 years of age have better health status and lung function over a 4-year period than older patients.[18] Thus, earlier disease should not be confused with milder disease; the former is related to age, whereas the latter relates to the severity of airflow limitation.[19] On the basis of this evidence, treatment of younger patients who have mild disease (i.e., earlier treatment) may provide the greatest benefit over time.

COPD due to smoking is associated with more severe emphysema and more rapid decline in lung function than COPD from biomass exposure, which is characterized primarily by airway-wall thickening and improved lung function after the use of bronchodilators.[20] Patients with asthma leading to COPD may have more symptoms, exacerbations, and hospitalizations and, paradoxically, a lower mortality rate than patients with smoking-associated COPD.[21]

DIAGNOSIS

The approach to persons at risk for COPD (because of environmental exposure, respiratory symptoms, a family history, or a combination of these factors) is summarized in Figure 2. Persons with normal spirometric values should be encouraged to adopt a healthy lifestyle and avoid injurious exposures. Such patients should also be monitored with annual spirometry because they are at increased risk for persistent airflow limitation (ratio of FEV_1 to forced vital capacity, <0.7).[14] Once such airflow limitation occurs, the diagnosis of COPD is confirmed.[5]

FEV_1, expressed as a proportion of reference values, defines the severity of airflow limitation, which, along with the intensity of dyspnea, the presence or absence of cachexia, and an assessment of the capacity to perform activities of daily life, provides additional prognostic information.[22] A history of exacerbations, especially two or more in a year or an episode requiring hospitalization, predicts future exacerbations and poor outcomes,[23] indicating a need for close monitoring and adequate therapy.[5]

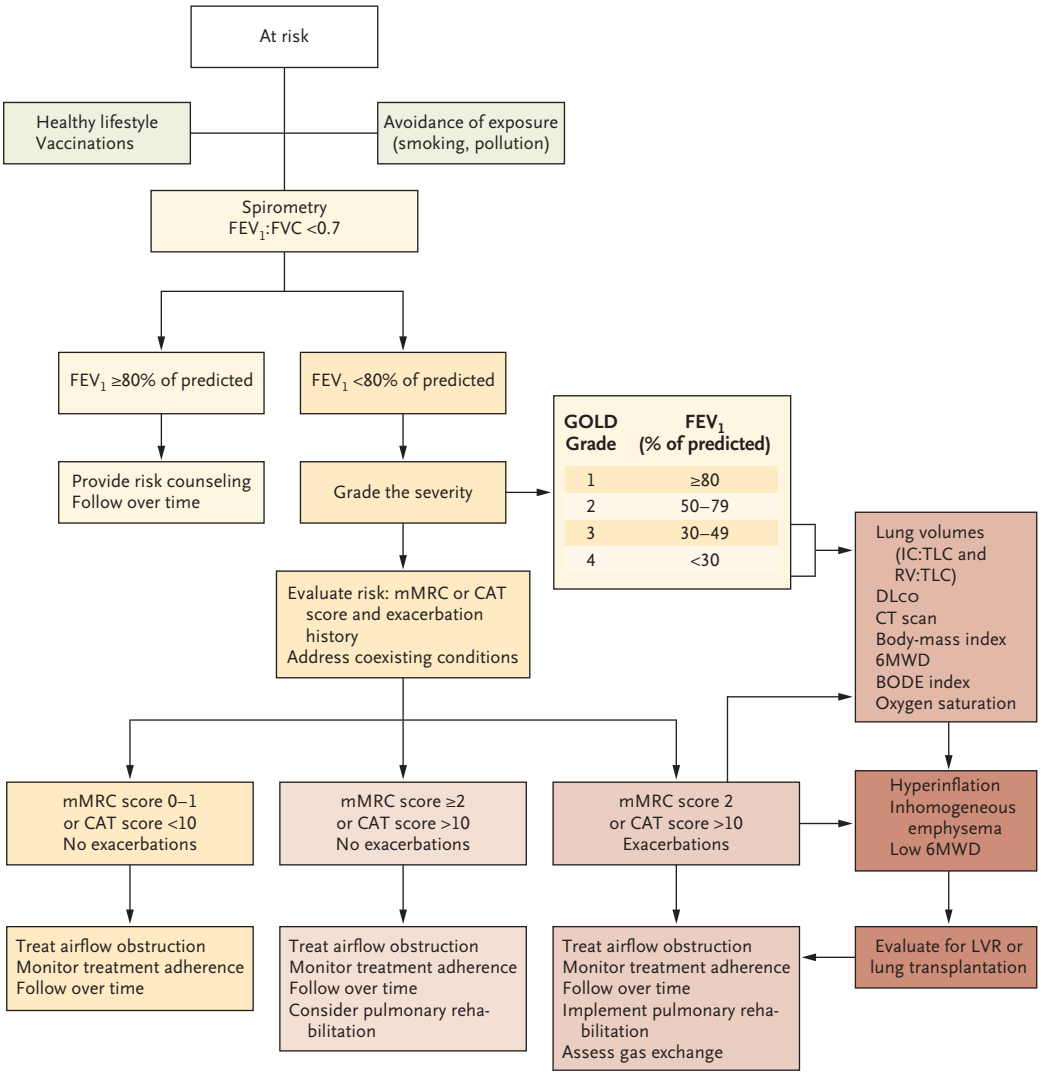

Figure 2. Algorithm for the Evaluation and Treatment of Persons with COPD or at Risk for COPD.

Most patients with mild symptoms (green) and no exacerbations per year do well with exposure control, increased physical activity, vaccinations, and use of long-acting bronchodilators. The green and yellow pathways are usually the domain of primary care practitioners. The brown pathways are best managed by health care professionals with experience in COPD management. The darker shades of yellow and brown indicate more severe disease or more complex therapy than the lighter shades. Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 1 indicates mild disease, and GOLD grade 4 very severe disease. The BODE index consists of the integration of body-mass index, the degree of airflow obstruction, the severity of dyspnea, and exercise capacity (6-minute walking distance [6MWD]). CAT denotes COPD Assessment Test, DL_{CO} diffusing capacity of the lung for carbon dioxide, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity, IC inspiratory capacity, LVR lung-volume reduction, mMRC modified Medical Research Council dyspnea scale, RV residual volume, and TLC total lung capacity.

COEXISTING CONDITIONS AND MULTIMORBIDITY

Patients with COPD often have certain coexisting conditions, including ischemic heart disease, atrial fibrillation, heart failure, osteoporosis, lung cancer, gastroesophageal reflux, anxiety, and depression.[24] Most of these disorders are characteristically seen in the elderly, but in patients with COPD they occur at younger ages.[10] Given the potential response to therapies, patients with COPD should be evaluated for coexisting condi-

tions, which should be treated, if present. The concept of COPD as one of a group of coexisting disorders (multimorbidity) deserves attention because treatment based on common pathobiologic processes may have a simultaneous effect on a variety of target organs.[25]

PHENOTYPING WITH CT IMAGING

Computed tomography (CT) of the chest has revolutionized the approach to assessing patients for COPD[26] by defining phenotypes with poor clinical outcomes. Chest CT detects and quantitates the emphysema phenotype, classically known as the "pink puffer" phenotype but better defined as the MOLT (multiorgan loss of tissue) phenotype, which is frequently associated with loss of mesenchymal tissue (bone, muscle, and fat).[27] Patients with this phenotype are at increased risk for lung cancer.[28] The presence of heterogeneous, predominantly upper-lobe emphysema identifies good candidates for bronchoscopic or surgical lung-volume reduction.[29,30] CT also detects airway luminal narrowing[31] and wall thickening associated with cough, phlegm production[4] or discoloration,[32] and exacerbations of COPD.[33] This "bronchitic phenotype" resembles the old clinical "blue bloater" in that it is associated with an increased incidence of metabolic syndrome and coronary artery disease and an increased risk of death.

Chest CT provides more relevant information than just those two phenotypes. It can identify bronchiectasis, early-stage lung cancer,[34] interstitial lung abnormalities, coronary calcifications, cardiomegaly, enlargement of the pulmonary vasculature, thoracic-wall and mediastinal abnormalities, osteoporosis, sarcopenia, and hiatal hernia, all of which affect health status[35-37] and could be the target of specific therapies. On the basis of its clinical yield, even without evidence from controlled trials, we think a chest CT should be obtained in most, if not all, patients with COPD (Fig. 2).

PHYSIOLOGICAL TESTING

A resting oxygen saturation of less than 90% should prompt measurement of arterial blood gases to determine whether supplemental oxygen is needed.[5] In patients with dyspnea on exertion, physiological testing can be informative. Hyperinflation is determined by measuring lung volumes, with air trapping indicated by a ratio of residual volume to total lung capacity that exceeds the normal value of 0.35. A low ratio of inspiratory to total lung capacity (<0.25) is associated with an increased risk of death[38] and, when accompanied by dynamic hyperinflation,[39] is a determinant of the severity of dyspnea. A low DL_{CO} (an indirect measure of emphysema) is a good predictor of oxygen desaturation, coexisting pulmonary hypertension, and lung cancer.[40] A 6-minute walking distance of less than 350 m is associated with increased mortality.[41] Cardiopulmonary exercise testing helps differentiate cardiac from respiratory compromise and can be used to guide pulmonary rehabilitation.[42] The multidimensional BODE index, which consists of the integration of four variables (body-mass index, degree of airflow obstruction, degree of dyspnea, and exercise capacity [6-minute walking distance]), provides better prognostic information (higher scores indicate a greater risk of death) than the FEV_1 alone[22] and is easily calculated (www.mdcalc.com/bode-index-copd-survival).

ENDOTYPES, BIOMARKERS, AND TREATABLE TRAITS

An endotype is a disease subtype defined functionally and pathologically by a molecular mechanism or by treatment response.[43] Endotypes should be identified by means of validated biomarkers.[44] Currently, only two blood tests meet this criterion for COPD endotypes that constitute treatable traits. The first test is the serum level of $alpha_1$-antitrypsin, which should be measured in all patients. A low level indicates a genetically determined COPD endotype that responds to long-term replacement of the missing protein.[45] The second test is the blood eosinophil count. In patients with frequent exacerbations despite appropriate bronchodilator treatment, the blood eosinophil count helps predict the response to inhaled glucocorticoids.[46] Eosinophil counts higher than 300 per cubic millimeter indicate a good response, values between 100 and 300 per cubic millimeter suggest a moderate response, and a low eosinophil count (<100 per cubic millimeter) is associated with minimal benefit and an increase in the risk of pneumonia.[47]

IMPLEMENTING THERAPY

PRIMARY AND SECONDARY PREVENTION

The most important approach for a disease with a large environmental component such as COPD is primary prevention,[2] as documented by the

decrease in mortality from smoking-induced diseases that is associated with the reduction in the prevalence of smoking in the United States (www.healthdata.org/data-visualization/tobacco-visualization). Also important is improvement in the lung function of children in regions where ambient pollution has been reduced.[17] Some trials suggest that simple changes in cooking, heating methods, and in-house ventilation in regions with indoor biomass use can improve lung health and reduce the incidence of COPD.[48] The appropriate use of vaccinations (influenza and pneumococcal vaccine) is essential, since they are associated with positive outcomes.[5]

GENERAL THERAPY

Smoking cessation reduces the risk of death, and pulmonary rehabilitation and pharmacologic therapy improve symptoms, exercise capacity, and quality of life.[5,49] The general approach to patients with COPD, shown in Figure 2, is to gear the complexity of therapy to the severity of the disease. Most patients with mild symptoms (a score of 0 or 1 on the modified Medical Research Council dyspnea scale [scores range from 0 to 4, with higher scores indicating more severe dyspnea] or a score of <10 on the COPD Assessment Test [scores range from 0 to 40, with higher scores indicating greater severity of symptoms]) and fewer than two exacerbations per year do well with exposure control, increased physical activity, vaccinations, and use of long-acting bronchodilators. The presence of more intense symptoms and the occurrence of more frequent exacerbations should prompt a more detailed evaluation and specialized management, with consideration of a referral for pulmonary rehabilitation, which improves health status, reduces dyspnea, and increases exercise capacity.[49]

PHARMACOTHERAPY

The Global Initiative for Chronic Obstructive Lung Disease suggests an initial approach based on the intensity of symptoms and the history of exacerbations, with a subsequent algorithm that includes a blood eosinophil count for adjustment of therapy.[5] We have integrated this information into a single algorithm (Fig. 3), adding the degree of airflow limitation and one phenotypic expression of the disease (the asthma–COPD overlap). Caregivers should supervise the use of inhalers, since incorrect use is a frequent cause of treatment failure, and should check for side effects of the medications, particularly inhaled glucocorticoids, because side effects increase the risk of pneumonia. Table S1 in the Supplementary Appendix shows a detailed list of pharmacologic agents used for patients with COPD.

A long-acting muscarinic antagonist (LAMA) is the initial drug of choice for patients with mild disease and no exacerbations.[50] If the patient has more severe dyspnea, severe airflow obstruction, and lung hyperinflation, combining a LAMA with a selective long-acting beta$_2$-agonist (LABA) is more effective[5,51-53]; the two agents can be provided in a single inhaler to simplify treatment. It is reasonable to start therapy with a combination of a LABA and an inhaled glucocorticoid in patients with a history of asthma, wheezes, rhinitis, polyps, or allergies; a history of exacerbations; an elevated blood eosinophil count (>150 per cubic millimeter); or a combination of these findings.[5,54] Although an inhaled glucocorticoid alone decreases the risk of exacerbations in patients with COPD, monotherapy is not recommended because of evidence that use of an inhaled glucocorticoid (fluticasone propionate) alone is associated with an increased risk of death, as compared with the combination of fluticasone and salmeterol.[5,55] If exacerbations continue (two or more or one requiring hospitalization), the combination of a LAMA, a LABA, and an inhaled glucocorticoid in a single canister decreases the risk of exacerbations, improves lung function, and may decrease the risk of death.[56,57] This review cannot address the details of all inhaler devices. However, high pressure and flows, requiring rapid and strong inhalations, are needed to properly deliver medications available as dry-powder inhalers, whereas good coordination and slower inhalations are preferred when medications are prescribed with the use of metered-dose inhalers. Soft-mist inhalers and nebulizers are most easily administered.[5]

For patients who have repeated exacerbations while receiving maximal inhaled therapy or who have side effects from inhaled glucocorticoids, oral macrolides are useful.[58] However, these agents should be avoided in patients with a prolonged QT interval on the electrocardiogram and cardiac arrhythmias. Care should be taken to monitor patients for the development of bacterial resistance in sputum and for impaired hearing. A potential alternative is the phosphodiesterase-4

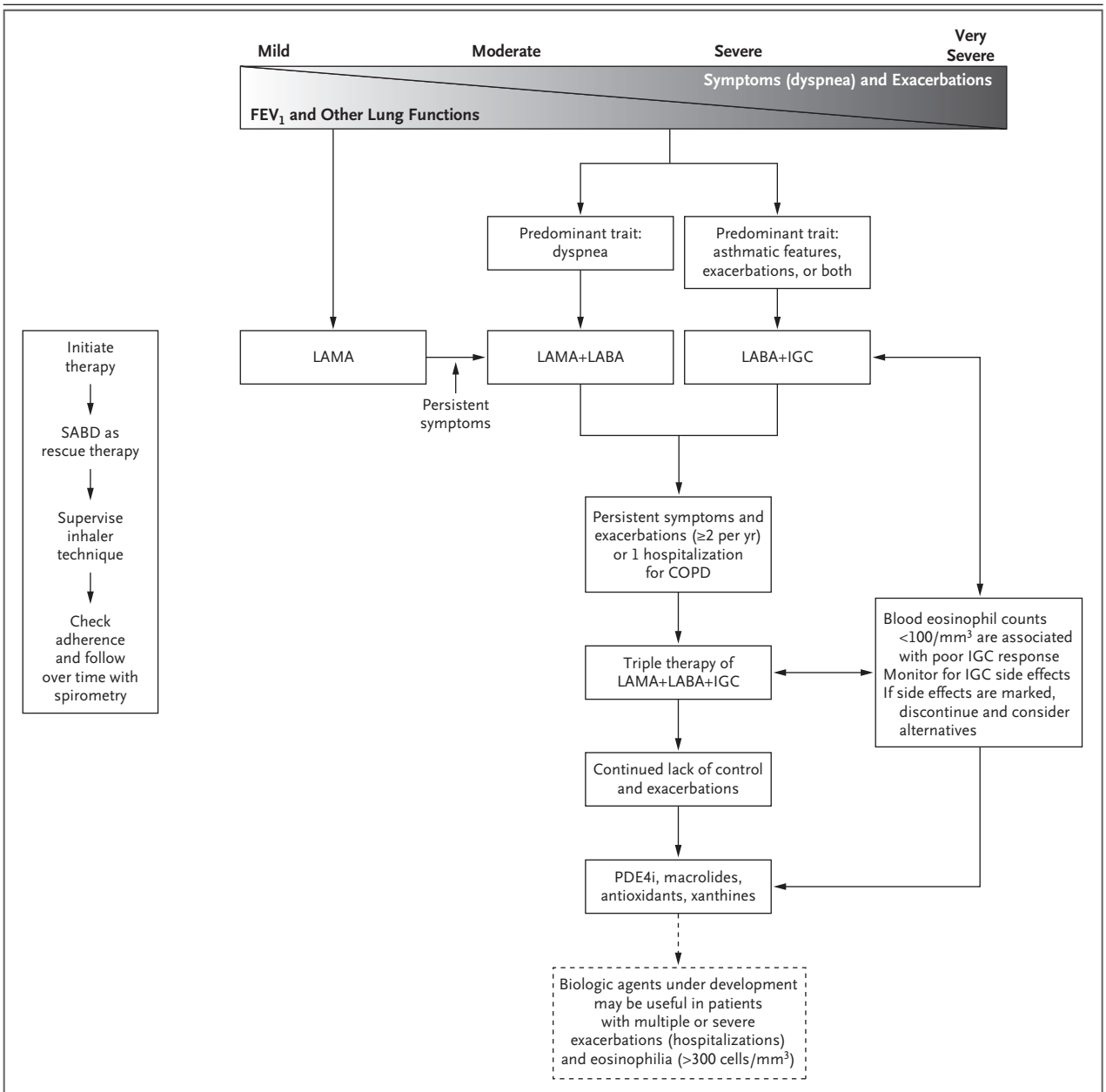

Figure 3. Algorithm for Pharmacotherapy in Patients with a Confirmed Diagnosis of COPD.

Integration of the lung-function compromise, severity of symptoms, and risk of exacerbations helps determine disease severity. Milder disease may benefit from a single inhaled, long-acting bronchodilator, preferably a long-acting muscarinic antagonist (LAMA). In patients with more compromised lung function and infrequent exacerbations of moderate intensity, a LAMA combined with a long-acting beta$_2$-agonist (LABA) in a single inhaler or dual inhalers may be used. A history of asthma, allergies, or rhinitis or an elevated blood eosinophil count (>300 per cubic millimeter) favors the initial use of an inhaled glucocorticoid (IGC) combined with a LABA. If the symptoms and exacerbations persist (more than two exacerbations per year or one hospitalization for COPD), triple therapy consisting of a LAMA, a LABA, and an IGC is useful. An array of systemic therapies (azithromycin, roflumilast, xanthines, and antioxidants) may be considered as third-line agents. The use of biologic agents requires further studies to validate their efficacy. PDE4i denotes phosphodiesterase-4 inhibitor, and SABD short-acting bronchodilator.

inhibitor roflumilast, which lowers exacerbation rates among patients with severe COPD.[59] Patients taking roflumilast should be monitored closely for gastrointestinal disturbances and weight loss. Although biologic agents are beneficial in patients with asthma, trials of mepolizumab and benralizumab have shown marginal benefits in patients with COPD and exacerbations. Oral antioxidants are popular in Europe and the Far East but not in the rest of the world.[5]

PULMONARY REHABILITATION AND OXYGEN THERAPY

Pulmonary rehabilitation is beneficial in patients with deconditioning and a limited ability to perform activities of daily living (Fig. 2). Comprehensive reviews of this aspect of COPD management are available elsewhere.[49,60] All patients with COPD should be evaluated for hypoxemia at rest. In patients with oxygen saturation that is lower than 88%, or a partial pressure of arterial oxygen (Pao_2) that is less than 55 mm Hg while the patient is breathing ambient air at sea level, supplemental oxygen will decrease the risk of death.[5] In patients with intermittent desaturation while exercising, however, supplemental oxygen is not effective.[61]

LUNG-VOLUME REDUCTION AND MECHANICAL VENTILATION

In patients with severely impaired lung function, decreased exercise endurance, and high scores on the BODE index, CT evaluation of lung anatomy will help determine whether lung-volume reduction (with the use of unidirectional valves, coils, or surgery) or lung transplantation may be of benefit.[5,30] Other techniques, such as transbronchial lung denervation, are being investigated. Patients in unstable condition who have chronic ventilatory failure (partial pressure of arterial carbon dioxide >7 kPa or 53 mm Hg) can be considered for noninvasive ventilation administered at home, which improves outcomes and decreases the rate of hospitalization.[62]

END-OF-LIFE ISSUES

Chronic respiratory insufficiency develops in a minority, but still a large number, of patients with COPD, leading to death from respiratory failure. A frank conversation with the patient and family members about the use of invasive therapies, as well as end-of-life decisions, will help determine the appropriate care for such patients.[5]

COPD EXACERBATIONS

A COPD exacerbation is clinically defined as "an increase in dyspnea, cough, or sputum purulence with or without symptoms of upper respiratory infection."[63] In pharmacologic trials, an exacerbation of COPD is defined as "an acute event characterized by worsening of the patient's respiratory symptoms that is beyond the day-to-day variation and that leads to a change in medications."[64] Exacerbations are considered to be mild when only worsening symptoms are reported; moderate when the patient receives antibiotics, systemic glucocorticoids, or both; and severe when the patient visits an emergency department or is hospitalized.[65] Exacerbations increase the risk of myocardial infarction, stroke, pulmonary embolism, and death. Myocardial infarction and pulmonary embolism should be ruled out in patients presenting with symptoms of a COPD exacerbation.[66] Frequent exacerbations are associated with worsening health status and a rapid decline in lung function and are a driver of health care costs, accounting for more than 20% of all readmissions occurring within 30 days after a hospitalization for the same diagnosis.[67]

EPIDEMIOLOGY AND CAUSES

Some patients with COPD have frequent exacerbations (two or more per year). These patients are identifiable by three factors: a history of exacerbations, the severity of airflow limitation, and the presence of gastroesophageal reflux.[68] Between 30% and 50% of exacerbations have a bacterial cause (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Chlamydia pneumoniae*), and viruses such as influenza virus and rhinoviruses are involved in up to 30% of cases.[69] Environmental pollution accounts for some cases, and the risk of exacerbations increases during the winter months in the northern and southern hemispheres.

PATHOPHYSIOLOGY AND PREVENTION

Exacerbations are associated with an airway and systemic inflammatory burst that results in

increased ventilatory demands. In patients with limited expiratory flow, tachypnea leads to air trapping and dyspnea,[70] which are mitigated by such therapies as bronchodilators and noninvasive ventilation that decrease tachypnea and lung volumes.[5] Hypoxemia develops in patients with milder disease, whereas ventilatory failure and hypercapnia, which are associated with a poor outcome, may develop in those with more severe compromise. Recovery from an exacerbation takes a long time, and patients with exacerbations have an impaired quality of life, diminished exercise capacity, and loss of lung function.[71,72] Exacerbation prevention includes regular exercise, smoking cessation, appropriate medications, influenza virus and pneumococcal vaccinations, and indoor protection during periods of high environmental pollution.[5,73]

TREATMENT OF THE ACUTE EVENT

Therapy includes short-acting inhaled beta$_2$-agonists, usually given by means of nebulizers. If the response is limited, short-acting anticholinergic agents should be added. Systemic administration of glucocorticoids improves airflow, gas exchange, and symptoms.[74] Treatment for only 5 days with 40 mg of prednisone or its equivalent daily is just as effective as a 10-day course.[5,65] This approach decreases the incidence of psychosis (especially in the elderly), electrolyte imbalance, hyperglycemia, and systemic hypertension. Antibiotics are beneficial, particularly in patients with purulent sputum and severe exacerbations.[65] Selection of the agent depends on local bacterial flora, with the duration of treatment ranging from 5 to 14 days. Patients with severe airflow limitation (FEV_1 <1 liter), hypoxemia, hypercapnia, and coexisting conditions should be hospitalized.

RESPIRATORY FAILURE

In patients whose oxygen saturation is less than 90%, arterial blood gases should be measured while the patients are breathing ambient air. If there is hypoxemia without hypercapnia, low-flow oxygen is indicated, with the goal of achieving a Pao_2 value of 60 to 65 mm Hg (oxygen saturation, 91 to 94%). Patients should be considered for noninvasive ventilation, which improves outcomes, including a reduced risk of death, if they have persistent hypercapnia with a pH of less than 7.35 but more than 7.15.[65,75] Noninvasive ventilation is not beneficial in patients whose condition is unstable and in those with shock, airways that cannot be protected, agitation, or craniofacial deformity. Such patients are better treated with conventional mechanical ventilation.

FUTURE DIRECTIONS

We now understand that COPD is more a syndrome than a single disease. The recognition of pre-COPD and early COPD as targetable entities should help guide the development of specific therapies for these stages of disease, which may significantly reduce the incidence of severe COPD. The revolution brought about by chest CT and a better understanding of the multidimensional nature of COPD and coexisting conditions has resulted in widespread use of pulmonary rehabilitation and the development of bronchoscopic techniques to reduce lung volumes in selected patients with emphysema. Therapies that improve lung structure, such as replacement therapy in patients with alpha$_1$-antitrypsin deficiency, indicate that it is possible to modify the course of COPD. More potent and longer-acting bronchodilator agents have become the cornerstone of therapy. A rational approach to the use of inhaled glucocorticoids, with lower doses and avoidance of systemic administration, and the benefits accrued with systemic antiinflammatory agents, have paved the way for precise therapies. These advances hold out promise for effective treatment of COPD.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Alvar Agustí, Victor Pinto-Plata, José María Marin, Ciro Casanova, Carlos Cabrera, Miguel J. Divo, Juan P. de Torres, and Francesca Polverino for their helpful insights and comments, and Dr. Sundeep Salvi for data on the global burden of COPD.

REFERENCES

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736-88.
2. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet 2017;389:1931-40.
3. Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pul-

monary disease. N Engl J Med 2019; 381:1248-56.
4. Boucher RC. Muco-obstructive lung diseases. N Engl J Med 2019;380:1941-53.
5. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. Am J Respir Crit Care Med 2017;195:557-82.
6. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet 2009;374:733-43.
7. Menezes AM, Hallal PC, Perez-Padilla R, et al. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. Eur Respir J 2007;30:1180-5.
8. Celli BR, Agustí A. COPD: time to improve its taxonomy? ERJ Open Res 2018; 4(1):00132-2017.
9. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J 2008;32: 962-9.
10. Divo MJ, Celli BR, Poblador-Plou B, et al. Chronic obstructive pulmonary disease (COPD) as a disease of early aging: evidence from the EpiChron Cohort. PLoS One 2018;13(2):e0193143.
11. Woodruff PG, Couper D, Han MK. Symptoms in smokers with preserved pulmonary function. N Engl J Med 2016; 375:896-7.
12. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. The presence of chronic mucus hypersecretion across adult life in relation to chronic obstructive pulmonary disease development. Am J Respir Crit Care Med 2016; 193:662-72.
13. Harvey BG, Strulovici-Barel Y, Kaner RJ, et al. Risk of COPD with obstruction in active smokers with normal spirometry and reduced diffusion capacity. Eur Respir J 2015;46:1589-97.
14. Petersen H, Sood A, Polverino F, et al. The course of lung function in middle-aged heavy smokers: incidence and time to early onset of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2018;198:1449-51.
15. Rodriguez-Roisin R, Han MK, Vestbo J, Wedzicha JA, Woodruff PG, Martinez FJ. Chronic respiratory symptoms with normal spirometry: a reliable clinical entity? Am J Respir Crit Care Med 2017;195:17-22.
16. Kohansal R, Martinez-Camblor 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.
17. Gauderman WJ, Urman R, Avol E, et al. Association of improved air quality with lung development in children. N Engl J Med 2015;372:905-13.
18. Morice AH, Celli B, Kesten S, Lystig T, Tashkin D, Decramer M. COPD in young patients: a pre-specified analysis of the four-year trial of tiotropium (UPLIFT). Respir Med 2010;104:1659-67.
19. Agustí A, Celli B. Avoiding confusion in COPD: from risk factors to phenotypes to measures of disease characterisation. Eur Respir J 2011;38:749-51.
20. Ramírez-Venegas A, Sansores RH, Quintana-Carrillo RH, et al. FEV1 decline in patients with chronic obstructive pulmonary disease associated with biomass exposure. Am J Respir Crit Care Med 2014; 190:996-1002.
21. Suzuki M, Makita H, Konno S, et al. Asthma-like features and clinical course of chronic obstructive pulmonary disease: an analysis from the Hokkaido COPD Cohort Study. Am J Respir Crit Care Med 2016;194:1358-65.
22. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005-12.
23. Müllerova H, Maselli DJ, Locantore N, et al. Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort. Chest 2015;147:999-1007.
24. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;186:155-61.
25. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Lancet 2007;370:797-9.
26. Bhatt SP, Washko GR, Hoffman EA, et al. Imaging advances in chronic obstructive pulmonary disease: insights from the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) study. Am J Respir Crit Care Med 2019; 199:286-301.
27. Celli BR, Locantore N, Tal-Singer R, et al. Emphysema and extrapulmonary tissue loss in COPD: a multi-organ loss of tissue phenotype. Eur Respir J 2018;51: 1-10.
28. de Torres JP, Bastarrika G, Wisnivesky JP, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. Chest 2007;132:1932-8.
29. 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;348:2059-73.
30. Criner GJ, Sue R, Wright S, et al. A multicenter randomized controlled trial of Zephyr Endobronchial Valve treatment in heterogeneous emphysema (LIBERATE). Am J Respir Crit Care Med 2018;198:1151-64.
31. Castaldi PJ, Dy J, Ross J, et al. Cluster analysis in the COPDGene study identifies subtypes of smokers with distinct patterns of airway disease and emphysema. Thorax 2014;69:415-22.
32. Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. Chest 2000;117: 1638-45.
33. Agustí A, Edwards LD, Rennard SI, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS One 2012; 7(5):e37483.
34. The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
35. Diaz AA, Valim C, Yamashiro T, et al. Airway count and emphysema assessed by chest CT imaging predicts clinical outcome in smokers. Chest 2010;138:880-7.
36. Han MK, Kazerooni EA, Lynch DA, et al. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. Radiology 2011;261:274-82.
37. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med 2011;364: 897-906.
38. Casanova C, Cote C, de Torres JP, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;171:591-7.
39. O'Donnell DE, Laveneziana P. The clinical importance of dynamic lung hyperinflation in COPD. COPD 2006;3:219-32.
40. de-Torres JP, Marín JM, Casanova C, et al. Identification of COPD patients at high risk for lung cancer mortality using the COPD-LUCSS-DLCO. Chest 2016;149:936-42.
41. Spruit MA, Polkey MI, Celli B, et al. Predicting outcomes from 6-minute walk distance in chronic obstructive pulmonary disease. J Am Med Dir Assoc 2012;13:291-7.
42. Puente-Maestu L, Palange P, Casaburi R, et al. Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. Eur Respir J 2016;47:429-60.
43. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet 2008;372:1107-19.
44. Cazzola M, MacNee W, Martinez FJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008;31:416-69.
45. Silverman EK, Sandhaus RA. Alpha$_1$-antitrypsin deficiency. N Engl J Med 2009; 360:2749-57.
46. Agusti A, Fabbri LM, Singh D, et al. Inhaled corticosteroids in COPD: friend or foe? Eur Respir J 2018;52:1801219.
47. Pavord ID, Lettis S, Anzueto A, Barnes N. Blood eosinophil count and pneumo-

nia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis. Lancet Respir Med 2016;4:731-41.
48. Zhou Y, Zou Y, Li X, 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(3):e1001621.
49. Casaburi R, ZuWallack R. Pulmonary rehabilitation for management of chronic obstructive pulmonary disease. N Engl J Med 2009;360:1329-35.
50. Troosters T, Celli B, Lystig T, et al. Tiotropium as a first maintenance drug in COPD: secondary analysis of the UPLIFT trial. Eur Respir J 2010;36:65-73.
51. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol–glycopyrronium versus salmeterol–fluticasone for COPD. N Engl J Med 2016;374:2222-34.
52. Calzetta L, Rogliani P, Matera MG, Cazzola M. A systematic review with meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable COPD. Chest 2016;149:1181-96.
53. Calverley PMA, Anzueto AR, Carter K, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. Lancet Respir Med 2018;6:337-44.
54. Martinez FJ, Vestbo J, Anderson JA, et al. Effect of fluticasone furoate and vilanterol on exacerbations of chronic obstructive pulmonary disease in patients with moderate airflow obstruction. Am J Respir Crit Care Med 2017;195:881-8.
55. Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775-89.
56. Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet 2018;391:1076-84.
57. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med 2018;378:1671-80.
58. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365:689-98.
59. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet 2009;374:695-703.
60. Rochester CL, Vogiatzis I, Holland AE, et al. An official American Thoracic Society/European Respiratory Society policy statement: enhancing implementation, use, and delivery of pulmonary rehabilitation. Am J Respir Crit Care Med 2015;192:1373-86.
61. The Long-Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. N Engl J Med 2016;375:1617-27.
62. Murphy PB, Rehal S, Arbane G, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. JAMA 2017;317:2177-86.
63. 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.
64. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. Chest 2000;117:Suppl 2:398S-401S.
65. Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2017;50:49.
66. Celli BR. Dissecting COPD exacerbations: time to rethink our definition. Eur Respir J 2017;50:50.
67. Bhatt SP, Wells JM, Iyer AS, et al. Results of a Medicare bundled payments for care improvement initiative for chronic obstructive pulmonary disease readmissions. Ann Am Thorac Soc 2017;14:643-8.
68. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363:1128-38.
69. Papi A, Bellettato CM, Braccioni F, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med 2006;173:1114-21.
70. Pinto-Plata VM, Livnat G, Girish M, et al. Systemic cytokines, clinical and physiological changes in patients hospitalized for exacerbation of COPD. Chest 2007;131:37-43.
71. Cote CG, Dordelly LJ, Celli BR. Impact of COPD exacerbations on patient-centered outcomes. Chest 2007;131:696-704.
72. Donaldson GC, Law M, Kowlessar B, et al. Impact of prolonged exacerbation recovery in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2015;192:943-50.
73. Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline. Chest 2015;147:894-942.
74. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. N Engl J Med 1999;340:1941-7.
75. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50(2):1602426.