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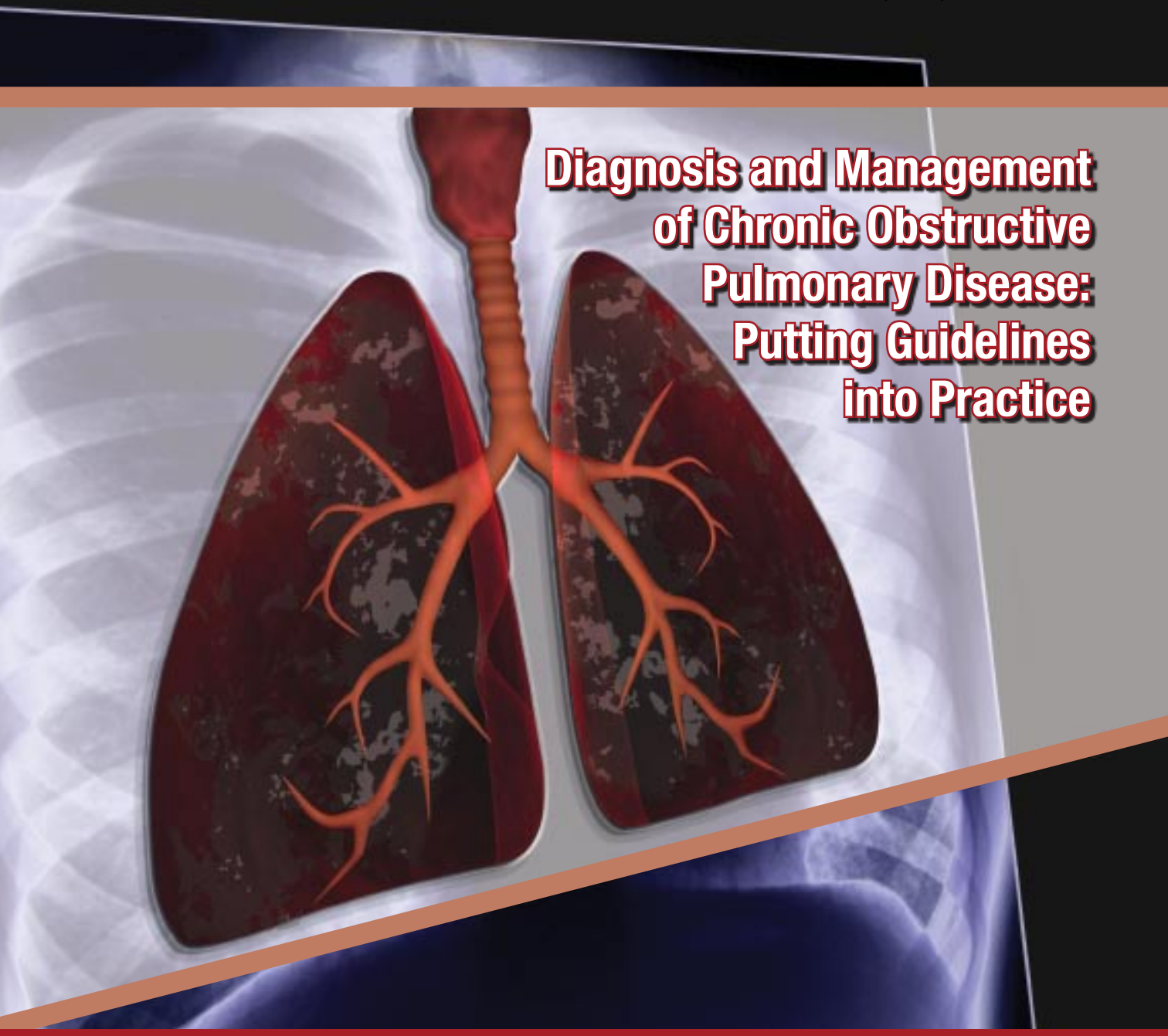

## Diagnosis and Management of Chronic Obstructive Pulmonary Disease: Putting Guidelines into Practice

Supported by an educational grant from Boehringer Ingelheim Pharmaceuticals, Inc. and Pfizer Inc.

# OPENING STATEMENT

APRIL 2008 • VOLUME 25 • SUPPLEMENT 1

This supplement to *Federal Practitioner* on chronic obstructive pulmonary disease (COPD), sponsored by a grant from Boehringer Ingelheim Pharmaceuticals, Inc. and Pfizer Inc, was developed with the aim of helping primary care providers in federal practice (chiefly, within the health care systems of the VA and DoD) make sense of and apply evidence-based recommendations for diagnosing and managing COPD. It is our hope that, after reading this supplement, you will be able to:

- Identify patients at risk for COPD and recognize the disease in its early stages.
- Confirm a suspected COPD diagnosis and assess disease severity using spirometry and other appropriate measures.
- Effectively apply the "step-up" approach to risk modification and pharmacologic treatment of stable COPD.
- Discuss the multisystem approach to COPD management, including the proper use of oxygen supplementation, pulmonary rehabilitation, lung volume reduction, and lung transplantation.
- Describe measures used to reduce the frequency and severity of acute COPD exacerbations.
- Identify conditions that are associated or commonly coexist with COPD and discuss key points of their management in the setting of COPD.

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# Diagnosis and Management of Chronic Obstructive Pulmonary Disease: Putting Guidelines into Practice

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# The State of COPD

Michael R. Littner, MD

With many organizations updating their COPD guidelines in recent years, it is imperative for federal clinicians to stay abreast of the current recommendations for practice.

Chronic obstructive pulmonary disease (COPD) results in obstruction to a person's airflow. It is a preventable and treatable condition, with partial, though not full, reversibility of the airflow obstruction possible.[1–3] The disease is a common cause of morbidity and mortality worldwide. In the United States, COPD currently is the fourth leading cause of mortality.[1]

Whereas mortality from heart disease has fallen sharply in recent years, age-adjusted mortality from COPD rose almost 100% between 1970 and 2002.[1] In addition, COPD mortality is increasing among women—who died in equal numbers to men in 2000.[1] And the COPD mortality rate is projected to continue to increase in the foreseeable future.[2]

COPD is of particular concern in the VA health care system because rates of cigarette smoking, the major cause of COPD, are higher in veterans than in the general population. After adjusting for age and sex, the smoking prevalence is 33% among VA patients, compared with 23% in the general population.[4] In addition, according to a recent study conducted among VA patients, the independent risk factors for death and rehospitalization in patients discharged after a severe COPD exacerbation include age, male gender, prior hospitalizations, and certain comorbid conditions—factors that characterize the majority of veteran patients.[5] The risk of death in such COPD patients was 21% at one year and 55% at five years.[5]

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## DIFFICULTIES WITH DIAGNOSIS

The diagnosis of COPD is sometimes difficult to establish because other obstructive lung diseases, such as asthma, share the disease's hallmark airflow obstruction. COPD and asthma have differing etiologies and pathophysiologies, however, which means the common conditions may coexist in one individual. Furthermore, while COPD and asthma share many treatment options, the approach to treating the two conditions differs, with the emphasis on bronchodilators in COPD treatment and anti-inflammatory agents in asthma.[1,3,6–9]

COPD often is not recognized until the patient's airway and lungs have been damaged substantially, most likely due to the slow progression of the disease. It tends to "sneak up" on patients until airway obstruction reaches a critical point and COPD-related symptoms are evident.

In differentiating between COPD and asthma, diagnostic confusion may result from relying too heavily on how much pulmonary function improves—indicated by improved forced expiratory volume in one second ($FEV_1$)—after a bronchodilator is used a single time in the laboratory. Yet guidelines of the Global Initiative for Obstructive Lung Disease (GOLD) state clearly that the degree of reversibility of airflow limitation should not be the basis for diagnosing COPD, differentiating COPD from asthma, or predicting the response to long-term treatment with bronchodilators or glucocorticosteroids.[1] Rather, the diagnoses of asthma and COPD are both based predominantly on clinical history. For a COPD diagnosis, pulmonary function testing provides the required confirmation of obstruction.

## RECENT MANAGEMENT GUIDELINES

Including the most current GOLD guidelines, five major guidelines on the management of COPD have been issued or updated recently by prominent professional organizations (Table).[1,3,6–8] Of these five guidelines, all but the American College of Physicians (ACP) guidelines grade and use information and evidence from a variety of sources, including randomized, controlled trials; cohort studies; case control studies; recommendations from public policy organizations, such as the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention; and, when necessary, consensus. For the most part, these four guidelines are similar except that the GOLD guidelines emphasize pulmonary function staging and the other three guidelines emphasize clinical staging with such symptoms as dyspnea.

The ACP guidelines differ from the other four guidelines in being based almost solely on randomized, controlled trials of intervention studies of pharmaceutical agents and procedures, such as pulmonary rehabilitation. In addition, whereas the other

**Table. Guidelines for the management of chronic obstructive pulmonary disease (COPD)[1,3,6–8]**

| Organization | Guideline name | Date published or updated |
|---|---|---|
| Global Initiative for Obstructive Lung Disease (GOLD)[1] | Global Strategy for the Diagnosis, Management and Prevention of COPD | 2007 |
| American Thoracic Society and European Respiratory Society (ATS/ERS)[3] | Standards for the Diagnosis and Management of Patients with COPD | 2005 |
| VA/DoD Clinical Practice Guideline Working Group[6] | Management of Chronic Obstructive Pulmonary Disease | 2007 |
| National Institute for Clinical Excellence (NICE)[7] | Clinical Guideline 12: Chronic Obstructive Pulmonary Disease | 2004 |
| American College of Physicians (ACP)[8] | Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease | 2007 |

four guidelines emphasize immediate and short-term symptomatic benefit to individual patients, such as a reduction in dyspnea, the ACP guidelines focus on long-term benefit to groups of patients with COPD, such as improvement in health status and reduction in the number of exacerbations. The ACP guidelines recommend reserving long-acting bronchodilators and inhaled corticosteroids for patients with an $FEV_1$ of less than 60% predicted to improve health status and reduce the number of exacerbations.[8]

## SUPPLEMENT OVERVIEW

In the articles that follow, COPD experts guide the reader through a concise but comprehensive review of COPD diagnosis and management, including how to recognize the condition in its early stages and identify patients at risk, manage stable disease with pharmacotherapy and with adjunctive and surgical therapies, manage common comorbid conditions, and prevent and treat acute exacerbations. While this supplement references current practice guidelines, it also emphasizes that veterans represent a unique group of patients who, while similar to the general population in some ways, differ from it in being predominantly male and elderly and, generally, having more comorbidities. This review provides clinicians who serve this population with valuable information on the diagnosis and management of COPD.

### *Author disclosures*

*Dr. Littner reports being a member of the speakers bureaus for GlaxoSmithKline; Boehringer Ingelheim Pharmaceuticals, Inc; and Dey, LP and a member of the Pulmonary Advisory Board for Dey, LP.*

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# Early Recognition and Diagnosis

Amir Sharafkhaneh, MD, PhD, Charlie Lan, DO, Sheila Goodnight-White, MD, and Nicola Hanania, MD

Individuals with COPD often do not seek medical help until they experience significant quality of life impairment. By identifying patients with mild COPD, clinicians can intervene to improve the course of this usually progressive disease.

Chronic obstructive pulmonary disease (COPD) is associated with substantial morbidity and mortality worldwide.[1,2] It is responsible for about three million deaths annually or 5% of all global deaths, making it the fifth leading cause of death worldwide. In the United States alone, an estimated 11.7 million adults have been diagnosed with COPD, and nearly 125,000 patients die of the disease each year.[3,4] Yet COPD is largely a preventable disease and responds well to treatment. Without intervention, however, COPD is usually progressive.

Clinicians therefore need to recognize individuals who are at risk for developing COPD or who have mild disease so management can be initiated before these patients experience substantial declines in lung function. This is not an easy task, however, because symptoms of early COPD are nonspecific, and patients often ignore them for many years before seeking medical advice. As a result, practitioners must be aware of risk factors for COPD, be alert to possible signs and symptoms of disease in high risk individuals, and know how to confirm their clinical suspicions.

## WHEN TO SUSPECT COPD

COPD represents an inflammatory response of the lungs to noxious gases and particles. Early in the course of disease, both symptoms and physical findings tend to be nonspecific.

### Symptoms and medical history

Patients typically ignore early respiratory symptoms of COPD, such as cough, sputum production, and dyspnea, and seek medical attention only when the disease has progressed and dyspnea interferes with daily activities.[5] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) therefore recommends that clinicians consider a diagnosis of COPD in any patient with such symptoms and a history of exposure to tobacco smoke or occupational dusts and chemicals, the chief etiologic agents of COPD. GOLD, a joint initiative of the U.S. National Heart, Lung, and Blood Institute and the World Health Organization (WHO), was designed to increase awareness of COPD, improve prevention and management of the disease by developing diagnostic criteria and management guidelines, and reduce COPD-associated morbidity and mortality.

According to a survey of 573 individuals with COPD, 58% of respondents had daily shortness of breath; 53% coughed every day; and 49% had nighttime awakenings several times a week caused by coughing, wheezing, or shortness of breath.[6] Many respondents reported breathlessness during daily activities: 72% when walking up one flight of stairs, 46% during light housework, 44% while washing or dressing, and 32% when talking. Overall, 34% of respondents reported that COPD prevented them from holding a job, and those who did work missed an average of 18.7 days a year for COPD-related reasons.[7]

In addition to eliciting a patient's history of classic COPD symptoms, smoking history, and possible exposures to environmental pollutants, the VA/DoD COPD clinical practice guidelines identify the following other important elements of the initial evaluation: (1) prior medical history of asthma, allergies, or recurrent respiratory illness; (2) family history of COPD; (3) history of prior COPD exacerbations or hospitalizations; and (4) presence of comorbid conditions, especially coronary artery disease, congestive heart failure, and anxiety.[8]

### Physical findings in COPD

Findings of physical examination in a patient with early COPD may be nonspecific. As COPD progresses, the patient may exhibit tachypnea, tachycardia, or central cyanosis. Pursed-lip breathing and use of accessory respiration muscles are other signs of COPD. Examination of the chest may reveal hyperinflation, decreased diaphragmatic excursion, hyperresonance, and distant breath sounds or wheezing. Destruction of alveoli can result in evidence of pulmonary hypertension, such as jugular venous distention, peripheral edema, and a split-second heart sound. Pulse oximetry, which should be included in the vital sign component of a COPD evaluation, may demonstrate arterial oxygen desaturation.

## CONFIRMING THE DIAGNOSIS

Spirometry, which measures both forced expiratory volume in one sec-

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ond ($FEV_1$) and forced vital capacity (FVC), is used to confirm the COPD diagnosis. Postbronchodilator $FEV_1$/FVC of less than 0.7 (70%) demonstrates the presence of some irreversible airflow limitation and a diagnosis of COPD—provided the patient's clinical history, symptoms, and risk factors point to a high probability of this diagnosis. In asthma, which sometimes is confused with COPD, airflow limitation often is completely reversible.

## Spirometric classification

Both the American Thoracic Society and GOLD have developed a simple classification of COPD based on $FEV_1$ (Table).[5,9] Although $FEV_1$ does not fully explain the complex clinical pathophysiology of COPD, it is a simple, reproducible spirometric measurement that provides a reasonable marker for predicting COPD morbidity and mortality.[10,11] The classification system helps clinicians communicate to patients the severity of their COPD, which fosters understanding of the disease and reinforces the importance of smoking cessation and adherence to the overall management plan.

## Other severity measures

Assessment of disease severity is important for determining disease prognosis, formulating a treatment regimen, and evaluating response to treatment. For example, in a patient with severe COPD, reduction of exacerbation frequency can be used as an endpoint for treatment response—even though the patient may not perceive improvement in dyspnea with the intervention. In addition to spirometric classification, COPD severity is established by the patient's level of symptoms, the degree to which symptoms affect his or her daily life, and the presence of complications (such as respiratory failure, right heart failure, weight loss, and arterial hypoxemia).

**Table. Spirometric classification of severity of chronic obstructive pulmonary disease[9]**

| Stage | Spirometry findings |
|---|---|
| I: Mild | $FEV_1$[a]/FVC[b] < 70%; $FEV_1 \geq 80\%$ predicted |
| II: Moderate | $FEV_1$/FVC < 70%; $FEV_1 \geq 50\%$ and < 80% predicted |
| III: Severe | $FEV_1$/FVC < 70%; $FEV_1 \geq 30\%$ and < 50% predicted |
| IV: Very severe | $FEV_1$/FVC < 70%; $FEV_1$ < 30% predicted or < 50% predicted plus chronic respiratory failure |

[a]$FEV_1$ = forced expiratory volume in one second. [b]FVC = forced vital capacity.

The patient's health status can be assessed using disease-specific clinical measures, such as the Saint Georges' Respiratory Questionnaire and the Chronic Respiratory Questionnaire. Degree of breathlessness can be evaluated with the modified Medical Research Council scale. Exercise tolerance can be assessed through the six-minute walk test or incremental exercise testing in a laboratory.

A group of investigators developed a relatively simple approach to determining disease severity that uses a multidimensional grading system to assess respiratory and systemic expressions of COPD. This index—which gives a composite score for body mass index, airway obstruction, dyspnea, and exercise capacity (BODE)—was found to be better than $FEV_1$ measurement at predicting risk of death from any cause and from respiratory causes in patients with COPD.[12]

## TREATING STABLE COPD

GOLD treatment recommendations for patients with stable COPD are characterized by a stepwise increase in therapy, depending on disease severity.[5] For patients with stage I disease, short-acting bronchodilators used on an as-needed basis are recommended to control symptoms. For patients with stage II to IV disease, the guidelines recommend adding scheduled maintenance therapy with one or more long-acting bronchodilators when symptoms are not adequately controlled, along with as-needed short-acting bronchodilators for rescue treatment. Also consider adding pulmonary rehabilitation—exercise training, nutritional counseling, and patient education—in an effort to reduce symptoms, minimize activity limitations, and enhance quality of life. The guidelines recommend adding inhaled corticosteroids to maintenance bronchodilator therapy for patients with stage III and stage IV disease who have had frequent exacerbations. Finally, long-term oxygen therapy, designed to increase $PaO_2$ to 60 mm Hg or greater or arterial oxygen saturation to 90% or greater, should be added in patients with stage IV disease and evidence of hypoxemia on room air.[5,9] (These treatments are discussed in greater detail in the articles that follow.)

## A FINAL WORD

Failure to recognize COPD early in the disease course may lead to poor symptom control and activity limitations. Such failure also results in utilization of health care resources and, in turn, to the high social and economic burden associated with this disease. None of the available pharmacologic

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# Risk Modification and Pharmacologic Management of Stable Disease

Nicholas J. Gross, MD, PhD

Current pharmacologic measures, combined with risk reduction strategies, can slow disease progression, improve quality of life, and even reduce mortality in patients with COPD.

The goals of therapy for patients with stable chronic obstructive pulmonary disease (COPD) are, according to the most recent version of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, to: relieve symptoms, prevent disease progression, improve exercise tolerance, improve health status, prevent and treat complications, prevent and treat exacerbations, and reduce mortality. There is evidence that current pharmacologic therapies, in combination with certain lifestyle modifications and prophylactic measures, can be used to promote each of these ends.[1]

This article discusses strategies designed to help patients reduce the risk of COPD onset and progression. It reviews risk modification for patients at risk; describes the "step-up" approach to COPD therapy, which is advocated in the GOLD, VA/DoD, and American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines[1–3]; outlines the pharmacologic agents most commonly used to treat COPD; and highlights potential adverse effects and drug interactions for which clinicians should be on guard.

## RISK MODIFICATION

Nonpharmacologic measures to reduce the risk of COPD onset and progression include smoking cessation, prophylactic vaccinations against influenza and pneumococcal infection, pulmonary rehabilitation, attention to the comorbidities that are common in COPD, and appropriate lifestyle and dietary measures.

Cigarette smoking is responsible for about 75% to 80% of COPD.[4,5] For patients who still smoke, no therapy is as important as smoking cessation in helping to prevent COPD onset and in reducing COPD progression and associated mortality. The VA offers structured, multidisciplinary smoking cessation programs at most, if not all, of its hospitals and clinics. The VA urges its health care providers to make full use of these important services for their patients.[2]

Vaccination, particularly against influenza, is another simple, economical, and clinically effective prophylactic measure for patients with COPD.[1] Influenza vaccination should be given annually in the fall. Pneumococcal vaccination is recommended for patients with COPD who are aged 65 or older or who are younger than 65 years and have a forced expiratory volume in one second ($FEV_1$) of less than 40% predicted value.[1] Pneumococcal vaccination should be given twice in a lifetime, separated by an interval of six or more years.

Pulmonary rehabilitation also can have a major impact on quality of life, improving exercise tolerance and reducing hospitalization time for patients with COPD. In fact, preliminary evidence suggests that it may prolong survival in COPD.[1] The GOLD guidelines recommend pulmonary rehabilitation for patients with moderate COPD (defined as an $FEV_1$ between 80% and 50% of predicted value) or more severe disease.[1]

## STEP-UP THERAPY

Unlike asthma, COPD tends to progress over several years or decades, and its treatment is mainly symptom-directed. Initially, therefore, pharmacotherapy may consist of a single agent used on an as-needed basis. As symptoms progress, pharmacotherapy is intensified in a stepwise manner. The GOLD guidelines provide an illustration of this step-up approach that details recommended pharmacotherapy at each successive stage of COPD (Figure 1).[1]

Typically, over the course of several years, patients experience acute exacerbations, characterized by a rapid worsening of symptoms and often associated with a viral respiratory infection. Acute exacerbations, which may become more frequent and severe as the disease progresses, are serious and often require an escalation in therapy. Following such an exacerbation, the overall treatment plan should be reviewed and a step up in therapy, such as the addition of a second bronchodilator or the introduction of inhaled glucocorticoid therapy, may be prescribed.

## PHARMACOTHERAPY

The pharmacologic agents currently used to treat COPD include

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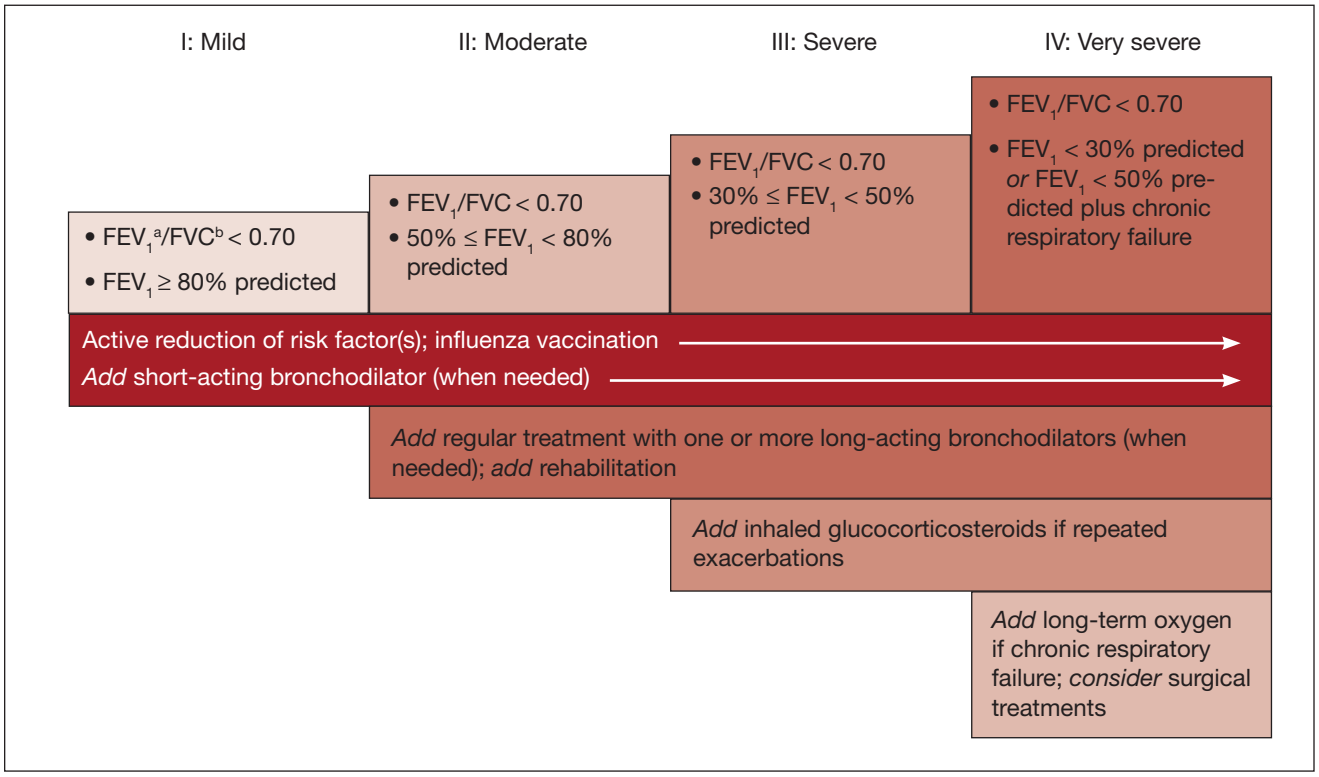


Figure 1. Therapy at each stage of chronic obstructive pulmonary disease, as recommended by the GOLD guidelines. Adapted with permission from: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Executive Committee. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=989. Updated December 2007. Accessed February 7, 2008.[1] [a]$FEV_1$ = forced expiratory volume in one second. [b]FVC = forced vital capacity.

short- and long-acting $beta_2$-selective agonists, short- and long-acting anticholinergics, and combinations of these agents (Table).[1] A variety of inhaled corticosteroids are available, but only one—fluticasone—is currently FDA-approved for use in COPD and, then, only in a fixed-dose combination product (fluticasone propionate 250 µg and salmeterol 50 µg inhalation powder). In the United States, no inhaled glucocorticoid monotherapy is approved for treating COPD. The methylxanthines theophylline (sustained release) and aminophylline also are used to treat COPD.[1]

Both the GOLD guidelines and the ATS/ERS position paper include recommendations about which agents to use at each stage of COPD. In addition, Tashkin and Cooper have provided an algorithm illustrating two alternative pathways for introducing bronchodilator therapy, leading from GOLD stage I to GOLD stages III and IV disease.[6]

For GOLD stage I (an $FEV_1$ of 80% predicted value or above), symptoms usually can be well controlled with as-needed use of a short-acting bronchodilator, such as the $beta_2$-adrenergic receptor agonist albuterol, the anticholinergic ipratropium, or a combination product, given by metered-dose inhaler (MDI). It should be noted that ipratropium, alone or in combination, is not FDA-approved for rescue therapy.[6]

In GOLD stage II (an $FEV_1$ between 50% and 80% of predicted value), maintenance treatment is more appropriate than as-needed bronchodilation because symptoms are likely to be present on most days. Maintenance treatment may consist of more frequent administration of the short-acting agents used in stage I. As the GOLD guidelines state, however, long-acting agents are more effective, more convenient, and more likely to be of benefit.[1,6]

Long-acting agents that may be used at this stage include the once-daily, anticholinergic agent tiotropium and the twice-daily, beta-adrenergic agonists salmeterol and formoterol. These medications should be used

**Table. Drug formulations commonly used in stable COPD[a,b]**

| Drug | Inhaler (µg) | Solution for nebulizer (mg) | Oral (mg) | Duration of action (hrs) |
|---|---|---|---|---|
| **Short-acting beta$_2$-agonists** | | | | |
| Levalbuterol | 45/puff (MDI[c]) | 0.31, 0.63, and 1.25/3 mL | – | 4–6 |
| Albuterol | 108/puff (MDI) | 1.25 and 2.5/3 mL | 4, 5, and 8 (tablet); 0.024% (syrup) | 4–6 |
| **Long-acting beta$_2$-agonists** | | | | |
| Formoterol | 12 (DPI[d]) | 0.02/2 mL | – | 12+ |
| Arformoterol | – | 0.015/2 mL | – | – |
| Salmeterol | 50 (DPI) | – | – | 12+ |
| **Short-acting anticholinergics** | | | | |
| Ipratropium bromide | 17/puff (MDI) | 0.5 | – | 6–8 |
| **Long-acting anticholinergics** | | | | |
| Tiotropium | 18 (DPI) | – | – | 24+ |
| **Combination short-acting beta$_2$-agonists plus anticholinergic in one inhaler** | | | | |
| Albuterol/ ipratropium | 120/21/puff (MDI) | 2.5/0.5/3 mL | – | 6–8 |
| **Methylxanthines** | | | | |
| Aminophylline | – | – | 100 and 200 | Variable, up to 24 |
| Theophylline (SR[e]) | – | – | 100–600 | Variable, up to 24 |

Continued on next page

as approved and not more often for quick relief of breakthrough dyspnea. Short-acting bronchodilators should continue to be prescribed for rescue use between doses of the prescribed maintenance agent.[6]

When the long-acting agent is tiotropium, the short-acting agent should be albuterol, because tiotropium and ipratropium are both anticholinergic agents, and it is more effective to use a rescue bronchodilator from a different class than that used in maintenance therapy. When the long-acting agent is salmeterol or formoterol, ipratropium or an albuterol/ipratropium combination could be used—although ipratropium products are not FDA approved for rescue use. Albuterol also can provide effective rescue therapy for patients taking salmeterol or formoterol. The use of inhaled corticosteroids is not recommended in stage II unless the patient is experiencing frequent acute exacerbations despite optimal bronchodilator treatment.[1,6]

In GOLD stage III (an $FEV_1$ between 30% and 50% of predicted value), the increase in dyspnea and exercise intolerance may warrant an intensification of bronchodilator therapy. To this end, an additional, long-acting bronchodilator may be used to complement the bronchodilator used in the patient's stage II therapy. At this stage, therefore, the patient may receive both tiotropium once daily and salmeterol or formoterol twice daily.[6] The two bronchodilator classes are compatible, and studies show that using both improves quality of life and lung function more than using a single long-acting agent.

The acute, life-threatening exacerbations patients often begin to experience in stage III may be associated with stepwise declines in lung function and quality of life, and contribute significantly to national health care costs. Inhaled corticosteroids have

**Table. Drug formulations commonly used in stable COPD[a,b] (continued)**

| Drug | Inhaler (µg) | Solution for nebulizer (mg) | Oral (mg) | Duration of action (hrs) |
|---|---|---|---|---|
| **Inhaled glucocorticosteroids** | | | | |
| Beclomethasone | 40 and 80 (MDI) | – | – | – |
| Budesonide | 90 and 180 (DPI) | 0.25, 0.5, and 1/2 mL | – | – |
| Fluticasone | 50 (DPI); 44, 110, and 220 (MDI) | – | – | – |
| Mometasone | 200 (DPI) | – | – | – |
| Flunisolide | HFA: 80 (MDI); CFC: 250 (MDI) | – | – | – |
| **Combination long-acting beta$_2$-agonists plus glucocorticosteroids in one inhaler** | | | | |
| Fluticasone/ salmeterol | 100/50, 250/50, and 500/50 (DPI); 45/21, 115/21, and 230/21 (MDI) | – | – | – |
| **Systemic glucocorticosteroids** | | | | |
| Prednisone | – | – | 5–60 | – |
| Methylprednisolone | – | – | 4, 8, 16, 24, and 32 | – |

[a]This table was adapted by the author from Figure 5.3-4 in: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Executive Committee. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=989. Updated December 2007. Accessed February 7, 2008.[1]
[b]COPD = chronic obstructive pulmonary disease. [c]MDI = metered-dose inhaler. [d]DPI = dry powder inhaler. [e]SR = sustained release.

been shown to reduce the frequency of these events, and it is appropriate to add them to the patient's pharmacotherapy at this stage.

Since no inhaled corticosteroid has FDA approval as monotherapy for COPD, this addition usually takes the form of substituting a long-acting beta-agonist in combination with an inhaled corticosteroid for the long-acting beta-agonist the patient had been taking. At present, the only such combination approved for COPD therapy is salmeterol/fluticasone in a 250/50-µg formulation. The only justification for using inhaled corticosteroids in COPD is to avoid acute exacerbations. Several large, well conducted studies have demonstrated that their use does not alter the long-term, age-related decline in lung function typical of COPD.

When corticosteroid use is justified, the inhaled route is strongly preferred over oral administration, as it minimizes the risk of systemic complications. Although a two-week course of oral corticosteroids has been shown to be of benefit in controlling acute exacerbations,[7] long-term oral corticosteroid use, even in modest doses, has been associated with osteoporosis and other adverse effects and should be avoided whenever possible.

For GOLD stage IV (an $FEV_1$ below 30% predicted value), all therapies prescribed in previous COPD stages should be continued. For patients who are very symptomatic, a methylxanthine, such as theophylline, may be added.[1] To avoid adverse effects, the dose should be modest. A regimen consisting of theophylline 300 mg/day, by mouth is very unlikely to lead to toxicity. Theophylline is popular with patients and often improves symptoms by mechanisms that are not yet well understood.[1,3]

At GOLD stage IV, long-term oxygen therapy also should be considered. This is indicated when arterial oxygen saturation falls below 88%, with or without hypercapnia, or $PaO_2$ drops as low as 55 mm Hg.[1] Treatment decisions always must take into account any comorbid conditions, particularly coronary artery disease and chronic heart failure, which are so commonly associated with severe COPD.

Antibiotics do not have a role in the maintenance treatment of COPD, though a short course may be beneficial in managing acute exacerbations

associated with infectious causes.[1] There is also some evidence that patients with persistently purulent sputum, a possible indication of bronchiectasis, may benefit from antibiotic therapy if they have concomitant dyspnea and a high level of sputum production.[1]

There is no role for alpha-1 antitrypsin therapy in COPD unless the patient has documented alpha-1 antitrypsin deficiency.[1] Likewise, nonsteroidal anti-inflammatory agents, such as the leukotriene modifiers and cromones, have no place in COPD therapy unless the patient has coexistent asthma. Other pharmacologic treatments that either are not recommended or are of questionable value in COPD include mucolytic agents, antioxidants, and opioids.

## POTENTIAL ADVERSE EFFECTS OF PHARMACOTHERAPY

Fortunately, most therapeutic agents used in the treatment of COPD have been shown to be relatively free of serious adverse effects throughout their widespread use over several years.

Beta-agonists, both short- and long-acting, can cause such transient adrenergic effects as elevated heart rate, tremor, and palpitations; rarely, tachyarrhythmias occur.[1] Slight transient decreases in serum potassium levels and $PaO_2$ can occur, but these drops tend to be of minor clinical significance.[1]

The FDA has attached a black box warning to all long-acting beta-agonists,[8] following a study that showed a small but statistically significant increase in mortality among asthmatic patients who used salmeterol as compared to those who used a placebo.[9] Although the study design had some serious shortcomings that make it difficult to interpret this finding, and the subjects of the trial were asthmatic, the black box warning has been attached to all formulations of both formoterol and salmeterol, including those that are approved only for COPD.

Anticholinergic agents, such as ipratropium and tiotropium, are poorly absorbed, which limits systemic effects.[1] Dry mouth is a fairly common occurrence but is usually mild.[1] Difficult urination has been reported occasionally, but as the GOLD guidelines point out, there is a lack of data to prove a true causal relationship between the drug and these symptoms.[1] Nevertheless, urinary retention is listed on the product labeling as an adverse effect of anticholinergic agents used for COPD.

Pupil dilatation can occur if an anticholinergic drug gains access to the eye. This can occur when the patient is using a nebulized solution of ipratropium with a poorly fitting face-mask, or when a patient inadvertently places an ipratropium-contaminated finger in his or her eye. Patients should be warned to keep their fingers free of any drug.

Glucocorticoids, given by mouth or systemically, have frequent, well known adverse effects that require use of the lowest effective dosage. Inhaled corticosteroids are less absorbable and tend to be administered in much smaller doses. Some, such as fluticasone, are eliminated by a single pass through the hepatic circulation, making them less likely—at least theoretically—to result in significant systemic levels.

Long-term use of inhaled corticosteroids does, however, result in adverse effects in some patients. Skin bruising is common. More serious adverse effects include a reduction in bone mineral density, which is a precursor to osteoporosis.[1] Glaucoma and cataracts, a slight increase in the incidence of pneumonia, and mild inhibition of the hypophyseal-adrenal axis have been associated with inhaled corticosteroids in some studies.

Although serious adverse effects are rare, clinicians should bear in mind that inhaled corticosteroid use is a relatively new addition to COPD therapy. Since patients with COPD may begin therapy in their 50s and receive continuous treatment for the following 30 years, no current studies can predict accurately the potential adverse effects of corticosteroid treatment over this length of time in the typically older COPD patient population. For this reason, it is important to avoid use of inhaled corticosteroids until patients reach the stage at which such therapy is justified by the occurrence of frequent acute exacerbations.

The adverse effects of methylxanthines became well known when their use was much more common. The dosages recommended today are quite modest by comparison. Nevertheless, the methylxanthines have a relatively narrow therapeutic index, and accidental overdosage is a risk. Toxicity is dose-related. At low blood levels, nausea, vomiting, heartburn due to reflux, and headache can occur.[1] At high blood levels, atrial and ventricular arrhythmias and grand mal seizures can occur, sometimes with fatal outcomes.[1]

Metabolism and inactivation of methylxanthines can be delayed by numerous factors, particularly in congestive heart failure, hepatocellular disease, infection, or fever and with the coadministration of such medications as erythromycin, quinolone antibiotics, and cimetidine. In such cases, monitoring of serum theophylline or aminophylline levels may be indicated, and the dosage of the methylxanthine may require adjustment. ●

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Continued from page 5

interventions can delay disease progression, but most maintenance medications can improve exercise tolerance and symptoms and decrease exacerbations. Although the presence of airflow limitation is key to assessing COPD severity, patients with mild disease may have chronic cough and sputum production for many years while demonstrating relatively minor or even no spirometric abnormality. While it has not been proven that such individuals will go on to develop moderate or severe COPD, presence of these symptoms suggests high risk for COPD, indicating that these patients should be targeted for preventive intervention, especially smoking cessation.

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# Adjunctive and Surgical Therapy for Stable Disease

Claudia G. Cote, MD and Bartolome Celli, MD

A multisystem approach to evaluating and treating COPD has shown this condition to be fully treatable.

The idea that chronic obstructive pulmonary disease (COPD) is untreatable has been proven false. Today, it is widely recognized that a comprehensive, multisystem approach to COPD management may have a significant impact on such patient outcomes as functional capacity, health-related quality of life (HRQoL), rate and severity of exacerbations, rate and frequency of hospitalizations, and survival.[1–3]

This article describes the components of multisystem COPD evaluation and management. It discusses both the adjunctive treatments that have measurable systemic benefits in the management of stable COPD and the surgical procedures that may be considered for certain patients.

## A NEW TREATMENT PARADIGM

The treatment of COPD, which previously focused solely on respiratory symptoms, now addresses the multisystemic manifestations of this condition, such as impaired functional capacity[4] and malnutrition.[5] This new paradigm requires clinicians to pursue a more integrated approach to COPD's evaluation and treatment.

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One tool that can be used to assess the multisystemic impact of COPD and to predict survival is the body mass index, degree of airflow obstruction, functional dyspnea, and exercise capacity (BODE) index (Table).[6] This index was developed and validated in a large population consisting primarily of veteran patients. Total BODE index scores range from 0 to 10, with scores of 7 or higher suggesting a poor prognosis.

It is important to evaluate COPD from a comprehensive multisystemic standpoint and to recognize that all manifestations of the disease are amenable to treatment. The pharmacologic therapy of COPD should be complemented with domiciliary oxygen supplementation; pulmonary rehabilitation; and, in some cases, such interventions as lung volume reduction (LVR) or lung transplantation.

## AUGMENTATION THERAPY FOR ALPHA-1 ANTITRYPSIN DEFICIENCY

Some veterans with COPD have alpha-1 antitrypsin deficiency. These patients usually present with severe reductions in forced expiratory volume in one second ($FEV_1$) at a younger age than patients without the deficiency. Although the deficiency is relatively rare, occurring in an estimated one of every 2,500 Americans,[7] the World Health Organization, the American Thoracic Society, the European Respiratory Society, and the Alpha-1 Foundation's Medical and Scientific Advisory Committee recommend that all individuals diagnosed with COPD be tested for this deficiency.[8]

Once identified, supplemental administration of an alpha-1 proteinase inhibitor may be indicated, particularly if the patient is a young nonsmoker.[9] Although it is not entirely clear which patients are the best candidates for replacement therapy, those with mild to moderate COPD in whom progression of the disease can be stalled, seemingly, would stand to benefit most from such treatment.

## COUGH SUPPRESSION AND EXPECTORATION

While mucokinetic agents are utilized widely in COPD, little evidence supports the efficacy of this use. Only one multicenter, controlled study of organic iodide demonstrates a symptomatic benefit of these drugs in managing chronic bronchitis.[10] The oral administration of acetylcysteine is controversial since a large trial of patients with COPD failed to show any substantial benefit for the drug in preventing lung function deterioration or COPD exacerbations.[11]

## OXYGEN THERAPY

Hypoxemia, defined as a $PaO_2$ of 55 mm Hg or lower, is often seen in advanced COPD. Since hypoxemia in COPD is associated with increased mortality and health care resource utilization (HCRU),[12] it is recommended that patients with stages III and IV COPD be evaluated by annual arterial blood gas studies.[1]

The results of the Nocturnal Oxygen Therapy Trial and Medical Research Council studies showed that supplemental oxygen therapy improves survival in hypoxemic patients with COPD.[13,14] Supplemental oxygen should be provided to such patients for at least 15—and, ideally, 24—hours a day to achieve improved survival.[14] Other beneficial effects of long-term supplemental oxygen therapy include reductions in polycythemia, pulmonary hypertension, dyspnea, and nocturnal arrhythmias and improvements in neuropsychiatric testing and exercise tolerance.[12]

Based on previous studies and current practice recommendations, the following findings are indications for initiating long-term oxygen therapy:

- a $PaO_2$ of 55 mm Hg or lower while breathing room air, or less than 60 mm Hg with signs of tissue hypoxia, such as polycythemia; or
- an arterial oxygen saturation of 88% or less—or 89% with signs of tissue hypoxia.

If hypoxemia is exclusively nocturnal, use oxygen only at night. If it occurs exclusively with exercise, use oxygen only with exertion.

A measurement of $PaO_2$ after 30 minutes of breathing room air provides the most accurate clinical basis for initiating oxygen therapy. After an initial diagnosis of hypoxemia, pulse oximetry may be used as a basis for adjusting oxygen delivery.

## PULMONARY REHABILITATION

Pulmonary rehabilitation is essential to the comprehensive management of symptomatic COPD. It has been shown to improve symptoms, HRQoL, and exercise performance,[15] while decreasing HCRU.[16] Patients with symptomatic, moderate to severe disease are the best candidates for pulmonary rehabilitation, with the aim of preventing the disabling effects of end-stage COPD. The rehabilitation program should have a multidisciplinary approach to patients' evaluation and treatment and sufficient resources to teach and supervise proper use of inhalers and nebulizers, breathing techniques, chest physical therapy, postural drainage, physical therapy, exercise conditioning (of the upper and lower extremities), oxygen utilization, and activities of daily living (imparting such techniques as work simplification and energy conservation).[15]

Pulmonary rehabilitation affects outcomes that predict survival in COPD. In an observational study comparing 246 veterans who did and did not complete a pulmonary rehabilitation program, pulmonary rehabilitation participants experienced an initial 19% improvement in the BODE index, compared to an initial 4% worsening for nonparticipants.[17] This improvement corresponded with decreased two-year mortality (7% versus 39% for participants and nonparticipants, respectively) and reduced length of hospital stay at one year (a 20% decrease versus a 35% increase for participants and nonparticipants, respectively). The insufficient number of VA pulmonary rehabilitation programs remains a hurdle to its widespread application.

**Table. The BODE[a] index[6]**

| Component | Score assigned for measured value[b] | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| Body mass index | > 21 | ≤ 21 | – | – |
| Airflow obstruction, as indicated by $FEV_1$[c] (% of predicted value) | ≥ 65 | 50–64 | 36–49 | ≤ 35 |
| MRC[d] dyspnea scale | 0–1 | 2 | 3 | 4 |
| Exercise capacity, as demonstrated by distance walked in 6 min (m) | ≥ 350 | 250–349 | 150–249 | ≤ 149 |

[a]BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity. [b]Individual component scores are added to arrive at a total score that ranges from 0 to 10. Total BODE scores of 7 or higher suggest a poor prognosis. [c]$FEV_1$ = forced expiratory volume in one second. [d]MRC = Medical Research Council.

## SURGICAL AND NONSURGICAL LVR

Several surgical therapies for COPD have been introduced over the years, most of which attempt to alleviate symptoms of emphysema. For patients with heterogeneous emphysema, who remain symptomatic in spite of optimal pharmacologic therapy, domiciliary oxygen supplementation, and pulmonary rehabilitation, LVR surgery should be considered.[18]

When properly selected, patients with emphysema who are treated with LVR surgery show improvement in lung function, exercise capacity, symptoms, HRQoL, and survival.[19] LVR surgery also has been shown to improve disease severity as measured by the BODE index,[20,21] and there are indications that such changes translate into a survival benefit, though not all patients with emphysema benefit from the procedure.[21]

Ideal candidates for LVR surgery have inhomogeneous upper lobe disease, limited exercise performance

after completing a comprehensive course of pulmonary rehabilitation, an $FEV_1$ between 20% and 35% predicted value, a diffusing capacity for carbon monoxide higher than 20% predicted value, significant hyperinflation, and a low comorbid burden.[22]

LVR also can be achieved nonsurgically without exposing patients to operative risks. Nonsurgical LVR involves the delivery of a washout solution and fibrin-based glue through bronchoscopically placed, one-way valves in order to seal, scar, and collapse target regions of abnormal lung tissue.[23] In addition, emergent techniques that utilize biological substances have been shown to be capable of inducing closure of emphysematous areas in selected patients with advanced COPD.[24]

Surgical LVR remains the technique most commonly used. Currently, experience with nonsurgical LVR is limited. Since the two techniques have not been compared in controlled, randomized, clinical trials, there is not yet an evidentiary basis for recommending one technique over the other.

## LUNG TRANSPLANTATION

COPD is the number one indication for lung transplantation. Several issues must be considered when evaluating a candidate for this procedure, including the patient's projected survival without transplantation, degree of disability, and presence of comorbid conditions.[25]

In general, patients should be younger than 65 years and free of medical conditions that could shorten survival. Patients with a BODE index score above 7 have a very poor prognosis without transplant and, therefore, are good candidates.[26] In patients with diffuse, severe emphysema, lung transplantation normalizes pulmonary function and improves both exercise capacity and HRQoL. The effect of lung transplantation on survival remains controversial.[25]

## A TREATABLE DISEASE

COPD is fully treatable. Pharmacologic and nonpharmacologic interventions improve patient outcomes and prolong survival. For patients whose symptoms persist despite optimal pharmacologic therapy, domiciliary oxygen supplementation, and pulmonary rehabilitation, LVR and lung transplantation should be considered. ●

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# Prevention and Management of COPD Exacerbations

Ryland P. Byrd, Jr., MD, Jayant B. Mehta, MD, and Thomas M. Roy, MD

Several strategies can help reduce the frequency and severity of COPD exacerbations. When a patient appears to have an exacerbation despite these efforts, ruling out other conditions in the differential diagnosis is essential to providing appropriate treatment.

Exacerbations of chronic obstructive pulmonary disease (COPD) are characterized by increases in sputum volume or purulence or worsening dyspnea. Patients with COPD experience such decompensations an average of one to three times each year. About 3% to 16% of COPD exacerbations require hospitalization with an expected mortality ranging from 3% to 10%.[1]

Helping patients to avoid exacerbations or lessen their severity is therefore the clinician's first priority, achieved by such strategies as smoking cessation and pulmonary rehabilitation. Because comorbid conditions that can mimic an exacerbation are common in COPD, it is essential to verify any apparent exacerbations with a careful and comprehensive clinical evaluation. Once the diagnosis has been established, the exacerbation can be eased with therapies that optimize physiologic function and decrease airway inflammation. Most patients can be treated at home.[2]

## PREVENTING OR REDUCING ACUTE EXACERBATIONS

Breaking the smoking habit is the best way to improve the course of COPD. Pulmonary rehabilitation, patient education regarding disease management, and vaccination also play a role in preventing or reducing acute exacerbations.

### Smoking cessation

Smoking is the primary cause of COPD, and smoking cessation is the most effective way to preserve lung function, which is essential for avoiding exacerbations. Indeed, the frequency of COPD exacerbations is associated significantly with lung function decline as measured by the forced expiratory volume in one second ($FEV_1$).[3] In order to succeed, smoking cessation efforts must help the patient address the physical, psychological, and behavioral aspects of tobacco dependence. Effective programs combine counseling and pharmacotherapy, with pharmacotherapy nearly doubling long-term cessation rates seen with counseling alone. The patient who stops smoking over the long term derives the greatest health benefits.

### Pulmonary rehabilitation

Pulmonary rehabilitation, a structured management program, supplements medical evaluation and treatment with exercise training, education, psychological therapy, and nutritional counseling. This training typically is considered for patients with moderate to severe COPD but can benefit patients at all stages of disease. Patients should participate in a program for at least two months to optimize improvement in physical deconditioning and weight and mood state control.[4] Pulmonary rehabilitation has been shown to reduce the frequency of acute exacerbations and the number of hospitalizations for patients experiencing an acute exacerbation.[5,6]

### Self-management education

Continuing patient education in self-management is necessary to achieve optimal medical therapy and fewer exacerbations. Indeed, data on patient adherence to COPD therapy are discouraging. According to a recent study, only about 63% of patients with COPD follow their prescribed medication regimen.[7] Likewise, only 32% of patients who receive combined therapy of smoking cessation drugs and counseling remain smoke-free at 12 months.[8] In addition, only 45% to 70% of patients who require long-term oxygen therapy use the oxygen as prescribed.[9]

Ongoing self-management education under the supervision of a case manager improves adherence and reduces the unanticipated use of health services. Well thought out management guidelines and improved pharmaceutical agents for COPD cannot replace the need for continuous reassessment of the social and psychological barriers that commonly prevent the patient from benefiting from modern advances in COPD treatment.[10] Demonstrated health and economic benefits to the patient and society, respectively, make it likely that, in the

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future, self-management education programs will be incorporated routinely into COPD management plans.[11]

### Vaccinations

Influenza is one of many causes of exacerbations of COPD that can be limited effectively by annual vaccination. The vaccine is reported to reduce the incidence of any respiratory illness and pneumonia by more than 50% and to reduce the risk of death from infection by more than two thirds.[12]

Patients with COPD also have a high rate of pneumococcal infection, probably because of impaired pulmonary clearance mechanisms. As a result, *Streptococcus pneumoniae* is the primary pathogen in community-acquired pneumonia among patients with COPD. Pneumococcal polysaccharide vaccine is effective in preventing pneumococcal pneumonia and bacteremia in immunocompetent individuals. The CDC recommends the vaccine for patients at high risk for infection, such as those with COPD.[13] Unfortunately, the effectiveness of this vaccine in individuals with chronic respiratory illness has not been uniform. Nonetheless, most physicians recommend the vaccination to their patients with COPD.[12]

## RECOGNIZING ACUTE EXACERBATIONS

Definitions of acute exacerbations of COPD vary. The most widely accepted definition is based on clinical criteria, with an acute exacerbation of COPD considered a sudden or subacute onset of worsening dyspnea, increased sputum volume, or the presence of sputum purulence. Such intermittent episodes of worsening of symptoms and lung function characterize the natural history of COPD and contribute to the morbidity, mortality, and quality-of-life issues associated with this disorder.

Other disease processes can mimic an acute exacerbation of COPD: Pneumonia, myocardial ischemia, congestive heart failure, pneumothorax, or pulmonary embolism may be misdiagnosed as an exacerbation of COPD. Other disorders that increase ventilatory demand, such as sepsis and metabolic acidosis, also may imitate COPD exacerbations and should be considered in the differential diagnosis.

Differentiating a COPD exacerbation from other conditions rests on the physical examination, laboratory and radiologic studies, electrocardiography (ECG), and pulmonary function testing.

### Physical examination

Patients with an acute exacerbation of COPD may be tachycardic, tachypneic, or cyanotic and have varying degrees of respiratory distress, depending on their baseline pulmonary function and the severity of the exacerbation. Patients with ventilatory failure and hypercarbia may be confused and somnolent. The pulmonary examination may reveal the use of accessory muscles of respiration, hyperinflation of the lungs, diminished air movement, and wheezing. Paradoxical movement of the abdomen or a prominent second heart sound, or other evidence of pulmonary hypertension, also may be present.

### Laboratory tests

Arterial blood gas analysis is helpful in assessing the degree of hypoxemia as well as hypercarbia. A complete blood cell count may reveal leukocytosis, especially when a respiratory infection is responsible for the exacerbation. Serum electrolytes may demonstrate an elevated bicarbonate level, indicating chronic respiratory failure. Gram staining of expectorated sputum may help identify the pathogen responsible for the exacerbation. A serum theophylline level should be obtained if the patient is taking this medication as an outpatient.

### Radiologic studies

Chest roentgenograms help identify the presence of pneumonia. They also help to exclude pneumothorax and pulmonary edema from the differential diagnosis. If there is clinical suspicion of pulmonary thromboembolic disease, it is appropriate to obtain a spiral computed tomography scan of the chest and ultrasound of the lower extremities.

### ECG

ECG is useful in ruling out myocardial infarction. The ECG results may reveal the presence of atrial tachyarrhythmia, such as multifocal atrial tachycardia.

### Pulmonary function testing

Although pulmonary function testing is not useful for diagnosing an acute exacerbation of COPD, it may help in determining the severity of the exacerbation and the need for systemic steroids. An exacerbation often leaves patients unable to tolerate pulmonary function testing, however, or the exacerbation may make it difficult to perform the test properly.

## MANAGING ACUTE EXACERBATIONS

Most patients with an acute exacerbation of COPD can be evaluated in an outpatient clinic and managed at home, though many of the diagnostic modalities discussed here may not be available in the clinic setting. Treatment for mild or moderate exacerbations is pharmacologic (Table). Patients with severe exacerbations may require nonpharmacologic therapies as well and may need immediate treatment in an emergency department (ED) or hospitalization.

## Outpatient management

Outpatient management is appropriate if the patient has stable vital signs, has an unimpaired level of consciousness, does not exhibit evidence of respiratory distress, and has adequate disease resources to manage his or her disease at home (Figure). Pulse oximetry, if available, is advisable because hypoxemia can develop or worsen with an exacerbation and can be life threatening. The patient with a low percent of arterial oxygen saturation should be referred to an acute care facility.

In the outpatient setting, acute exacerbations typically are managed with increased doses of short-acting bronchodilators. As soon as possible, administer a short-acting beta$_2$-agonist a short-acting anticholineric, or a combination of both, using a metered dose inhaler with a spacer or aerosol nebulization. Because albuterol has a more rapid onset of action than ipratropium, it typically is used alone or in combination with ipratropium.[14] Albuterol has more adverse effects than ipratropium, however, and certain patients may benefit from increased administration of ipratropium.[15] Avoid using methylxanthines for an acute exacerbation of COPD, as they have not demonstrated a clear reduction in symptoms or hospital admissions and are associated with adverse effects.[14,16]

Up to half of COPD exacerbations are caused by bacterial infection of the airways.[17] Antibiotic treatment of such exacerbations hastens their resolution. The choice of antibiotic is best determined by stratifying the exacerbation as complicated or uncomplicated. In an uncomplicated exacerbation, the patient has experienced fewer than three exacerbations in the past 12 months, has a baseline $FEV_1$ of greater than 50% predicted value, does not have cardiac disease, and has not been exposed to antibiotics in the past three months. In this case, the patient should be treated with amoxicillin, doxycycline, combined trimethoprim and sulfamethoxazole, second- or third-generation cephalosporins, or extended-spectrum macrolides.[18,19]

The patient with a complicated exacerbation has experienced three or more exacerbations in the past 12 months, has a baseline $FEV_1$ of less than 50% predicted value, has cardiac disease, and has been exposed to antibiotics in the past three months. This type of patient should be treated with a combination beta-lactam/beta-lactamase inhibitor or fluoroquinolones.[19]

The increased airway inflammation that is now recognized as an integral part of COPD exacerbations can be decreased with the use of systemic glucocorticosteroids. Oral glucocorticosteroids therefore should be an option in the outpatient treatment of an acute exacerbation of COPD. Consider a prednisone course of seven to no more than 14 days. Shorter courses have been shown to be as effective as 14-day courses.[20]

Instruct the patient to seek medical attention from his or her health care provider if symptoms do not improve within 48 to 72 hours after outpatient therapy begins. The patient may require referral to an acute care facility.

**Table. Medications for treatment of acute COPD[a] exacerbations**

**Short-acting bronchodilators**
- Beta$_2$-adrenergic agonists: albuterol, levalbuterol, metaproterenol, pirbuterol
- Anticholinergic agent: ipratropium

**Corticosteroids**
- Oral: prednisone, methylprednilisone
- Intravenous: methylprednilisone

**Antibiotics**
- Uncomplicated exacerbation[b]: doxycycline, trimethotrim/sulfamethoxazole, second- or third-generation cephalosporins, extended-spectrum macrolides
- Complicated exacerbation[c]: beta-lactam/beta-lactamase inhibitor, fluoroquinolones

[a]COPD = chronic obstructive pulmonary disease. [b]The patient with an uncomplicated exacerbation has experienced fewer than three exacerbations in the past 12 months, has a baseline forced expiratory volume in one second ($FEV_1$) of greater than 50% predicted value, does not have cardiac disease, and has not been exposed to antibiotics in the past three months. [c]The patient with a complicated exacerbation has experienced three or more exacerbations in the past 12 months, has a baseline $FEV_1$ of less than 50% predicted value, has cardiac disease, and has been exposed to antibiotics in the past three months.

## Inpatient management

The patient who has unstable vital signs, has altered mental status, exhibits respiratory distress, or cannot manage his or her illness at home should be referred to a higher care facility.

Because patients referred to an acute care facility typically are in respiratory distress, they generally will undergo simultaneous treatment and a diagnostic workup to rule out other diseases. Arterial blood gas analysis; levels of serum electrolytes, blood

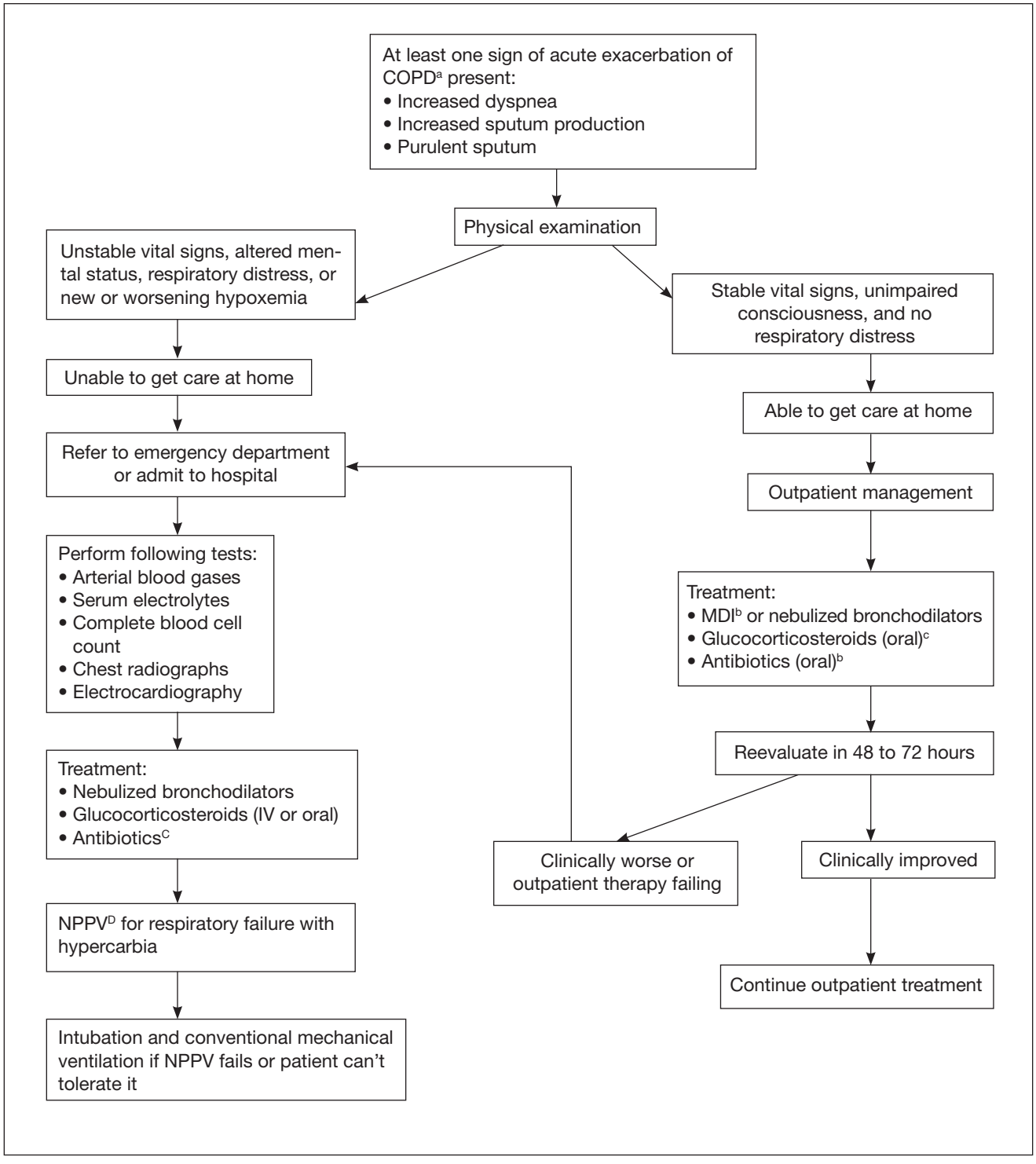


Figure. Algorithm for assessing and managing acute exacerbations of COPD. [a]COPD = chronic obstructive pulmonary disease. [b]MDI = metered-dose inhaler. [c]Antibiotic selection is based on the stratification of the patients as having a complicated or uncomplicated exacerbation. [d]NPPV = noninvasive positive pressure ventilation.

urea nitrogen, and creatinine; complete blood cell count with a differential white blood cell count; chest radiographs; ECG; and sputum sampling for Gram stain and bacterial cultures are standard. It's also important to obtain a serum theophylline level if the patient is receiving this medication on an outpatient basis.

As in outpatient management, inpatient therapy at an acute care facility typically consists of administering a short-acting beta$_2$-agonist, anticholineric, or a combination of both. Since patients at acute care facilities are more ill than those treated as outpatients, these medications are usually delivered by aerosol nebulization. Once again, the adverse effect profile of albuterol may limit its use in favor of ipratropium, and methylxanthines should be avoided.[15,16]

Antibiotic selection is based on the same stratification profile as in outpatient therapy. Since patients with more complicated COPD cases generally require more hospitalizations, they usually are treated with a beta-lactam/beta-lactamase inhibitor or fluoroquinolones. The antibiotics typically are administered intravenously, as are glucocorticosteroids.[18,19] Once the acute exacerbation is controlled, antibiotics and glucocorticosteroids can be given orally for a total of seven to 14 days.

## NONPHARMACOLOGIC TREATMENTS

The two major nonpharmacologic treatments for severe exacerbations of COPD are supplemental oxygen therapy and ventilatory support.

### Supplemental oxygen

Oxygen therapy is of great benefit for acute respiratory failure during COPD exacerbations. The primary objectives are to raise the $PaO_2$, thereby preventing life threatening hypoxemia, and to optimize oxygen delivery to peripheral tissues. In patients referred to the ED or admitted to the hospital for an acute exacerbation of COPD, initial treatment should include low flow oxygen therapy to maintain a percent saturation of greater than 90%. Even though it is appropriate to begin oxygen therapy before the patient is fully assessed in the ED or an inpatient unit, the therapy should be used judiciously. The worsening of ventilation perfusion mismatch (an imbalance between alveolar ventilation and pulmonary capillary blood flow) in a patient with hypercarbia may result in increased hypoventilation and respiratory acidosis.[21]

### Ventilatory support

The primary therapeutic goal of ventilatory support in patients with acute respiratory failure is to reduce the work of breathing and relieve symptoms, decreasing morbidity and mortality.

Ventilation support can be provided noninvasively or invasively. Noninvasive positive pressure ventilation (NPPV) is the delivery of mechanically assisted or generated breaths without placement of an artificial airway, which requires tracheal intubation. Typically, positive airway pressure is delivered through a tightly fitting nasal mask or facial mask. NPPV reduces the length of hospital stay, decreases the need for invasive mechanical ventilation, eases the work of breathing, and reduces mortality. These advantages are greatest for patients with acute exacerbations of COPD accompanied by hypercarbia, and NPPV should be considered in carefully selected patients who are in respiratory failure.[22] The improvement in gas exchange and acid-base balance associated with NPPV reflects improved alveolar ventilation.[23]

Conventional mechanical ventilation is appropriate when NPPV fails or the patient is not a candidate for NPPV. Deteriorating gas exchange unresponsive to conservative measures and respiratory distress are the most common reasons for invasive mechanical ventilation in patients with acute respiratory failure caused by a COPD exacerbation.[24] Conventional mechanical ventilation is associated with increased hospital mortality—although this increase appears to be related to the severity of the underlying lung disease, not mechanical ventilation per se.[25]

## THE BOTTOM LINE

COPD causes substantial morbidity and mortality worldwide. Preventive health measures may reduce the frequency and severity of acute exacerbations, which should be managed with short-acting bronchodilators, antibiotics, and glucocorticosteroids. The patient with a mild to moderate exacerbation may be treated at home with follow-up. For more severe exacerbations, the patient may require hospitalization, supplemental oxygen therapy, and noninvasive or invasive ventilatory support. ●

*Author disclosures*

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# COPD and Comorbid Disease: Beyond Dyspnea

Mark B. Stephens, MD, MS and Kenneth S. Yew, MD

Recognition and appropriate management of coexisting medical conditions in patients with COPD are essential to improving quality of life and reducing mortality.

Much of the focus in the management of chronic obstructive pulmonary disease (COPD) is on reducing symptoms related to airflow obstruction. Associated comorbidities, however, contribute significantly to overall mortality in patients with COPD. In fact, the leading causes of death in such patients are lung cancer and cardiovascular disease.[1] To improve the quality of life for patients with COPD, therefore, it is essential that clinicians know how to recognize and manage common COPD comorbidities.

## LUNG CANCER

After controlling for smoking, COPD remains an independent risk factor for lung cancer, which is two to five times more common in smokers with COPD than in smokers without COPD.[2] The absolute risk of lung cancer correlates with the severity of COPD.[2]

Most patients with lung cancer present with advanced disease. Early diagnosis of lung cancer is particularly challenging in patients with COPD because many signs and symptoms (such as cough, weight loss, and dyspnea) are common in both diseases.[3] The U.S. Preventive Services Task Force and the American College of Chest Physicians have found insufficient evidence to advocate for or against routine lung cancer screening.[3]

The importance of smoking cessation cannot be overemphasized. Tobacco smoke induces chronic inflammation, which plays a role in the pathogenesis of cardiovascular disease and pulmonary hypertension (PH) as well as lung cancer.[4] The Lung Health Study, a multicenter, randomized, controlled trial, clearly showed that those who quit smoking have substantially reduced rates of death from lung cancer, cardiovascular disease, and other cancers.[1] For patients with established lung cancer, treatment guidelines are readily available from the American College of Chest Physicians.[5]

## CARDIOPULMONARY DISEASE

### Atherosclerotic coronary artery disease

Ischemic heart disease, not respiratory failure, is the leading cause of death in patients with COPD. Patients with COPD are at increased risk for cardiovascular morbidity and mortality independent of other cardiovascular risk factors, including tobacco use.[6] The measured forced expiratory volume in one second ($FEV_1$) is as significant a predictor of mortality as serum cholesterol level.[7] It is essential, therefore, that clinicians manage comorbid coronary artery disease in accordance with accepted guidelines in patients with COPD. This includes the use of aspirin, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and statins.[8]

### Congestive heart failure

Roughly 14 million people in the United States have COPD,[9] and five million Americans have congestive heart failure (CHF).[10] Compared to patients without COPD, the relative risk of developing CHF for patients with COPD is 4.5 (CI, 4.25 to 4.95).[11] Clinically, it can be very difficult to differentiate the two conditions since dyspnea is common to both. The use of two-dimensional echocardiography and B-type natriuretic peptide (BNP) can help clinicians distinguish CHF from COPD to guide appropriate treatment (Table 1).[6]

When the left ventricular ejection fraction is less than 40%, an elevated BNP level suggests the need for full CHF therapy, including diuretics, ACE inhibitors, and cardioselective beta-blockade. In patients with COPD and moderate to severe CHF, the benefits associated with beta-blocker treatment clearly outweigh the risks.[12] If the ejection fraction is normal and the BNP level is below 100 pg/mL, treatment should be focused on COPD. If the BNP level is intermediate or left ventricular mass is increased, the patient should be treated with diuretics and ACE inhibitors in addition to COPD therapies.

### Pulmonary hypertension

COPD is the most common respiratory cause of PH. Between 20% and 35% of patients with COPD have concomitant PH.[13] Chronic hypoxia leads to neomuscularization of the pulmonary arterioles, vascular remodeling, local vasoconstric-

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tion, and increased pulmonary artery pressures.[14] Inflammation, typically brought on by exposure to tobacco smoke, results in local tissue remodeling, which further increases pulmonary arteriolar pressure.[15] PH is considered when mean pulmonary artery pressures exceed 25 mm Hg.

PH in COPD is most common in patients with severe airflow limitation. Nearly 50% of patients who have COPD and an $FEV_1$ value that is less than 25% predicted will have mean pulmonary artery pressures exceeding 25 mm Hg.[16] While the degree of PH associated with COPD is usually mild, it adversely affects survival. Five-year survival is 36% for patients with pulmonary artery pressures between 25 and 40 mm Hg[17] and less than 20% for patients with pulmonary artery pressures greater than 40 mm Hg.[18]

The diagnosis of COPD-associated PH can be difficult (Figure). Signs of right-sided heart failure often are obscured by obesity or hyperinflation. Electrocardiographic changes associated with cor pulmonale, including right axis deviation, increased P wave amplitude in the inferior leads (II, III, and aVF), and an $S_1Q_3T_3$ pattern or right bundle branch block, may be suggestive of PH. Echocardiography is less helpful in diagnosing PH than CHF because hyperinflation is common in patients with COPD and it obscures proper estimation of right ventricular pressures. Ultimately, the definitive diagnosis is based on right heart catheterization.[15]

Treatment of COPD-associated PH is straightforward. Patients are given supplemental oxygen to maintain a $PaO_2$ of at least 55 mm Hg. As of yet, there is no clear indication for treating patients with prostanoid or phosphodiesterase inhibitor medications.[15] Lung transplantation may improve quality of life for candidates with advanced disease who meet physical and psychological criteria, although it is not clear that transplantation improves survival.[19]

**Table 1. The use of BNP[a] and echocardiography to diagnose and treat CHF[b] in patients with COPD[c,6]**

| Findings | CHF diagnosis | Treatment |
|---|---|---|
| **BNP** | | |
| < 100 pg/mL | Not likely | Treat for COPD |
| 100–500 pg/mL | Moderate | Consider diuretics and ACE[d] inhibitors |
| > 500 pg/mL | Definitive | Diuretics and ACE inhibitors |
| **Two-dimensional echocardiography** | | |
| Ejection fraction < 40% | Definitive | Diuretics, ACE inhibitors, and beta-blocker |
| Ejection fraction > 40% with increased LV[e] mass | Moderate | Diuretics and ACE inhibitors |
| Normal echocardiography | Excluded | Treat for COPD |

[a]BNP = B-type natriuretic peptide. [b]CHF = congestive heart failure. [c]COPD = chronic obstructive pulmonary disease. [d]ACE = angiotensin converting enzyme. [e]LV = left ventricular.

## MALNUTRITION

Pulmonary cachexia, which occurs in moderate to severe COPD, is vexing to both patients and physicians. One third to one fifth of patients with COPD show signs of muscle wasting.[20] Low body mass index has been associated with increased mortality in several[21,22]—but not all[23,24]—studies that have considered nutritional status in COPD. Causes of weight loss in COPD include inadequate caloric intake, increased energy expenditure due to increased work of breathing, muscle wasting, and systemic effects of chronic inflammation.[25]

While weight loss in patients with COPD is associated with poor prognosis, a recent systematic review of 11 randomized, controlled trials, including 352 participants, concluded that "nutritional support had no significant effect on anthropometric measures, lung function or exercise capacity in patients with stable COPD."[26] Given this lack of evidence, nutritional support should be offered only after clinical nutritional assessment since, paradoxically, nutritional oversupplementation can reduce overall caloric intake.[27] Future therapies to treat pulmonary cachexia may include ghrelin,[28] anabolic agents, or anti-inflammatory therapies.[29]

## MENTAL HEALTH

Mental health issues are common in patients with COPD. In fact, 30% to 60% meet diagnostic criteria for mental illness.[30] Published studies suggest that anywhere from 10% to 90% of patients with COPD have underlying anxiety,[31] and 7% to 80% have underlying depression.[30] The frequency of depression and anxiety are far higher in patients with COPD than in the population at large, in which the point prevalence of depression is 7% to 19%[32] and the point prevalence of

anxiety is up to 15%.[33] Additionally, patients with underlying mental disease are far more likely to have COPD than other chronic illnesses, probably as a result of concomitant tobacco use.[34]

Patients with COPD and untreated anxiety or depression are more likely to have poor outcomes following acute COPD exacerbations.[35] They are also less likely to engage in rehabilitative programs.[30] This leads to significantly lower quality of life[36] and worsened disease progression.[37] Patients with COPD also have greater levels of hypochondriasis and hysteria,[38] leading many physicians to consider them more challenging to care for than patients with other chronic medical conditions.[39]

Smoking is a common denominator in the pathophysiology of both COPD and underlying mental illness. Pulmonary damage resulting from chronic tobacco exposure leads to hypoxia, which creates the subjective sensation of dyspnea as well as other cognitive effects. Compared with nonhypoxic controls, hypoxic patients with COPD score lower on tests requiring memory inputs, high levels of attention, and higher order cognitive processing.[40] Patients who quit smoking have better outcomes on these types of tests than those who continue to smoke.[41]

Several nonpharmacologic therapies focused on cognitive-behavioral techniques and pulmonary rehabilitation are available to treat mental illness in COPD. While little trial data specifically guides the pharmacologic treatment of comorbid anxiety and depression in patients with COPD, several classes of drugs are available for this purpose (Table 2). Bupropion and nortryptyline have been examined specifically within the context of tobacco cessation in depressed patients with COPD.[42]

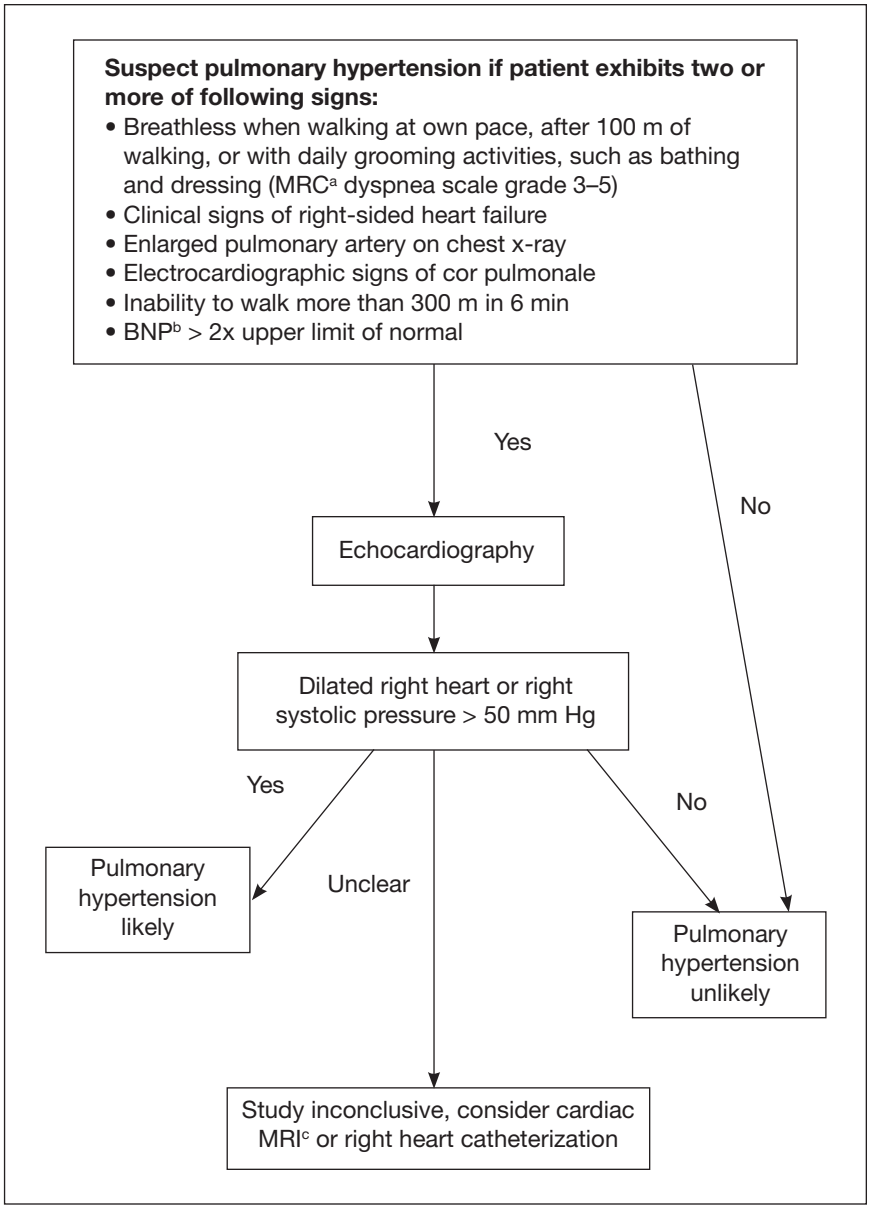


Figure. Diagnosis of pulmonary hypertension in patients with chronic obstructive pulmonary disease.[15] [a]MRC = Medical Research Council. [b]BNP = B-type natriuretic peptide. [c]MRI = magnetic resonance imaging.

## SLEEP DISORDERS

The Sleep Heart Health Study revealed no differences in daytime sleepiness, sleep latency, sleep efficiency, duration of sleep stages, rapid eye movement time, or arousal index between individuals with and without spirometric evidence of airway obstruction. Total sleep time was slightly longer in those without COPD. Researchers noted no trends toward poorer sleep by these objective measures with increasing severity of COPD.[43] Investigators also found no significant difference in the

**Table 2. Medications for treatment of anxiety and depression in patients with chronic obstructive pulmonary disease**

| Medication | Dosage |
|---|---|
| **Tricyclic antidepressants** | |
| Imipramine | Begin 25–50 mg PO at bedtime; increase 25 mg every 3–4 days to a maximum of 100 mg/day in elders or 300 mg/day in young, healthy patients |
| Amitriptyline | Begin 25–50 mg PO at bedtime; increase by 25 mg every 2–3 days (10–25 mg in elders) to a maximum of 100 mg/day in elders or 300 mg/day in young, healthy patients |
| Nortriptyline | Begin 25–50 mg PO at bedtime; increase by 25 mg every 2–3 days (10–25 mg in elders) to a maximum of 100 mg/day in elders or 300 mg/day in young, healthy patients |
| Clomipramine | Begin 25 mg PO in divided doses with food at bedtime; increase by 25 mg every 4–7 days (10–25 mg in elders) to a maximum of 100 mg/day in the first 2 weeks of therapy; thereafter, maximum dosage is 250 mg/day; discontinue gradually |
| **Selective serotonin reuptake inhibitors** | |
| Fluoxetine | 20–60 mg/day PO; begin at 20 mg/day |
| Sertraline | 50–200 mg/day PO; begin at 50 mg/day |
| Paroxetine | 10–50 mg/day PO; begin at 10–20 mg/day |
| Citalopram | 20–60 mg/day PO; begin at 20 mg/day |
| Escitalopram | 10 mg/day PO |
| **Other** | |
| Bupropion | 100 mg/day PO; titrate after 3 days to 100 mg PO three times daily; maximum dosage is 450 mg/day |

prevalence of obstructive sleep apnea (OSA) between those with mild obstructive lung disease and those with normal lung function. This suggests that, at least for patients with mild COPD, sleep disorders (including OSA) are not more prevalent than in the general population.

Patients with moderate to severe COPD, however, tend to have reduced sleep efficiency and total sleep time, delayed sleep onset, and increased arousals during sleep.[13] Nocturnal hypoxemia may be a contributing factor. These patients also have decreased $PaO_2$—which, owing to the kinetics of the oxygen-hemoglobin dissociation curve, results in substantial decreases in arterial oxygen saturation if $PaO_2$ is reduced even modestly during sleep.

An early study suggested an association between solitary nocturnal hypoxemia and mortality,[44] but a recent systematic review[45] identified two randomized, clinical trials of oxygen supplementation in patients with COPD and no significant daytime hypoxemia ($PaO_2$ greater than 60 mm Hg) that found no effect on sleep quality or mortality.[46,47] Weitzenblum and Chaouat found no association between nocturnal hypoxemia and increased mortality, polycythemia, or PH.[48] Similarly, a recent systematic review found insufficient data to support the use of noninvasive, intermittent, positive pressure ventilation to augment conventional oxygen therapy in patients with stable COPD, hypoxemia, and hypercapnia.[49] These data support current recommendations that supplemental oxygen therapy be used only for patients with daytime resting hypoxemia.[50] Patients with COPD and OSA, however, have more severe arterial oxygen desaturation and are at greater risk for PH.[43]

Treatment of sleep problems in patients with COPD involves counseling on general sleep hygiene; avoidance of alcohol before bedtime; and cautious, short-term use of hypnotics.

## SUMMARY

Most patients with COPD have at least one comorbid disease, and clinical diagnosis is challenging. Targeted laboratory testing (BNP) and ancillary imaging (echocardiography) can help clinicians differentiate various cardiopulmonary causes of dyspnea. Recognizing and address-

ing anxiety and depression can improve quality of life and slow disease progression.

### *Author disclosures*

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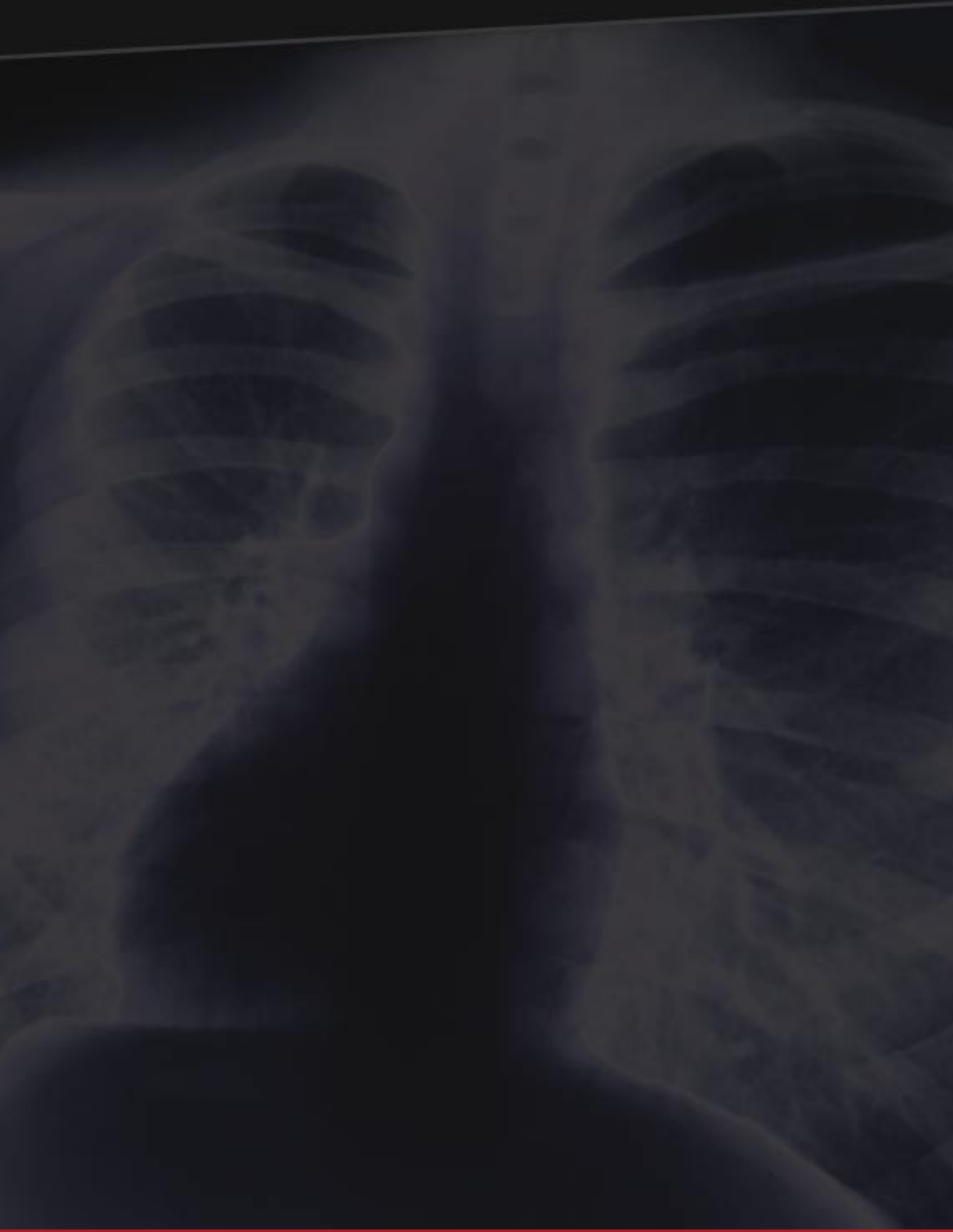

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