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## **An Official American Thoracic Society/European Respiratory Society Statement: Research Questions in Chronic Obstructive Pulmonary Disease**

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# An Official American Thoracic Society/European Respiratory Society Statement: Research Questions in Chronic Obstructive Pulmonary Disease

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**Background:** Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity, mortality, and resource use worldwide. The goal of this Official American Thoracic Society (ATS)/European Respiratory Society (ERS) Research Statement is to describe evidence related to diagnosis, assessment, and management; identify gaps in knowledge; and make recommendations for future research. It is not intended to provide clinical practice recommendations on COPD diagnosis and management.

**Methods:** Clinicians, researchers, and patient advocates with expertise in COPD were invited to participate. A literature search of Medline was performed, and studies deemed relevant were selected. The search was not a systematic review of the evidence. Existing

evidence was appraised and summarized, and then salient knowledge gaps were identified.

**Results:** Recommendations for research that addresses important gaps in the evidence in all areas of COPD were formulated via discussion and consensus.

**Conclusions:** Great strides have been made in the diagnosis, assessment, and management of COPD as well as understanding its pathogenesis. Despite this, many important questions remain unanswered. This ATS/ERS Research Statement highlights the types of research that leading clinicians, researchers, and patient advocates believe will have the greatest impact on patient-centered outcomes.

## Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality. Global Burden of Disease studies have estimated that COPD is the third leading cause of death worldwide (1) and in the United States (2). Mortality appears to

be decreasing worldwide (3); despite this, COPD still caused more than 3 million deaths in 2010 alone (1). It is also the second leading cause of disability-adjusted life-years lost (4). COPD-related mortality more than doubled among women over a 20-year observation period (5), and exacerbations now account for 50

to 75% of the costs associated with COPD (6).

Given the 10-year interval since publication of the Official American Thoracic Society (ATS)/European Respiratory Society (ERS) Standards for the Diagnosis and Treatment of Patients with COPD (7), leaders of the societies felt a need to

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\*Project co-chairs; should be considered co-first authors.

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summarize evidence related to the diagnosis, assessment, and management of COPD; identify knowledge gaps and research questions; and make recommendations for future research. Clinical information from the ATS/ERS Standards (7) is included as context for discussion, but this Research Statement is not intended to be a clinical practice guideline, because other documents are available that provide specific clinical recommendations for the diagnosis and management of stable COPD (8, 9). Clinical recommendations related to COPD exacerbations are similarly not provided because there is a forthcoming ATS/ERS clinical practice guideline that specifically addresses the topic.

## Methods

### Committee Composition

Each society selected two co-chairs on the basis of their expertise in COPD and/or

group facilitation. The co-chairs invited individuals to participate in the project on the basis of their expertise in research or clinical aspects of COPD. The participants were then divided into seven groups, a leader was chosen for each group, and topics were assigned to each group.

### Literature Search and Evidence

#### Appraisal

One of the co-chairs performed a literature search of Medline for each topic. The results of the searches were sent to the groups, who reviewed and selected the studies that they deemed relevant to their topic. Group members were allowed to supplement the literature search with their own searches and to identify relevant studies from other sources. The literature search conducted for this research statement was not a systematic review of the evidence.

#### Research Recommendations

Each group appraised and summarized the existing evidence and then identified salient knowledge gaps. Preliminary research recommendations were formulated to address these gaps. The recommendations were formulated via discussion and consensus. Guideline methodology was not used to formulate or grade the recommendations because they are research recommendations and not patient care recommendations.

#### Document Development

Group leaders sent drafts to either the diagnosis (B.R.C.) or treatment (M.D.) co-chair, who collated and edited the contributions from the groups. The diagnosis and treatment drafts were then sent to the remaining co-chairs (J.A.W. and K.C.W.), who collated and edited the drafts into a single document. The final draft was sent to all participants for review and feedback, including patient advocates and representatives. Multiple cycles of revision, review, and feedback followed until all participants agreed on a version of the draft.

## Definitions

### COPD

The ATS and ERS define COPD as a preventable and treatable disease state characterized by airflow limitation that is not fully reversible (7). The airflow limitation is usually progressive and associated with a chronic inflammatory response of the lungs to noxious particles or gases. Cigarette smoking

is the most common risk factor for COPD (10), but others are increasingly being recognized (e.g., biomass fuels,  $\alpha_1$ -antitrypsin deficiency). Dyspnea and exacerbations represent the most prominent respiratory manifestations of COPD. In most patients, COPD represents the pulmonary component of a chronic multimorbidity. It is particularly common among the elderly and associated with many common risk factors, such as smoking, pollution, aging, inactivity, and diet (11).

### Outcomes

Outcomes are the results of an intervention. Traditionally, many outcomes measured in COPD research have been physiological, such as lung function (e.g., FEV<sub>1</sub>) or functional capacity (e.g., 6-min-walk distance). Physiological outcomes are desirable because they are readily measured, provide information about disease progression, and are related to clinical outcomes such as mortality and exacerbations. Anatomical outcomes have also been used in studies of COPD, such as histological or imaging findings. Physiological and anatomical outcomes make research easier, more efficient, and less costly.

There is increasing recognition, however, that the relationship between many surrogate outcomes (i.e., physiological and/or anatomical outcomes) and outcomes that matter to patients (i.e., “patient-centered” or “patient-important” outcomes, such as dyspnea, quality of life, frequency of exacerbations, frequency of hospitalizations, and mortality) is modest at best, and interventions that improve surrogate outcomes frequently do not affect patient-centered outcomes. As a result, there is increasing emphasis on (1) using patient-centered outcomes in clinical research, and (2) finding high-quality surrogate outcomes that reliably predict patient-centered outcomes (12).

We recommend:

- Studies that determine which outcomes matter most to patients with COPD and, therefore, are truly patient-centered outcomes in this population.
- Studies that correlate physiological and anatomical outcomes with patient-centered outcomes, to identify high-quality surrogate outcomes that may be used in future research.
- Preferential use of patient-centered outcomes to inform judgments related to patient care until surrogate outcomes have been identified that

**Table 1.** Differential Diagnosis of Chronic Obstructive Pulmonary Disease

Diagnosis	Suggestive Features
COPD	Midlife onset Slowly progressing symptoms Long history of smoking
Asthma	Early onset Varying symptoms Symptoms during the night/early morning Presence of allergy, rhinitis, and/or eczema A family history
Congestive heart failure	Airflow limitation that is largely reversible Fine basilar crackles on auscultation Dilated heart on chest radiography Peripheral edema History of ischemic heart disease Volume restriction not airflow limitation on pulmonary function tests
Bronchiectasis	Large volume of purulent sputum Commonly associated with bacterial infection Coarse crackles on auscultation Clubbing Bronchial dilation and bronchial wall thickening on chest radiography/CT
Tuberculosis	Onset at all ages Lung infiltrate on chest radiography Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Younger onset and in nonsmokers History of rheumatoid arthritis/fume exposure? Hypodense areas on expiration on CT
Diffuse panbronchiolitis	Affects mostly male nonsmokers Almost all have chronic sinusitis Diffuse small centrilobular nodular opacities and hyperinflation on chest radiography and HRCT

*Definition of abbreviations:* COPD = chronic obstructive pulmonary disease; CT = computed tomography; HRCT = high-resolution computed tomography.

strongly correlate with patient-centered outcomes.

## Clinical Presentation and Initial Assessment

The diagnosis of COPD is first suspected when a patient (1) complains of a cough, sputum production, dyspnea, or recurrent lower respiratory infections (13); (2) reports risk factors for the disease, such as exposure to cigarette smoke or environmental or occupational pollutants; or (3) presents with an acute exacerbation. Additional medical history is then obtained to assess for each of the following: further evidence that COPD is present, evidence that an alternative disease is not the cause of the symptoms, evidence that comorbidities are present, the ability to perform activities of daily living, other effects of the condition, and the availability of social support (7).

The purpose of the physical examination is to identify respiratory and systemic effects of COPD. A normal physical examination is common in mild COPD, with signs becoming apparent as the disease progresses. Examples include quiet breath sounds, a prolonged expiratory duration, signs of hyperinflation of the lungs, cyanosis, and weight loss. Detection of diminished breath sounds and hyperresonance have a positive likelihood ratio of greater than 5.0, meaning that the combination of findings is a moderately strong predictor that COPD is present. In addition, the respiratory rate, oxygen saturation at rest and with exertion, weight, height, body mass index (BMI), breathlessness (using the modified Medical Research Council dyspnea score [mMRC]), and functional capacity are routinely measured. Functional capacity is best determined by an exercise test, such as timed walking distances or walking speed. Exercise tests have been shown to predict mortality particularly well in patients with COPD (14).

Chest radiography is generally performed during the initial diagnostic evaluation of patients with suspected COPD to exclude other diseases that may cause similar symptoms and signs (Table 1) and to establish the presence of concomitant respiratory diseases. It is frequently normal in early COPD. The radiographic changes associated with COPD include lung hyperinflation and hyperlucent areas in the lungs with peripheral trimming of vascular markings. Chest radiography is not performed during routine follow-up of a stable patient with COPD.

Computed tomography (CT) can estimate the degree of emphysema and its distribution and identify bronchial wall thickening and gas trapping. These estimates correlate with lung function abnormalities, but there are substantial variations among those interpreting the studies, particularly when features are subtle (15, 16). To mitigate interpreter variability, numerous quantitative techniques have been applied (17, 18). These techniques have not become routine clinical practice, however, due to the complex and time-consuming nature of the quantitative analysis (with the exception of emphysema), differences in the algorithms used by equipment manufacturers, the need for specialized software, the requirement of meticulous segmentation and analysis of airways, the lack of a standardized CT protocol to assess emphysema, and the lack of agreement on complex measurements (e.g., airway wall dimensions) (19–22).

Additional advantages of CT scanning are that it can help differentiate between structural abnormalities that cause airflow limitation (e.g., emphysema, bronchiolitis, and bronchiectasis), identify abnormalities that are associated with clinically significant features (i.e., phenotypes), and detect both pulmonary comorbidities (e.g., lung cancer, interstitial lung disease, pulmonary hypertension) and nonpulmonary comorbidities (e.g., coronary artery calcifications, heart failure, diseases of the mediastinum) (23). The risk of lung cancer is increased among patients with COPD, but it is inversely related to the degree of airflow obstruction (24). The presence of airflow obstruction should raise awareness of the risk for lung cancer; indeed, patients with COPD are considered good candidates to be screened for lung cancer, especially if they have radiological

emphysema or a low diffusion capacity for carbon monoxide ( $D_{LCO}$ ) (24).

We recommend:

- Studies to determine whether there is a role for routine CT scanning among patients with newly diagnosed COPD.
- Studies to identify CT findings that reliably and consistently correlate airway dimension measurements with lung function, using pulmonary function tests as the reference standard.
- Studies to identify CT findings that are associated with clinically significant features (i.e., phenotypes) and differential responses to treatment.
- Studies to determine the optimal CT protocol and quantification methods. The results may allow CT scans performed using different types of CT scanners to be compared with one another, which would facilitate longitudinal assessment, multicenter trials, and multicenter clinical care.

## Diagnosis

Diagnosis of COPD requires confirmation of an airflow limitation that is not fully reversible via spirometry and the history of a potentially causative exposure (e.g., smoking). Airflow limitation that is not fully reversible is defined by a low post-bronchodilator  $FEV_1/FVC$  ratio (7).

The threshold  $FEV_1/FVC$  ratio that should be used to confirm an airflow limitation is uncertain. A post-bronchodilator  $FEV_1/FVC$  ratio of less than 0.7 has traditionally been the criterion for airflow limitation (7, 8). This threshold may result in more frequent identification of airflow limitation and, hence, diagnosis of COPD among the elderly (25) and less frequent diagnosis among young adults less than 45 years of age (26) compared with a threshold based on the lower limit of normal (LLN) of  $FEV_1/FVC$ . Although these observations are particularly relevant for epidemiological studies, advocates for the fixed ratio argue that it identifies a number of patients with significant pulmonary pathology and respiratory morbidity not detected by the LLN (27), and advocates for the LLN argue that the fixed ratio is more likely to yield false-positive results (25).

Screening asymptomatic individuals for COPD using spirometry is controversial. There is evidence that screening detects undiagnosed COPD (28). However, asymptomatic individuals with mild airflow limitation (Global Initiative for Chronic Obstructive Lung Disease [GOLD] grade 1) may not have faster lung function decline or a lower quality of life than asymptomatic individuals with normal lung function (29), and there are no data showing that outcomes improve among individuals who are identified as having COPD before developing symptoms, that early treatment provides any benefit in asymptomatic individuals, or that screening is cost effective (30).

We recommend:

- Studies that measure the accuracy of various tools (e.g., questionnaires) to detect symptoms in patients at risk for COPD, using spirometry as the reference standard.
- Studies that compare outcomes among individuals diagnosed with COPD on the basis of an  $FEV_1/FVC$  ratio less than 0.70 with those among individuals diagnosed with COPD on the basis of an  $FEV_1/FVC$  below the LLN.
- Studies that compare outcomes among symptomatic individuals whose COPD diagnosis is based on the combination of an airflow limitation confirmed by spirometry and a history of exposure to the causative agent with those among symptomatic individuals whose COPD diagnosis has not been confirmed with spirometry but rather is based on an alternative approach. Examples of alternative approaches include various combinations of symptoms, imaging findings, and physiological abnormalities measured by complementary tests such as forced oscillation techniques.
- Studies that evaluate case-finding strategies using questionnaires, mini-spirometers, and office spirometry in areas where access to conventional spirometry requires specialized assessment.
- Studies that examine the impact of ascertainment (e.g., by spirometric screening vs. spirometry performed due to symptoms and an exposure history) on medium- and long-term outcomes in individuals with COPD.

- Studies that evaluate the impact of age on the importance of identifying an airflow limitation (i.e., is it more important to identify asymptomatic airflow limitation in a 30-yr-old than an 80-yr-old?).

## Assessment after Diagnosis

### Disease Severity

The severity of a disease relates to the extent of functional impairment of the target organ(s). Classification of COPD severity by spirometry alone (Table 2) predicts patient-centered outcomes, such as health status (31), use of healthcare resources (32), frequency of exacerbations (33, 34), and mortality (35). However, this approach is primarily intended for populations (36) and is not a substitute for clinical judgment in the evaluation of the severity of disease in individual patients.

The BMI and functional dyspnea (i.e., dyspnea that affects functional ability, employment, quality of life, or health status [37]) also predict patient-centered outcomes. The BMI is obtained by dividing the weight (in kg) by the height (in  $m^2$ ); values less than  $21 \text{ kg}/m^2$  are associated with increased mortality (38, 39). The severity of functional dyspnea can be assessed using the mMRC (Table 3) (40). Increased mMRC levels of dyspnea are associated with increased mortality (41). Exacerbation frequency, health status, and level of physical activity are also predictors of mortality (42).

Several composite indices of disease severity have been developed (Table 4) (43–50). Although the prognostic accuracy of each of these indices has been confirmed in separate studies, few studies have directly compared one index to another. The GOLD Global Strategy for the Diagnosis, Management, and Prevention of COPD (8) proposed a multidimensional assessment of COPD for the purposes of treatment selection. The assessment includes: (1) high/low symptoms using the mMRC dyspnea scores, the COPD Assessment Test, or the clinical COPD questionnaire; (2) the severity of airflow limitation; and (3) the number of yearly exacerbations. Patients with high symptoms (mMRC dyspnea score  $\geq 2$ , COPD Assessment Test score  $\geq 10$ , or clinical COPD questionnaire score  $\geq 1$ ) and GOLD grade 3 or 4 spirometry and/or frequent exacerbations (two or more exacerbations in the

**Table 2.** Spirometric Classification of the Severity of Chronic Obstructive Pulmonary Disease

Severity of Obstruction	Post-bronchodilator FEV <sub>1</sub> /FVC	FEV <sub>1</sub> % Predicted
At risk	>0.7	≥80
Mild COPD	≤0.7	≥80
Moderate COPD	≤0.7	50–80
Severe COPD	≤0.7	30–50
Very severe COPD	≤0.7	<30

*Definition of abbreviation:* COPD = chronic obstructive pulmonary disease.

At risk are (1) patients who smoke or have exposure to pollutants; (2) patients who have cough, sputum, or dyspnea; and (3) patients who have a family history of chronic respiratory disease.

preceding year and/or one hospitalization) are considered at high risk for further exacerbations and, indirectly, poor clinical outcomes. The proposed approach has not yet been fully validated and is the subject of current research (51–53).

Concomitant chronic diseases may contribute to the severity of disease in patients with COPD, and inclusion of comorbidities in the multidimensional evaluation of patients with COPD is useful in the context of comprehensively evaluating patients with COPD (50, 54).

We recommend:

- Studies that determine which index or indices best stratify patients for the purpose of determining disease severity or recommending treatment.
- Studies that determine if short-term changes in these indices or other measures (e.g., lung function, CT findings, biomarkers) are useful surrogate markers of medium- or long-term patient-centered outcomes, thus shortening the time needed to complete therapeutic trials.
- Studies that contribute to a better understanding of the pathogenesis, impact, prevention, and treatment of concomitant diseases in patients with COPD.

### Disease Activity

Activity of a disease relates to the level of activation of the biological processes that drive disease progression. Disease activity is a different concept than disease severity. In theory, identifying and treating active pathological processes may mitigate or eliminate disease progression.

The biological processes that drive disease progression in COPD are likely to be related to the balance between the pulmonary and systemic inflammatory responses to inhalational injury and the subsequent repair process (55). It is unclear how to measure the activity of these processes. Potential surrogate markers include the rate of change of clinical markers of disease progression, because faster rates of disease progression presumably indicate more disease activity. Examples of clinical markers include worsening dyspnea and health status, loss of exercise capacity, cough and sputum production, active smoking, appearance or worsening of comorbidities, weight loss, and frequency of exacerbations (56, 57). Other measures can be categorized as functional markers (e.g., FEV<sub>1</sub> decline, deterioration of DL<sub>CO</sub>, progressive hyperinflation), structural markers (e.g., progression of emphysema, worsening of airway dimensions, appearance or

worsening of bronchiectasis), and biological markers (e.g., biological markers in the lung, circulating blood, exhaled air, and/or urine).

Disease progression in established COPD is heterogeneous (58), ranging from rapid progression to stable or even improved lung function. This suggests that disease activity is also variable.

We recommend:

- Studies that relate potential biomarkers of disease activity (e.g., rate of lung function decline, increased exacerbation frequency, inflammation, lung tissue destruction, and repair responses induced by inhalational injury) to patient-centered outcomes to validate the biomarkers as clinically useful measures of disease activity.
- Studies that evaluate the impact of disease activity on treatment response and, conversely, the effects of treatment on disease activity.

### Phenotyping

A phenotype is the observable properties (i.e., phenotypic traits) of an organism, which are determined by its genotype and modulated by its environment (59). Some phenotypes influence the clinical course of COPD. A clinical COPD phenotype has been defined as “A single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (e.g., symptoms, exacerbations, response to therapy, rate of disease progression, or death)” (60).

Clinical phenotyping may be complicated for several reasons. First, the presentation of some clinical phenotypes may change due to the effect of therapy and/or the natural course of the disease. Second, although a COPD phenotype describes differences between individuals with COPD, a given patient can have more than one clinical phenotype. Finally, two prevalent diseases can coexist (e.g., COPD and obstructive sleep apnea, or COPD and asthma).

Only a few COPD phenotypes have been validated. They include α<sub>1</sub>-antitrypsin deficiency, frequent (two or more per year) exacerbations, chronic bronchitis, and upper lobe emphysema with poor exercise tolerance after rehabilitation in patients with severe airflow limitation. Other COPD phenotypes have been proposed but

**Table 3.** Modified Medical Research Council Dyspnea Scale

Grade	Description
0	Not troubled with breathlessness, except during strenuous exercise.
1	Troubled by shortness of breath when hurrying or walking up a slight hill.
2	Walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace on a level surface.
3	Stops for breath after walking about 100 m or after a few minutes on a level surface.
4	Too breathless to leave the house or breathless when dressing or undressing.

**Table 4.** Composite Prognostic Indexes in Chronic Obstructive Pulmonary Disease

Composite Index	Components	Reference
BODE	BMI, FEV <sub>1</sub> , mMRC, 6MWD	43
mBODE	BMI, FEV <sub>1</sub> , mMRC, peak V <sub>O<sub>2</sub></sub>	44
eBODE	BMI, FEV <sub>1</sub> , mMRC, 6MWD, exacerbation rate	45
BODEx	BMI, FEV <sub>1</sub> , mMRC, exacerbation rate	46
Inflammatory BODE	BODE, inflammatory biomarkers, age, and hospitalization history	47
ADO	Age, mMRC, FEV <sub>1</sub>	48
DOSE	mMRC, FEV <sub>1</sub> , smoking status, exacerbation rate	49
CODEx	Comorbidity, obstruction, dyspnea, and previous severe exacerbations	50

*Definition of abbreviations:* 6MWD = 6-minute-walk distance; ADO = age, dyspnea, and airflow obstruction index; BMI = body mass index (kg/m<sup>2</sup>); BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity index; BODEx = exacerbations replace 6MWD in the original BODE; CODEx = comorbidities, airflow obstruction, dyspnea, and exacerbations index; DOSE = dyspnea, airflow obstruction, smoking status, and exacerbations index; eBODE = exacerbations added to original BODE; FEV<sub>1</sub> = forced expiratory volume in 1 second (severity of airflow obstruction); inflammatory BODE = inflammatory markers added to original BODE; mBODE = modified BODE in which 6MWD is replaced by peak oxygen consumption; mMRC = level of dyspnea according to the Modified Medical Research Council questionnaire.

still require validation confirming their relationship with clinically meaningful outcomes: severe hypoxemia, disproportionate symptoms, persistent systemic inflammation, chronic airway bacterial colonization, emphysema predominance with pulmonary hyperinflation and lung cancer, the asthma/COPD overlap syndrome, premature or early severe airflow limitation (<55 yr), out-of-proportion pulmonary hypertension (mean pulmonary arterial pressure > 40 mm Hg), COPD in never smokers, and the four new patient types (i.e., types A, B, C, and D) proposed by GOLD (8). Even if some of these phenotypes are associated with clinically meaningful outcomes, many experts believe that research should focus on those phenotypes where outcomes can be modified with therapy. In fact, exploratory therapeutic interventions in targeted populations are performed for the validation of a clinical phenotype.

We recommend:

- Studies to relate potential phenotypic traits with outcomes. Such evidence may provide more individualized prognostic information.
- Studies to relate potential phenotypic traits with response to therapy. Such evidence may identify specific types of patients who are more or less likely to respond to a given therapy,

facilitate the development of personalized medicine, and increase the priority of future research studies that plan to enroll phenotypes whose outcomes can be potentially modified by therapy.

- Studies to enhance understanding of the treatment impact of various COPD phenotypes (e.g., asthma/COPD overlap,  $\alpha_1$ -antitrypsin deficiency, bronchiectasis, etc.).

#### Comorbidities

COPD is frequently associated with one or more comorbidities and/or systemic effects. Therefore, in many patients, COPD can be considered just the pulmonary component of the multimorbidity that is characterized by concomitant chronic diseases (e.g., hypertension, atherosclerosis, chronic heart failure, lung cancer, osteoporosis, depression, etc.) and systemic effects (e.g., weight loss, muscle weakness) that are not fully explained by aging and other common risk factors (e.g., smoking, diet, inactivity, lifestyle, etc.) (61–63). Chronic comorbidities are prominent contributors to the clinical severity of patients with COPD, as they often affect important patient-centered outcomes.

Ischemic heart disease is a particularly common comorbidity, contributing to worsening health and functional status (64),

increased risk of a longer exacerbation (64), more dyspnea (64), and decreased survival (65). COPD is also associated with an increased incidence of lung cancer (24, 66) and prevalence of diabetes, hypertension, and other cardiovascular diseases, even after controlling for tobacco smoking in some studies. The Toward a Revolution in the treatment of Chronic obstruction (TORCH) trial enrolled patients with moderate to severe airflow limitation and demonstrated that 26% of deaths were due to cardiovascular causes, 21% were due to cancer, and only 35% were directly attributable to COPD (67). Among patients with mild airflow limitation, cancer and cardiovascular disease accounted for 50% and 20% of the deaths, respectively.

More recent evidence supports the clustering of certain comorbidities with COPD (68), thereby suggesting potential common pathobiological pathways for these diseases. There is also increasing evidence that acute exacerbations of respiratory symptoms in patients with COPD may be caused by extrapulmonary mechanisms and exacerbations of concomitant chronic diseases, such as systemic arterial hypertension, acute heart decompensation, atrial fibrillation, and pulmonary embolism (69). Conversely, COPD exacerbations appear to impact the risk of cardiovascular events (70). Although acute exacerbations of respiratory symptoms occur more frequently in patients with COPD, they also occur with significant frequency in smokers without COPD, suggesting that they are not specific for COPD (71, 72). Patients with COPD have a similar prevalence of sleep apnea as the general population. When this overlap syndrome exists, patients are treated with continuous positive airway pressure, because this has been shown to decrease mortality (73).

We recommend:

- Studies to confirm or exclude an association between specific comorbidities and COPD.
- Studies to elucidate pathobiological mechanisms linking COPD to its comorbidities.
- Studies to explore the mechanisms of exacerbations of respiratory symptoms in patients with COPD.
- Studies to determine the nature and optimal therapeutic management of patients with concomitant chronic diseases, particularly heart failure and/or ischemic heart disease.

## Pathophysiology and Pathology

Tobacco smoke is the major risk factor for COPD worldwide, although other inhaled noxious particles and gases may also contribute. Inhalation of such substances causes a chronic inflammatory response and oxidative stress in the lungs of some individuals, leading to the abnormalities characteristic of COPD (74). In addition, other pathobiological processes probably contribute, as the disease continues to progress in a substantial proportion of patients, even after inhalation of the offending agent ceases. Such processes may include genetic and epigenetically determined responses (75, 76), an imbalance of proteinases and antiproteinases (76), an abnormal interaction between environment and microbiome (76), alteration of the microbiome (77), a chronic immune response (78), inappropriate control of programmed cell death (79), accelerated lung aging (80), pulmonary endothelial cell dysfunction (81), and abnormal ion transport due to CFTR dysfunction (82).

These mechanisms collectively cause pathological changes in four compartments of the lungs: the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature (83–87). The pathological changes that give rise to the physiological abnormalities that characterize COPD include emphysema, mucus hypersecretion, ciliary dysfunction, airflow limitation, hyperinflation, abnormal gas exchange, pulmonary hypertension, and various systemic effects (e.g., limb muscle weakness) (88, 89).

We recommend:

- Studies that elucidate pathways driving the chronic inflammatory response and oxidative stresses that lead to the abnormalities characteristic of COPD.
- Studies that elucidate the role of genetics, proteinases and anti-proteinases, the lung microbiome, programmed cell death, mucus hypersecretion, and the pulmonary vasculature in the pathogenesis of COPD.
- Studies that compare the pathogenesis, pathology, histology, progression, prognosis, comorbidities, and treatment response of smoking-induced

COPD with COPD related to other factors, including biomass fuels or occupational exposures.

- Studies that determine the influence of race, sex, and socioeconomic status on the natural history and pathobiology of the disease.

## Management

### Smoking Cessation

Stopping smoking increases life expectancy at any age. Those who have smoked cigarettes since early adulthood but stop at 30, 40, or 50 years of age gain about 10, 9, and 6 years of life expectancy, respectively, compared with those who continue smoking (90). Smoking cessation reduces the rate of decline of lung function in patients with COPD and, therefore, is an important goal of treating smokers with COPD (91). It has been hypothesized that objective evidence of disease may motivate smokers to quit. This was supported by a study that found that communicating the results of spirometry in terms of the smoker's "lung age" (i.e., the age at which a healthy individual acquires similar results) improved the likelihood of smoking cessation (92). However, other data are conflicting. Two studies found that smokers whose spirometry identified COPD had higher quit rates than smokers whose spirometry did not identify COPD (93, 94), whereas another study found that confronting smokers with abnormal spirometry results did not improve smoking cessation rates (95).

Smokers with COPD have particularly strong nicotine dependence (96). Despite this, they appear to be just as responsive as smokers without COPD to pharmacotherapy directed at smoking cessation. This is supported by the observation that smoking quit rates were similar in trials that enrolled smokers with mild to moderate COPD compared with trials that enrolled general populations of smokers (97–100). It is unknown whether these findings apply to patients with severe COPD because such patients have been scarcely studied. It is likely that some comorbidities affect responsiveness to smoking cessation interventions and others do not. As examples, studies have shown that depression negatively impacts smoking cessation (101), whereas cardiovascular disease does not (102).

Pharmacologic aids for smoking cessation can be allocated into two categories: controllers (e.g., nicotine patch, bupropion, and varenicline), which target long-term abstinence, and relievers (e.g., nicotine gum) for rapid relief of acute cravings for tobacco or heightened withdrawal symptoms. Generally speaking, the controller medication is taken on a regular dosing schedule and the reliever is used on an as-needed basis to manage acute urges to smoke or breakthrough withdrawal symptoms. Although this strategy is intuitive, its outcomes have not been studied in controlled trials. Pharmacologic therapy with two controller agents to aid smoking cessation is recommended by some guidelines due to improved efficacy compared with single agents (103–106), but the optimal combination of agents and the duration of therapy remain unknown.

The combination of pharmacotherapy plus counseling improves smoking cessation compared with either pharmacotherapy or counseling alone (107, 108). However, the optimal intensity of counseling is unknown. In a study in which smokers with COPD received both counseling and nicotine replacement therapy, the intensity of the counseling related to improvement in the quit rate (109). In contrast, another study found no differences between smokers who received either low- or high-intensity counseling in addition to pharmacotherapy (100).

Electronic cigarettes (i.e., e-cigarettes) are devices that, when puffed like a cigarette, produce vapors that can contain nicotine. This eliminates inhalation of most of the toxic constituents of tobacco cigarettes, although the risks of e-cigarettes are incompletely understood. E-cigarettes are growing in popularity because they have behavioral features similar to those of conventional cigarettes, yet are presumed to be a less harmful alternative that can decrease both cravings and withdrawal symptoms. They are being used as either a substitute for conventional cigarettes or as an aid to quitting smoking (110–112). Additional research on e-cigarettes has become an urgent need, because the presumed benefits of e-cigarettes are unproven and the long-term risks are unknown, yet e-cigarettes are commercially available and becoming increasingly popular (113). In particular, the efficacy of e-cigarettes as a smoking cessation strategy is unknown. A concern is that individuals who might otherwise avoid regular cigarette smoking due to fear of



adverse health effects might be attracted to presumably safer electronic cigarettes and thereby become addicted to nicotine. In such individuals, the e-cigarettes might serve as a gateway to regular cigarette smoking. The Forum of International Respiratory Societies, which includes the ATS and ERS, has published a position statement on e-cigarettes (114).

Patients frequently fail to quit smoking and, therefore, ask whether decreased smoking is sufficient to derive some benefit. Although one study suggests that smoking reduction improves respiratory symptoms (115), it is unclear if smoking reduction slows the rate of lung function decline (116–119) like smoking cessation (91). However, studies suggest that smoking reduction is associated with a greater probability of future cessation (119).

Electronic health records provide an opportunity to both identify smokers and offer treatment. However, one systematic review found that electronic health records were only associated with improvement in the documentation of smoking and not greater prescription of smoking cessation medications or referral to smoking cessation programs. In contrast, even brief programs that targeted patient-level interventions were more likely to increase referral to smoking cessation programs (120).

Marijuana smoking is now legal in two states within the United States for recreational purposes and for medical purposes in several others, yet the risk of marijuana smoking on the development of COPD is uncertain. As an example, multiple studies have found that long-term marijuana smoking is associated with symptoms of COPD, but an association with fixed airflow obstruction has been inconsistent (121). The reasons for the inconsistent findings are not understood.

We recommend:

- Studies comparing the smoking quit rate of individuals who undergo spirometry with the smoking quit rate of those who do not undergo spirometry, using different techniques to add value to the spirometry results (e.g., lung age, functional limitation). Among those undergoing spirometry, quit rates should be compared among those with and without airflow obstruction.
- Studies to clarify the optimal approach to achieve abstinence from

smoking. Examples include a controller plus a reliever versus a controller or reliever alone, various combinations and durations of pharmacological agents, various intensities of counseling, and add-on therapies if initial therapy fails.

- Studies that measure the potential benefits (i.e., smoking quit rate, incidence of COPD, and incidence of lung cancer) and harms (i.e., addiction rate, toxicology, carcinogenesis, and cost-effectiveness) of e-cigarettes, both short- and long-term.
- Studies that compare outcomes among patients who have quit smoking, reduced the amount that they smoke, or continued smoking the same amount.
- Studies investigating the genetic basis of smoking addiction and cessation.
- Studies comparing existing smoking cessation strategies and seeking novel smoking cessation strategies and drugs.
- Studies to determine whether marijuana smoking increases the incidence of COPD and, if so, to identify which individuals are at greatest risk.

### Standard Pharmacological Therapies

Lung function is improved and the frequency of acute COPD exacerbations is reduced by long-acting  $\beta$ -agonists (LABAs), inhaled corticosteroids (ICS), combined LABA/ICS, and long-acting antimuscarinic antagonists (LAMAs) (67, 122, 123). Health-related quality of life is also improved by ICS, LABAs, LABA/ICS, and LAMAs (67, 122, 123). LABA/ICS and LAMAs may improve mortality in unselected patients with COPD (66, 122), although the evidence for this effect is limited because the studies had a low event rate due to the inclusion of patients at low risk for mortality (124).

The rate of decline of lung function might be reduced by inhaled medications according to several subgroup analyses. The first subgroup analysis (125) of a randomized trial (67) suggested that LABAs alone, ICS alone, and LABA/ICS may reduce the rate of decline of lung function among patients with varying severities of COPD. The effect was modest, as the reduced rate of decline of lung function achieved with inhaled medications

was only about half that achieved with smoking cessation and sustained abstinence (125). The second subgroup analysis (126) of a randomized trial (122) suggested that LAMAs may reduce the rate of decline of lung function among patients with moderate COPD (i.e., GOLD stage 2), even though the randomized trial found no such effect among the entire population of patients with varying severities of disease.

One reason that the effects of inhaled medications appear modest or absent in heterogeneous populations of patients with COPD is that effects may vary among COPD subtypes, such as patients who have cardiac comorbidities, have an increased risk for mortality, or have predominant emphysema or bronchial disease (52, 127). Although the possibility that medications have differential effects on COPD subtypes is generally accepted, early efforts at individualizing treatment have had limited successes. Some treatments were found to prevent exacerbations preferentially in patients with a history of chronic bronchitis and a history of exacerbations (52), and patients with a history of two or more exacerbations during the previous year responded better to preventative therapy in some studies (128, 129). It is uncertain whether or not current smokers respond differently to treatment than former smokers, although there is some evidence that differences may exist (130).

An as-needed inhaled short-acting  $\beta$ -agonist is generally the first medication initiated, often with a standing dose of an inhaled long-acting bronchodilator (9). However, the optimal long-acting bronchodilator regimen is unknown. In a systematic review of seven randomized trials that directly compared a LAMA (i.e., tiotropium) with LABAs, meta-analyses found that the LAMA had a greater effect on reducing COPD exacerbations, exacerbation-related hospitalizations, and adverse effects, but there were no differences in mortality, all-cause hospitalizations, symptoms, or lung function (131).

The meta-analyses were limited by heterogeneity, suggesting that the differences between the LAMA and the LABAs may have been due to the specific LABA (i.e., salmeterol, formoterol, or indacaterol), the population studied, or genetic predisposition (132). In other words, whereas the LAMA was superior to the LABAs collectively, the possibility that one of the LABAs is superior to the LAMA

in some subgroups or the entire COPD population cannot be excluded. The meta-analyses evaluated only the 12-hour LABAs, because they preceded the introduction of 24-hour acting LABAs; however, a subsequent direct comparison between the LAMA tiotropium and the 24-hour LABA indacaterol confirmed the superiority of LAMAs in reducing exacerbations (133).

The LABA/ICS combination is sometimes given either instead of a long-acting inhaled bronchodilator alone or in addition to a LAMA. In some patients, the LABA/ICS combination improves health-related quality of life and reduces the risk of a COPD exacerbation (67). The combination also reduces the rate of lung function decline when compared with placebo but not when compared with a LABA alone or ICS alone (125). The LABA/ICS combination may have a modest effect on overall mortality (67). The primary adverse effect attributed to the LABA/ICS combination is an increased risk of pneumonia, although this effect may not be present to the same degree with all formulations of a LABA/ICS (134, 135).

The LABA/ICS combination is equivalent to a LAMA in exacerbation prevention in the only direct comparison with a LAMA (136). Several other outcomes (i.e., health status, mortality) favor the LABA/ICS combination over the LAMA, but confidence in these results is limited by the small number of events (136). Adding a LAMA to the LABA/ICS combination appears to reduce the rate of severe exacerbations and improve symptoms in patients with moderate or severe COPD (137).

LABA/LAMA combinations have been developed and appear to increase lung function to a greater degree than a LAMA alone (138). The effect of the LABA/LAMA combination on the frequency of COPD exacerbations is less certain because it reduced the frequency when compared with one LAMA (i.e., glycopyrrolate) but not when compared with another LAMA (i.e., tiotropium) (138). More studies are needed to determine the effect of the LABA/LAMA combination on other patient-centered outcomes.

Criteria for adding and withdrawing medications are uncertain. Few studies have investigated the benefits of adding medications (137, 139, 140), and, although one trial suggested that withdrawal of ICS may not increase the risk of moderate or

severe COPD exacerbations (141), there is an overall paucity of evidence about when COPD medications can be safely withdrawn. To monitor pharmacotherapy, tools are needed to facilitate objective assessment of the effects of medications (142–144).

Adherence to inhaled medications has a significant impact on patient-centered outcomes, including mortality and hospital admissions (145). Administrative database analysis suggests that less frequent dosing is one way to improve adherence (146). Additional strategies that may improve adherence include the method of administration (i.e., nebulizer, inhalers, etc.) and various behavioral approaches (e.g., assessing inhaler technique); however, the effectiveness of such interventions has not been confirmed due to insufficient study (147–149).

A high proportion of patients with COPD have poor inhaler technique, which appears to negatively affect outcomes (148). Choosing the right device for a given patient, educating on inhaler technique, and regularly checking inhaler use are important components of COPD management (150).

We recommend:

- Therapeutic trials that analyze outcomes among different COPD subtypes, particularly those subtypes that are at greatest risk for an undesirable outcome.
- Therapeutic trials that compare outcomes among current smokers with former smokers.
- Therapeutic trials that evaluate outcomes using different thresholds for initiating, adding, and withdrawing medications.
- Therapeutic trials that compare outcomes among patients treated with different medications (as opposed to placebo-controlled studies). Examples include:
  - Comparisons of LAMA therapy with each type of LABA therapy (i.e., salmeterol, formoterol, indacaterol, olodaterol, and vilanterol)
  - Comparisons of combination LAMA/LABA therapy with LABA/ICS, LAMA, and LABA therapy.
- Trials comparing strategies of pharmacological treatment (e.g., treatment initiation with one single agent and then further step-up if

symptoms are not controlled vs. immediate double or triple therapy).

- Studies of therapies aimed at improving cough, sputum production, and dyspnea, all of which are of important to patients.
- Studies assessing how pharmacological treatment complements rehabilitation programs.
- Real-life observational studies (i.e., effectiveness studies) that assess how the results of randomized trials (i.e., efficacy trials) may be applied to broader patient populations in usual care settings.
- Studies that determine the risk for pneumonia conferred by each formulation of the LABA/ICS combination as well as the etiology and natural history of pneumonia in patients treated with ICS.
- Studies that evaluate the effects of treating common comorbidities on COPD-specific outcomes as well as the effects of treating COPD on outcomes specific to common comorbidities.
- Studies that identify and validate instruments that objectively determine a patient's response to therapy.
- Studies that compare outcomes among patients managed with various strategies to improve adherence. Examples include inhaler choice and education.
- Studies that compare outcomes among patients who use an inhaler with those who use a nebulizer.
- Studies of patients who are diagnosed with COPD at an early age to determine if early intervention reduces disease progression.

## Novel Pharmacological Therapies

**Antiinflammatory therapies.** Chronic inflammation is likely to contribute to both the pathophysiology of COPD and its associated morbidities (151). However, inflammation is complex and, in COPD, seems to represent amplification of the normal response of the respiratory tract to inhaled irritants, mainly cigarette smoke and biomass (152, 153).

Many inflammatory cells and mediators are involved in COPD inflammation, so there are many potential targets. However, treatments that are too specific or downstream may have little

effect or target only a small proportion of patients (i.e., responder phenotypes), as demonstrated by single mediator antagonists that have proven ineffective, including tumor necrosis factor- $\alpha$ , IL-1 $\beta$ , and IL-5 blocking antibodies (154, 155).

Broad-spectrum antiinflammatory treatments seem more likely to be effective, but frequent side effects occur when such agents are given orally. This supports inhaled strategies, although this approach will likely have little effect on inaccessible areas of the lung or systemic features. Both ICS/LABA and ICS alone are antiinflammatory agents. The phosphodiesterase (PDE)-4 inhibitor, roflumilast, is a therapy with antiinflammatory properties that has some efficacy, but the dose is limited by side effects such as diarrhea, nausea, and headaches (156). There is *in vitro* evidence of LAMAs having antiinflammatory properties, but clinical studies have failed to confirm this effect (157). Inhibitors of p38 mitogen-activated protein kinase may be useful, but previous studies in rheumatoid arthritis demonstrated frequent side effects and loss of efficacy with time (i.e., tolerance). Oral p38 mitogen-activated protein kinase inhibitors have small effects (158) or no effects (159), and inhaled drugs are in development. Other kinases targeted for COPD include Janus-activated kinase, phosphoinositide-3-kinase, and spleen tyrosine kinase, but no clinical studies have been reported. Reversing corticosteroid resistance is currently being explored in large trials of low-dose theophylline and phase II studies with inhaled phosphoinositide-3-kinase  $\delta$  inhibitors (160).

Biomarkers may predict responsiveness to antiinflammatory therapies. As examples, a history of COPD exacerbations, circulating eosinophilia, and/or sputum eosinophilia predicts responsiveness to corticosteroids (161, 162). They might also predict responsiveness to a monoclonal antibody that appears to be effective in eosinophilic severe asthma (163, 164).

Antioxidant therapies may be useful in the prevention of exacerbations. However, their effect on stable inflammation and disease progression has yet to be proven. Although current drugs appear ineffective, there is recent interest in activators of Nrf2, which regulates antioxidant genes, particularly because Nrf2 function is defective in COPD.

**Long-term antibiotic therapy.** Long-term macrolides have been used to prevent recurrent exacerbations. In addition to their

antibacterial activity, other potentially beneficial effects of macrolides include an antiinflammatory effect, enhanced phagocytic activity of macrophages (165), increased antiviral effects (165, 166), and gastric prokinetic effects.

Randomized, placebo-controlled clinical trials have confirmed a reduction in the frequency of exacerbations of COPD with long-term use of macrolides. However, the trials used different drugs with different administration regimens and enrolled populations with different inclusion and exclusion criteria (167, 168). Thus, although the effect might be greater in older patients and milder COPD and less in current smokers (130), the patient population for which macrolides are indicated, the best dosage, and the optimal duration of treatment still need to be determined. The mode of action (i.e., antiinflammatory or antimicrobial), differential effects among the various macrolides, and effects of therapy on other patient-centered outcomes also need to be elucidated. The use of macrolides has been associated with increased risk of cardiovascular events in some database studies (169–171); however, the 1-year incidence of cardiovascular death was minimal (1 out of 558 patients who received a macrolide) in a trial that excluded patients with COPD who had a resting heart rate greater than 100 beats per minute, had a corrected QT (QTc) interval greater than 450 msec, or were using medications known to prolong the QTc interval or be associated with torsades de pointes, suggesting that the risk is low if patients are properly selected for macrolide therapy (167). In addition, chronic use of macrolides may be associated with the acquisition of antibiotic resistance. As a result, macrolides are initiated on a case-by-case basis after carefully weighing the benefits versus risks for each patient.

The fluoroquinolone moxifloxacin has been used as a 5-day pulse every 8 weeks to reduce the frequency of exacerbations in patients with moderate to severe COPD. In a randomized, placebo-controlled trial, moxifloxacin reduced exacerbations by 25% overall and up to 45% in the subgroup of patients with purulent or mucopurulent sputum at baseline (172). Results suggest that moxifloxacin is particularly effective in reducing bacterial exacerbations in patients who are likely to be colonized by bacteria other than *Pseudomonas aeruginosa*. However, the types of patients most likely

to benefit from long-term fluoroquinolone therapy, the best dosage, the optimal duration of treatment, the mode of action, the effects on other patient-centered outcomes, and whether there are differences among the various fluoroquinolones remain unknown.

Many other antibiotics exist that have never been studied, including other macrolides and fluoroquinolones as well as other classes of antibiotics. It is unknown whether such alternatives are less effective, similarly effective, or more effective than those that have been systematically studied. In addition, the long-term safety of such agents needs to be determined, including side effects and the emergence of bacterial resistance.

**Statin therapy.** Statins inhibit conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, which accounts for the immune modulating effects in both systemic and pulmonary circulation. In animal models, statins are antiinflammatory and have demonstrated beneficial effects on lung parenchyma, airways, and vasculature (173).

Predominantly observational evidence about the effects of statins in COPD suggested that statins are associated with a lower rate of FEV<sub>1</sub> decline (174), decreased airflow limitation (175), fewer rehospitalizations due to COPD (176), reduced cardiovascular morbidity and mortality (177, 178), decreased all-cause mortality (177, 178), and improved exercise tolerance and dyspnea among patients with coexisting hypertension (179). However, the National Institutes of Health and Canadian Institute of Health Research subsequently reported the results of a randomized trial that compared regular use of simvastatin with placebo, the STATCOPE study. The study found that simvastatin did not improve the frequency of acute exacerbations of COPD or other outcomes (lung function, health status, hospitalizations) in patients who do not have other indications for statin therapy. Subgroup analyses similarly found no differences (180).

We recommend:

- Continued scientific exploration of new antiinflammatory pathways and agents that mitigate the inflammatory response to inhalational injury.
- Controlled clinical trials that compare the effects of various long-term antibiotic regimens with one another.
- Controlled clinical trials of long-term antibiotic therapy that

compare outcomes among subtypes of patients with COPD, various dosages, and varying durations of therapy. Outcomes should include the emergence of bacterial resistance, in addition to the usual benefits and side effects.

- Controlled clinical trials that compare the effects of novel antiinflammatory agents with placebo on outcomes. If a beneficial effect is confirmed, then additional trials are warranted to compare outcomes among subtypes of patients with COPD, dosages, and durations of therapy.

### Managing Comorbidities

Management of the rising prevalence of multiple chronic comorbidities (i.e., patients with two or more chronic morbidities) is a major challenge facing healthcare systems worldwide (181). In many patients, COPD should be considered to be just one component of multiple chronic comorbidities. Generally speaking, patients with COPD and multiple chronic comorbidities are treated according to existing standards for each individual disease. In other words, comorbidities in patients with COPD are treated the same as in patients without COPD, and COPD is treated the same regardless of the comorbidity. Indeed, observational studies suggest that mortality of patients with COPD can be reduced by nonrespiratory treatments, including  $\beta$ -blockers, angiotensin-converting enzyme inhibitors (182), and statins (183).

We recommend:

- Studies that evaluate the effects of treating COPD on the outcomes of comorbid diseases as well as studies that evaluate the effect of treating comorbid diseases on COPD-related outcomes.

### Nonpharmacological Therapies

**Pulmonary rehabilitation.** Pulmonary rehabilitation is typically provided in a hospital-based, outpatient setting. Its benefits in this setting are well established, including reduced dyspnea, increased exercise capacity, improved quality of life, and reduced use of healthcare resources (184). Effects on physical activity are less studied and less consistent but are generally considered clinically significant. More recent research has focused on the

effectiveness of pulmonary rehabilitation in alternative settings.

Home-based pulmonary rehabilitation might improve patient-centered outcomes including health-related quality of life and exercise capacity, to an extent comparable to hospital-based programs (185). A randomized trial supports the effectiveness of home-based pulmonary rehabilitation. The trial compared cycle ergometer exercise training in the home with the same training in a pulmonary rehabilitation center (186). All patients had participated in a 4-week educational program before randomization to an exercise-training site. Dyspnea and exercise tolerance improved to an equivalent degree in both groups, and there were no significant safety issues in either group. However, critics have argued that the magnitude of benefit in the hospital-based pulmonary rehabilitation group was smaller than usual, potentially biasing the results toward no difference. This highlights the need for confirmatory studies before concluding that home-based pulmonary rehabilitation programs provide outcomes similar to hospital-based programs.

Community-based pulmonary rehabilitation has been compared with no pulmonary rehabilitation in a 2-year randomized trial, which found that community-based pulmonary rehabilitation improved dyspnea, exercise endurance, strength, and nutritional indices (187, 188). The total cost of the intervention was higher than usual care at 4 months, but this was offset at 24 months due to reduced hospital admission costs.

Pulmonary rehabilitation programs are also effective in patients after (severe) exacerbations. A systematic review identified clear benefits in terms of symptoms, health-related quality of life, and exercise tolerance as well as possible benefits in hospital readmission rates and survival (189).

Pulmonary rehabilitation and pharmacotherapy appear to be complementary approaches to COPD care with synergistic effects (190). Additional details about the evidence for pulmonary rehabilitation in patients with COPD are provided in an ATS/ERS Statement on Pulmonary Rehabilitation (184).

We recommend:

- Studies that compare the effects of home-based pulmonary

rehabilitation with hospital-based pulmonary rehabilitation.

- Studies that compare hospital-based, home-based, and community-based pulmonary rehabilitation in different subtypes of patients with COPD, to determine which settings are most appropriate for the various types of patients.
- Long-term studies that compare the effects of hospital-based, home-based, and community-based pulmonary rehabilitation on the maintenance of benefits. Of particular importance is evaluation of the effects of such programs on physical activity.
- Studies that compare the effects of various modalities, supervision protocols, and program durations on outcomes.
- Controlled trials of early intensive rehabilitation in patients recovering from exacerbations to evaluate its potential effect on readmission rates and other outcomes.
- Studies that evaluate strategies to maintain the benefits of pulmonary rehabilitation.

**Long-term oxygen therapy.** Long-term oxygen therapy (LTOT) reverses hypoxemia. A trial that compared LTOT with no oxygen therapy in patients with COPD with severe hypoxemia ( $\text{PaO}_2 \leq 55$  mm Hg) found that LTOT improved survival (191), whereas another trial that compared oxygen administered 19 h/d with oxygen administered 12 h/d found that the longer duration improved survival (192). In contrast, a trial that compared LTOT with no oxygen therapy in patients with COPD with moderate hypoxemia ( $\text{PaO}_2 < 69$  mm Hg) found no effect on survival, regardless of the duration used per day (193). The evidence has important limitations: the trials included relatively few patients and events (only 370 patients and 164 deaths, collectively), there was a paucity of women enrolled in the trials, and two of the three trials were conducted more than 30 years ago. A trial that compared nocturnal oxygen therapy (as opposed to continuous oxygen therapy) with no nocturnal oxygen therapy in patients with COPD with hypoxemia found no effect on survival (194).

These data suggest that LTOT has a mortality benefit that may be related to the severity of hypoxemia (i.e., the mortality benefit was seen only among patients with severe hypoxemia). Thus, LTOT is routinely

prescribed for patients with severe hypoxemia. The National Institutes of Health has funded a multicenter trial comparing supplemental oxygen with no supplemental oxygen among patients with mild to moderate hypoxemia, the Long-term Oxygen Treatment Trial (LOTT). Among patients in the supplemental oxygen group, those with hypoxemia at rest will be instructed to use the supplemental oxygen continuously, whereas those with hypoxemia during exertion will be instructed to use the supplemental oxygen with exertion and during sleep only.

LTOT incurs cost but has few adverse clinical effects (195). The major hazard is fires or explosions (196, 197). These consequences of LTOT are the reasons that prescribing LTOT for current smokers is controversial.

We recommend:

- Studies that measure the effects of LTOT on outcomes in various COPD subtypes. Examples of subtypes that warrant evaluation include patients with mild and moderate hypoxemia, desaturation with exertion, desaturation during sleep, comorbid heart disease, frequent exacerbations, decreased exercise capacity, or pulmonary hypertension.
- Studies that evaluate the effect of LTOT on physical activity and the relationship of this effect on other outcomes, such as quality of life, frequency of exacerbations, and mortality.
- Studies that compare the effects of various modalities of LTOT (e.g., continuous, exercise, sleep, combined, with or without flow titration) on outcomes in different patient subtypes.

#### **Noninvasive mechanical ventilation.**

Noninvasive mechanical ventilation (NIV) improves respiratory acidosis and decreases respiratory rate, severity of breathlessness, intubation rate, length of hospital stay, and mortality in patients with COPD who are experiencing acute on chronic respiratory failure (198–202). Despite the success of NIV for acute respiratory failure, the effects of long-term NIV in patients with COPD who have chronic respiratory failure remain controversial (203, 204). Some studies have shown benefits in health status, dyspnea, or blood gases, but there has been little or no impact on other outcomes such

as rehospitalization rates or mortality (205–207). An exception is a recent study that found that NIV may improve survival in patients with COPD with chronic respiratory failure (208). Uncertainty about the effects of NIV in patients with COPD with chronic respiratory failure has led to the use of NIV on an individual basis; more studies are necessary to confirm the effects of NIV and identify patients who are likely to benefit from NIV.

We recommend:

- Studies that assess the effects of long-term NIV in patients with COPD who have chronic respiratory failure.
- Studies that identify characteristics of patients who are most likely to benefit from long-term NIV.

**Lung volume reduction therapies.** Lung volume reduction approaches may be a useful complement to standard medical therapy for a select number of patients with advanced COPD. Patients who harbor giant bullae (i.e., isolated gas-filled cavities occupying one-third of the ipsilateral hemithorax) surrounded by relatively normal parenchyma can obtain significant improvements in lung mechanics, symptoms, functional performance, and health status from bullectomy (209).

The value of lung volume reduction surgery (LVRS) for other COPD phenotypes is controversial. The National Emphysema Treatment Trial suggested that patients with severe COPD (defined as an  $FEV_1 < 45\%$  predicted) with a predominance of emphysema in the upper lobes and with reduced exercise capacity (defined as maximal exercise capacity  $< 25$  W for women and  $40$  W for men on a standard incremental cycle ergometer test) may experience significant improvements in symptoms, health status, lung mechanics, exacerbation rates, and even survival with LVRS (210). However, the therapy is costly, with a cost-effectiveness ratio of \$98,000 per 1 quality-adjusted life year saved over 3 years (211). Moreover, 90% of patients who undergo LVRS experience significant air leaks after thoracotomy that result in a prolonged hospital stay and morbidity. For these reasons, several bronchoscopic methods are under investigation to selectively reduce lung volumes. However, none have received regulatory approval for use in COPD owing to limited efficacy

and concerns about increased risk of pneumonia and exacerbations (212).

We recommend:

- Studies to evaluate whether or not minimally invasive surgical techniques can reduce complication rates and improve perioperative outcomes and costs compared with conventional surgical techniques.
- Studies to evaluate whether or not the benefits of LVRS observed in trials during the late 1990s and early 2000s are still applicable in the current era in light of advances in medical management for COPD.
- Studies to evaluate bronchoscopic lung volume reduction techniques that are intended to increase benefits and reduce complications, especially those related to pneumonia.

**Lung transplantation.** COPD is the most common indication for lung transplantation, accounting for 35% of lung transplants (213). Among patients with severe COPD, lung transplantation improves survival (214, 215) and health-related quality of life (216).

Each patient requires an individualized assessment of his or her suitability. However, prognostic indices used to demonstrate the need for transplantation include (1) an  $FEV_1$  less than 20% predicted plus either a  $DL_{CO}$  less than 20% or homogenous emphysema on imaging (these criteria are associated with increased mortality after LVRS as compared with medical treatment), (2) evidence of secondary pulmonary hypertension (or cor pulmonale) despite adequate oxygenation, and (3) a history of hospitalization with acute hypercapnic respiratory failure with  $Pa_{CO_2}$  greater than 50 mm Hg (180). In addition, candidates need to be free of single major contraindications or multiple minor contraindications. A body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) score of 7 or more was proposed as another indicator for lung transplantation (215, 217); however, its applicability for this purpose is unclear.

Bilateral lung transplantation may be a better option than single lung transplantation, as it is associated with better long-term outcomes, at least among patients younger than 60 years (218). However, the advantages of bilateral lung transplantation over single lung transplantation are less clear if the risk of death while still on the waiting list is considered (219, 220).

We recommend:

- Studies to evaluate whether using a poor survival predicted by the BODE index as an indication for listing patients with COPD for lung transplantation is associated with better outcomes than using alternative indications for lung transplantation.
- Studies that compare outcomes after lung transplantation with those achieved by medical management alone.
- Studies to determine whether the anticipated improvements in symptoms and quality of life after lung transplantation are sufficient to justify the donor resource or whether improvement in mortality is also necessary.
- Studies that compare outcomes after bilateral and unilateral lung transplantation and assess which subtypes of patients benefit more from one rather than the other.

**Nutrition.** Low body weight in COPD may be a marker of systemic disease. If weight loss is observed, it may be a consequence of reduced oral intake, increased energy expenditure and metabolic alterations due to low-grade systemic inflammation, and increased protein consumption (221). Low body weight is associated with increased mortality and reduced health status, quality of life, and exercise capacity. However, the magnitude of weight loss does not correlate with the severity of airflow limitation (39, 222–224).

Several measurements have been considered as potential prognostic indicators. A BMI less than 21 kg/m<sup>2</sup> is associated with significantly worse clinical outcomes (39). Muscle or fat-free mass measurements may be even better predictors of clinical outcomes (223, 224). Acute involuntary weight loss is also important.

Nutritional intervention in COPD generally begins with dietary supplements once alternative causes of weight loss are excluded. Systematic reviews provide conflicting information. One systematic review found that dietary supplementation improved body weight and grip strength (225), whereas another systemic review found nonsignificant trends toward a beneficial effect of nutritional supplementation on anthropometric measures, lung function, and exercise capacity (226). Alternative metabolic treatments, including androgens and human

growth hormone, have also been tried, but their long-term effects remain unknown (227). Micronutrients may also play a role in COPD. Low vitamin D levels have been associated with both reduced lung function and emphysema (228). Few studies of vitamin D replacement have been conducted, and they have not shown benefits (229).

Obesity and its multiple chronic comorbidities are common and also need to be addressed in patients with COPD (228). We recommend:

- Studies to determine why some patients with COPD develop weight loss and malnutrition and other patients do not.
- Studies that evaluate the outcomes of nutritional therapies (e.g. dietary supplements, androgens, and human growth hormone) in patients with COPD with weight loss.

### **Integrative Management**

Integrated care programs or disease management programs are systematic approaches to reduce the fragmentation of patient care. Integrated care programs in COPD include patient self-education, coordinated care, self-management (230), home care (231), and interventions that address the rehabilitative and psychological aspects of the disease (232), with or without support via information technologies (233).

Early initiation of treatment for acute exacerbations has been the primary goal of most COPD integrative disease programs. Evidence regarding the effectiveness of integrative care programs is conflicting. A randomized trial found that an intensive self-management comprehensive educational program in patients previously hospitalized for exacerbations decreased hospital readmissions during the following year (230). Another randomized trial similarly reported that a single 1.5-hour education session, an action plan for self-treatment of exacerbations, and monthly nurse case management phone follow-ups reduced COPD-related hospitalizations or emergency room visits by 34% (234). However, a similar trial that compared comprehensive case management program with standardized COPD care was prematurely discontinued due to excessive mortality in the comprehensive case management group (235). Several other studies in COPD have failed to show significant improvement in outcomes with

predominantly nurse-led home management programs (236). Reasons for the disparate results are unclear, but it appears that close contact with patients who have a high disease burden is crucial for maximizing success. Variations in the program components, the duration of the intervention, and the outcomes measured have led to uncertainty about how to develop a successful integrative care model for COPD (237).

Evidence regarding telemedicine-based disease management in COPD is conflicting and limited by the small patient numbers, use of variable intensities of telemonitoring, and lack of prespecified treatment plans (238). In a randomized trial of patients with chronic respiratory failure (42% had COPD), those randomized to receive tele-assistance had fewer hospitalizations, less urgent calls, and decreased acute exacerbations. In the COPD subgroup, there were decreased home visits and hospitalizations among those who were managed via the tele-home care model, with a substantial cost savings at 6 months (239). In contrast, another study found that home-based COPD telemonitoring programs conferred no benefit in decreasing hospital or homecare costs (240, 241).

Self-management is receiving increasing attention in chronic diseases. Self-management studies should be designed with realistic outcome goals and ensure that the outcome goals, characteristics of optimal patient candidates, and essential elements of educational tools and processes are well defined. Studies should also demonstrate that self-management programs can be safely and broadly applied to patients with COPD.

We recommend:

- Studies that compare different combinations of components of integrative care programs, to identify which combinations optimize outcomes.
- Studies that measure the outcomes of integrative care in subtypes of patients with COPD.
- Studies that compare the outcomes of different durations of integrative care.
- Studies that assess the cost-effectiveness of integrative care in COPD.
- Studies that evaluate the effects of the educational/self-management components of pulmonary rehabilitation on patient-centered outcomes.

## End-of-Life Care

Studies have reported that most patients with COPD desire a discussion regarding end-of-life care with their physician, but these discussions occur only 30% of the time (242). When end-of-life discussions occur in patients with COPD, most occur during an acute exacerbation rather than a more stable state of their disease, and the skill of the providers leading the discussion is commonly inadequate (243–245). Similarly, palliative care is often not addressed or inadequately addressed with patients with COPD, permitting symptoms whose mitigation or elimination would provide patients with COPD comfort, such as dyspnea, cough, pain, and fatigue, and less commonly poor sleep quality, depression, and anxiety (246, 247). Up to 30% of patients with advanced COPD with multiple symptoms are not on optimized therapy (248).

Barriers that limit advanced care (i.e., both end-of-life and palliative) planning between patients with COPD and providers have been identified (249). Most notably, providers frequently believe that advanced care planning is difficult to do in COPD. Many factors contribute to this perception: inadequate information about the likely course of COPD, lack of agreement as to whether the primary care provider or the respiratory specialist is responsible for initiating advanced care planning, uncertainty about what defines end-of-life care in COPD (i.e., use of oxygen, being housebound, or frequent severe exacerbations), and uncertainty about whether end-of-life and palliative care are compatible with the goals of chronic disease management (249). Similar issues prevent patients with COPD and physicians from advanced care planning in the United States and Netherlands, despite the cultural and healthcare delivery system differences between the two countries (250).

We recommend:

- Studies that demonstrate the impact of palliative care and end-of-life discussions on outcomes in patients with stable COPD.
- Studies of educational approaches and tools to help clinicians better discuss palliative care and end-of-life care with patients with COPD.
- Studies to confirm the importance of optimized therapy in minimizing symptoms at the end of life.
- Studies that identify symptoms that occur despite optimized COPD care

and require palliation. Such studies should be followed by trials that compare the effects of various treatment options on those symptoms.

## Preoperative Evaluation

COPD is a risk factor for both intraoperative and postoperative pulmonary complications after lung resection. A cardiac evaluation is frequently performed as part of the preoperative assessment of patients with COPD because many of the risk factors for COPD are also risk factors for cardiac disease. Generally speaking, patients with acceptable exercise tolerance receive only an ECG, whereas patients with limited exercise capacity may undergo noninvasive cardiac testing to identify those with unsuspected cardiac disease who require additional evaluation (251–253). There is no evidence that prophylactic cardiac revascularization reduces postoperative risk in patients with COPD (254).

The FEV<sub>1</sub> and DL<sub>CO</sub> are routinely measured preoperatively to predict postoperative pulmonary function, morbidity, and mortality. Most patients whose FEV<sub>1</sub> and DL<sub>CO</sub> are both greater than 80% predicted do not undergo further preoperative testing (255, 256), whereas those whose FEV<sub>1</sub> or DL<sub>CO</sub> are less than 80% predicted undergo further assessment of their predicted postoperative pulmonary function (257, 258). Quantitative ventilation or perfusion lung scanning predicts postoperative pulmonary function by objectively measuring the contribution of individual lung lobes (256). The combination of ventilation and perfusion scanning offers no additive predictive benefit compared with either technique alone (259). The maximum symptom limited exercise testing, 6-minute-walk test, incremental shuttle walk test, and stair climb are alternative methods to predict postoperative pulmonary complications.

Perioperative risk increases when the predicted postoperative DL<sub>CO</sub> is less than 40% (260–262) or the predicted postoperative FEV<sub>1</sub> is less than 40% predicted. The latter has been associated with mortality rates ranging from 16 to 50% (263–266). Mortality rates as high as 60% have been reported when the predicted postoperative FEV<sub>1</sub> is less than 30% (267, 268). However, because many patients qualified as at high risk after calculation of

predicted postoperative lung function can undergo surgery safely, decisions are made on an individual basis (269).

Although the predicted postoperative FEV<sub>1</sub> is the best parameter in predicting postoperative complications after resection, its limitations are that it is unreliable in predicting outcomes among patients whose preoperative FEV<sub>1</sub> is greater than 70%, and it is most accurate in predicting lung function 3 to 6 months after a lobectomy (270). The post-lobectomy FEV<sub>1</sub> may be more than 30% lower than the predicted value during the first days to weeks postoperatively.

We recommend:

- Studies in patients with COPD undergoing lung resection that compare outcomes among patients who had their postoperative lung function predicted quantitatively with those among patients who had their postoperative lung function predicted qualitatively. Such studies should perform the comparison using different combinations of preoperative FEV<sub>1</sub> and DL<sub>CO</sub> in the quantitative arm(s).
- Studies in patients with COPD undergoing lung resection comparing outcomes among patients whose risk for perioperative complications was determined via predicted postoperative lung function measurements with those among patients whose risk was determined via exercise testing.

## Air Travel Risk Assessment

Commercial aircraft are pressurized to cabin altitudes of 8,000 ft (2,438 m), at which the partial pressure of inspired oxygen falls to the equivalent of 15.1% oxygen at sea level. In healthy individuals, oxygen saturation measured by pulse oximetry decreases to 89 to 94% during rest and to even lower levels during exercise or sleep. Patients with pulmonary disease have lower oxygen saturation at baseline; thus, the decrease that occurs at a high altitude may result in hypoxemia that can be severe. As an example, a stable patient with COPD with an oxygen saturation of 93% during rest at sea level may experience oxygen desaturation to 82% at rest during a commercial air flight and may experience symptoms of hypoxemia. Even lower levels of oxygen saturation may be encountered

during periods of in-flight mild exercise or sleep (271).

Patients with COPD who use oxygen at sea level are always prescribed supplemental oxygen during commercial air travel (272, 273). For patients who do not use oxygen at sea level, further assessment is generally performed if the resting preflight oxygen saturation is less than 92%. This may include a 50-m-walk test or a high-altitude simulation using either a hypobaric chamber or a high-altitude stimulation test (272, 274–277). High-altitude stimulation test involves breathing gases with lower than normal oxygen concentration. If oxygen desaturation occurs with any of these tests, then supplemental oxygen is generally prescribed. Although these tests identify patients in whom supplemental oxygen is necessary to mitigate in-flight hypoxemia, they cannot exclude the possibility of in-flight hypoxemia among patients who have a resting preflight oxygen saturation greater than 92% (277) or who do not desaturate during testing (273).

The in-flight flow rate is typically 2 L/min higher than the rate used at sea level. Commercial airlines routinely accept in-flight oxygen prescriptions of 2 L/min or 4 L/min. Higher levels of oxygen prescription are not available, and patients who need higher levels of inspired oxygen are discouraged from air travel.

We recommend:

- Studies to determine the impact of flight duration and comorbidities on in-flight respiratory complications in patients with COPD.
- Studies that directly compare different preflight strategies for determining which patients with COPD are at risk for in-flight respiratory complications.
- Studies that directly compare different preflight strategies for determining which patients with COPD will benefit from in-flight supplemental oxygen.
- Studies that determine the minimum level of oxygenation necessary to protect patients with

COPD from in-flight respiratory complications.

- Studies that determine whether in-flight respiratory complications are generally due to altitude-related hypoxia alone or also other factors (e.g., recycled cold dry air, immobility, etc.).

## Conclusions

COPD is a leading cause of morbidity, mortality, and resource use worldwide. Great strides have been made in the identification, pathogenesis, assessment, and treatment of COPD. Despite this, many important questions remain unanswered. This ATS/ERS Research Statement highlights the types of research that leading clinicians and researchers believe will have the greatest impact on outcomes, including studies that determine the impact of COPD-related clinical practice guidelines on outcomes in patients with COPD. ■

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