



## NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC™) GUIDELINE SYNTHESIS

### CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PART II. DIAGNOSIS AND MANAGEMENT OF ACUTE EXACERBATIONS

#### *Guidelines*

1. Veterans Health Administration/Department of Veterans Affairs (VHA/DOD). [VHA/DOD clinical practice guideline for the management of chronic obstructive pulmonary disease](#). Washington (DC): Veterans Health Administration; 1999 Aug. 116 p. [193 references].
2. American College of Physicians-American Society of Internal Medicine/American College of Chest Physicians (ACP-ASIM/ACCP). [Evidence base for management of acute exacerbations of chronic obstructive pulmonary disease](#). Ann Intern Med 2001 Apr 3;134(7):595-9 [3 references].
3. World Health Organization/National Heart, Lung, and Blood Institute (WHO/NHLBI). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease, 2001. Various p. [547 references].  
CURRENT NGC SUMMARY: [Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease](#).

**\*Please note:** The GOLD guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this synthesis.

#### **INTRODUCTION:**

A direct comparison of Veterans Health Administration/Department of Veterans Affairs (VHA/DOD), American College of Physicians-American Society of Internal Medicine/American College of Chest Physicians (ACP-ASIM/ACCP), and World Health Organization/National Heart, Lung, and Blood Institute (WHO/NHLBI) recommendations for the diagnosis and management of acute exacerbation of chronic obstructive pulmonary disease (COPD) is provided in the tables below. The VHA/DOD and WHO/NHLBI guidelines are very broad in scope, providing recommendations on diagnosis and management of both stable COPD and acute exacerbations; the WHO/NHLBI guideline also addresses prevention strategies. The ACP-ASIM/ACCP focuses only on diagnosis and management of acute exacerbation of COPD in the inpatient setting and does not provide recommendations for patients with stable disease. Recommendations concerning diagnosis and management of stable COPD are compared in [Part I](#) of this synthesis. Recommendations for pulmonary rehabilitation of patients with COPD are addressed in Part III of this synthesis.

Following the [content comparison table](#) and discussion, the areas of agreement and differences among the guidelines are identified. The evidence

surrounding disparate recommendations is explored in the discussion of areas of difference.

Abbreviations:

- ACP-ASIM/ACCP, American College of Physicians-American Society of Internal Medicine/American College of Chest Physicians
- COPD, Chronic obstructive pulmonary disease
- FEV<sub>1</sub>, Forced expiratory volume in one second
- ICU, Intensive Care Unit
- MDI, Metered dose inhale
- NIPPV, Noninvasive positive pressure ventilation
- SAIBA, Short-acting inhaled beta<sub>2</sub>-agonist
- VHA/DOD, Veterans Health Administration/Department of Veterans Affairs
- WHO/NHLBI, World Health Organization/National Heart, Lung, and Blood Institute

Note: To print the following tables, users may have to change their printer settings to landscape, print on legal size paper, and/or use a small font size.

<b>TABLE 1: COMPARISON OF SCOPE AND CONTENT</b>	
<b>OBJECTIVE AND SCOPE</b>	
<b>VHA/DOD (1999)</b>	<ul style="list-style-type: none"> <li>• To assist primary care providers or specialists in the early detection of symptoms, assessment of the clinical situation, determination of appropriate treatment, and delivery of individualized interventions.</li> <li>• To provide enough guidance for a broad range of clinical settings, while at the same time providing enough flexibility to accommodate local practice and individual situations.</li> <li>• To promote evidence-based management of persons with chronic obstructive pulmonary disease (COPD) and thereby improve clinical outcomes.</li> </ul>
<b>ACP-ASIM/ACCP (2001)</b>	To present evidence-based recommendations for the diagnostic evaluation, risk stratification, and therapeutic management of patients with acute exacerbations of COPD.
<b>WHO/NHLBI (2001)</b>	<ul style="list-style-type: none"> <li>• To recommend effective COPD management and prevention strategies for use in all countries.</li> <li>• To increase awareness of the medical community, public health officials and the general public that COPD is a public health problem.</li> <li>• To decrease morbidity and mortality from COPD through implementation and evaluation of effective programs for diagnosis and management.</li> <li>• To promote study into reasons for increasing prevalence of COPD including relationship with environment.</li> </ul>

	<ul style="list-style-type: none"> <li>To implement effective programs to prevent COPD.</li> </ul>
<b>TARGET POPULATION</b>	
<b>VHA/DOD (1999)</b>	<p>Veterans with COPD in both the outpatient and inpatient setting.</p> <p><i>Note: This guideline includes recommendations for patients with both chronic stable disease and patients with acute exacerbations of COPD. Recommendations concerning stable COPD are provided in <a href="#">Part I</a> of this synthesis.</i></p>
<b>ACP-ASIM/ACCP (2001)</b>	<p>Patients with acute exacerbations of COPD in the emergency department or inpatient setting.</p> <p><i>Note: Patients with stable COPD were not considered.</i></p>
<b>WHO/NHLBI (2001)</b>	<p>Individuals with COPD.</p> <p><i>Note: This guideline includes recommendations for patients with both chronic stable disease and patients with acute exacerbations of COPD. Recommendations concerning stable COPD are provided in <a href="#">Part I</a> of this synthesis.</i></p>
<b>INTENDED USERS</b>	
<b>VHA/DOD (1999)</b>	Physicians; Nurses; Nurse Practitioners; Physician Assistants; Respiratory Care Practitioners
<b>ACP-ASIM/ACCP (2001)</b>	Physicians; Respiratory Care Practitioners; Physician Assistants; Nurses
<b>WHO/NHLBI (2001)</b>	Physicians; Physician Assistants; Respiratory Care Practitioners; Nurse Practitioners; Nurses; Allied Health Care Practitioners; Public Health Departments
<b>INTERVENTIONS AND PRACTICES CONSIDERED</b>	
<b>VHA/DOD (1999)</b>	<p><i>Outpatient management of COPD</i></p> <ol style="list-style-type: none"> <li>Clinical assessment, including history, physical exam, spirometry, chest x-ray, laboratory tests, oximetry</li> <li>Evaluate for exacerbation</li> <li>Assessing severity of exacerbation (<i>See <a href="#">Part I</a> of this synthesis for specific interventions and practices for diagnosis and management of stable COPD</i>)</li> </ol> <p><i>Inpatient management of COPD</i></p> <ol style="list-style-type: none"> <li>Emergency department (cardiopulmonary resuscitation,</li> </ol>

	<p>mechanical ventilation)</p> <ol style="list-style-type: none"> <li>2. Clinical and laboratory evaluation</li> <li>3. Intensive care unit or hospital ward admission</li> <li>4. Pharmacotherapy <ul style="list-style-type: none"> <li>• Anticholinergics</li> <li>• Short-acting inhaled beta<sub>2</sub>-agonists (SAIBA)</li> <li>• Theophylline</li> <li>• Systemic steroids</li> <li>• Antibiotics</li> </ul> </li> <li>5. Oxygen therapy</li> <li>6. Discharge and follow-up</li> </ol>
<p><b>ACP-ASIM/ACCP (2001)</b></p>	<ol style="list-style-type: none"> <li>1. Risk stratification</li> <li>2. Diagnostic tests <ul style="list-style-type: none"> <li>• Chest x-ray</li> <li>• Spirometric testing</li> </ul> </li> <li>3. Therapeutic interventions <ul style="list-style-type: none"> <li>• Mucus clearance strategies</li> <li>• Bronchodilating agents</li> <li>• Corticosteroids</li> <li>• Antibiotics</li> <li>• Oxygen</li> <li>• Non-invasive mechanical ventilation</li> </ul> </li> </ol>
<p><b>WHO/NHLBI (2001)</b></p>	<p><i>Initial assessment/diagnosis</i></p> <p><i>Risk factor reduction</i></p> <ol style="list-style-type: none"> <li>1. Smoking prevention and cessation</li> <li>2. Occupational exposures</li> <li>3. Indoor/outdoor air pollution</li> </ol> <p><i>Management of stable COPD</i></p> <p><i>(Note: See <a href="#">Part I</a> of this synthesis for specific interventions and practices for diagnosis and management of stable COPD; see <a href="#">Part III</a> of this synthesis for specific interventions and practices for pulmonary rehabilitation.)</i></p> <p><i>Management of exacerbations</i></p> <ol style="list-style-type: none"> <li>1. Diagnosis and assessment of severity</li> <li>2. Home management <ul style="list-style-type: none"> <li>• Bronchodilator therapy</li> <li>• Glucocorticosteroids</li> <li>• Antibiotics</li> </ul> </li> <li>3. Emergency department or hospital management <ul style="list-style-type: none"> <li>• Pharmacotherapy</li> <li>• Oxygen therapy</li> </ul> </li> </ol>

	<ul style="list-style-type: none"> <li>• Mechanical ventilation</li> <li>• Hospital discharge and follow-up</li> </ul>
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**TABLE 2: COMPARISON OF RECOMMENDATIONS FOR ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)**

<i>Diagnosis and Initial Assessment</i>	
<b>Signs and symptoms of acute exacerbation</b>	
<b>VHA/DOD (1999)</b>	<p>An acute exacerbation of COPD is defined as an acute clinical deterioration in a patient's respiratory status due to a worsening of the underlying COPD. Symptoms and signs of acute exacerbation of COPD include:</p> <ol style="list-style-type: none"> <li>1. Increased dyspnea.</li> <li>2. Tachycardia.</li> <li>3. Increased cough.</li> <li>4. Increased sputum production.</li> <li>5. Change in sputum color or character.</li> <li>6. Accessory muscle use.</li> <li>7. Peripheral edema.</li> <li>8. Development of or increase in wheeze.</li> <li>9. Loss of alertness.</li> <li>10. Loss of energy.</li> <li>11. Fever.</li> <li>12. Increased respiratory rate.</li> <li>13. Decrease in FEV<sub>1</sub> or peak expiratory flow.</li> <li>14. Worsening of arterial blood gases or pulse oximetry.</li> <li>15. Chest tightness.</li> </ol>
<b>ACP-ASIM/ACCP (2001)</b>	<p>There is no widely accepted definition of acute exacerbation of COPD, but most published definitions encompass some combination of three clinical findings: worsening dyspnea, increase in sputum purulence, and increase in sputum volume.</p>
<b>WHO/NHLBI (2001)</b>	<p>Increased breathlessness is the main symptom of an exacerbation, and is often accompanied by wheezing and chest tightness, increased cough and sputum, change of the color and/or tenacity of sputum, and fever. Exacerbations may also be accompanied by a number of nonspecific complaints, such as malaise, insomnia, sleepiness, fatigue, depression, and confusion. A decrease in exercise tolerance, fever, and/or new radiological anomalies suggestive of pulmonary disease may herald a COPD exacerbation. An increase in sputum volume and purulence points to a bacterial cause, as does a prior history of chronic sputum production.</p>

	<b>Measurement of airflow limitation — Spirometry</b>
<b>VHA/DOD (1999)</b>	Measurement of peak expiratory flow rate and forced expiratory volume in 1 second (FEV <sub>1</sub> ) are optional. A decrease in FEV <sub>1</sub> or peak expiratory flow can be diagnostic of acute exacerbation.
<b>ACP-ASIM/ACCP (2001)</b>	For patients hospitalized with an acute exacerbation of COPD, acute spirometry should not be used to diagnose an exacerbation or to assess its severity.
<b>WHO/NHLBI (2001)</b>	Even simple lung function tests can be difficult for a sick patient to perform properly. In general, a PEF <100 L per minute or an FEV <sub>1</sub> <1.00 L indicates a severe exacerbation.
	<b>Assessing severity of exacerbation</b>
<b>VHA/DOD (1999)</b>	<p>Loss of alertness or a combination of two or more of the following parameters indicate a severe exacerbation:</p> <ul style="list-style-type: none"> <li>• Dyspnea at rest</li> <li>• Respiratory rate <math>\geq</math> 25 per minute</li> <li>• Heart rate <math>\geq</math> 110 per minute</li> <li>• Use of accessory muscles</li> </ul> <p>(See below for specific criteria for emergency ward, intensive care unit, or hospital admission.)</p>
<b>ACP-ASIM/ACCP (2001)</b>	Unlike the staging system for stable COPD, there are no standardized, validated grading systems for severity of an acute exacerbation. Probably the most commonly used system is that developed by Anthonisen and colleagues. In this system, patients with type 1 exacerbation (severe) have all three cardinal symptoms of acute exacerbation: worsening of dyspnea, increase in sputum purulence, and increase in sputum volume. Patients with type 2 exacerbation (moderate) exhibit two of the cardinal symptoms. Type 3 exacerbations (mild) have one of these clinical findings plus at least one of the following: an upper respiratory tract infection in the past 5 days, fever without other apparent cause, increased wheezing, increased cough, or a 20% increase in respiratory rate or heart rate above baseline.
<b>WHO/NHLBI (2001)</b>	Assessment of the severity of an acute exacerbation is based on the patients medical history before the exacerbation, symptoms, physical examination, lung function tests, arterial blood gas measurements, and other laboratory tests. The medical history should cover how long worsening or new symptoms have been present, the frequency and severity of breathlessness and coughing attacks, sputum volume and color, limitation of daily activities, and previous episodes/exacerbations and whether they required hospitalization, and the present treatment regimen. When

	<p>available, prior measurements of lung function and arterial blood gases are extremely useful for comparison with those made during the acute episode, as an acute change in these tests is more important than their absolute values. In patients with very severe COPD, the most important sign of severe exacerbation is a change in alertness of the patient and this signals a need for immediate evaluation in the hospital. (See below for specific criteria for hospital or intensive care unit admission.)</p>
	<p><b>Chest X-ray and Electrocardiography (ECG)</b></p>
<p><b>VHA/DOD (1999)</b></p>	<p><b>Outpatient management:</b>  In patients with evidence of respiratory infection, a white cell count and chest X-ray may be considered. Evidence of respiratory infection with a clear chest X-ray suggests that the exacerbation of COPD is due to purulent bronchitis. Antibiotic therapy should be considered.</p> <p>Patients with a clinical presentation and chest radiograph consistent with pneumonia should be considered for admission.</p> <p><b>Inpatient (emergency or hospital ward):</b>  Chest x-ray and ECG are indicated as part of the clinical and laboratory evaluation.</p>
<p><b>ACP-ASIM/ACCP (2001)</b></p>	<p>An admission chest radiography may be useful since it has been shown that up to 23% of patients admitted had changes in management related to findings on chest radiography. Chest radiography in patients visiting the emergency department may also be useful. To date, there is no evidence for or against the utility of chest radiography in the office setting.</p> <p>ECG: No recommendations offered.</p>
<p><b>WHO/NHLBI (2001)</b></p>	<p>Chest radiographs (posterior/anterior plus lateral) are useful in identifying alternative diagnoses that can mimic the symptoms of an exacerbation. Although the history and physical signs can be confusing, especially when pulmonary hyperinflation masks coexisting cardiac signs, most problems are resolved by the chest X-ray and ECG. An ECG aids in the diagnosis of right heart hypertrophy, arrhythmias, and ischemic episodes. Pulmonary embolism can be very difficult to distinguish from an acute exacerbation, especially in severe COPD, because right ventricular hypertrophy and large pulmonary arteries lead to confusing ECG and radiographic results. Spiral CT scanning and angiography, and perhaps specific D-dimer assays, are the best tools presently available for the diagnosis of pulmonary embolism in patients with COPD, but ventilation-perfusion scanning is of no value.</p>
	<p><b>Measurement of arterial blood gases</b></p>

<p><b>VHA/DOD (1999)</b></p>	<p>There is not a good relationship between spirometry and blood gases in COPD exacerbation, at least in Emergency Department (ED) patients; a PaO<sub>2</sub> less than 60 mmHg may be found in patients with a FEV<sub>1</sub> up to 54 percent of normal. For that reason, O<sub>2</sub> saturation should be obtained for patients with mild-to-moderate COPD exacerbations.</p> <p>Blood gases should be obtained to guide oxygen therapy in patients with known hypercapnia or where the status of CO<sub>2</sub> retention is unknown.</p> <p>Analysis of arterial blood gases is to be used initially in all cases when it is unknown whether the patient is a chronic CO<sub>2</sub> retainer and to determine acid-base status. Pulse oximetry, which should be continuously monitoring SaO<sub>2</sub>, is not sufficient until it is clear that the CO<sub>2</sub> level is not elevated or is stable and the acid-base status is known and is stable.</p> <p>Acceptable blood gases would include a PaO<sub>2</sub> close to 60 mmHg, a stable PaCO<sub>2</sub>, and a pH <math>\geq</math>7.25.</p>
<p><b>ACP-ASIM/ACCP (2001)</b></p>	<p>Indirect studies suggest that arterial blood gas analysis is helpful both in terms of gauging the severity of an exacerbation and in identifying patients currently in need of oxygen therapy and those potentially in need of mechanical ventilatory support.</p>
<p><b>WHO/NHLBI (2001)</b></p>	<p>In the hospital, measurement of arterial blood gases is essential to assess the severity of an exacerbation. A PaO<sub>2</sub> &lt; 8.0 kPa (60 mm Hg) and/or SaO<sub>2</sub> &lt; 90% when breathing room air indicate respiratory failure. In addition, a PaO<sub>2</sub> &lt; 6.7 kPa (50 mm Hg), PaCO<sub>2</sub> &gt; 9.3 kPa (70 mm Hg), and pH &lt; 7.30 point toward a life-threatening episode that needs ICU management.</p>
<p><b><i>Management of Acute Exacerbations General Management Considerations</i></b></p>	
	<p><b>Indications for outpatient/home management vs. inpatient management</b></p>
<p><b>VHA/DOD (1999)</b></p>	<p><b>Emergency department management:</b></p> <p>Loss of alertness or a combination of two or more of the following parameters indicate a severe exacerbation and suggest a need for referral to an emergency department.</p> <ol style="list-style-type: none"> <li>1. Dyspnea at rest.</li> <li>2. Respiratory rate <math>\geq</math> 25 per minute.</li> <li>3. Heart rate <math>\geq</math> 110 per minute.</li> <li>4. Use of accessory muscles.</li> </ol> <p><b>Intensive care unit (ICU) management:</b></p>

	<p>Any of the following would prompt admission to the ICU for closer observation and monitoring (adapted and modified from American Thoracic Society guidelines):</p> <ul style="list-style-type: none"> <li>• Severe dyspnea that responds inadequately to initial emergency room therapy.</li> <li>• Confusion, lethargy, or respiratory muscle fatigue.</li> <li>• Persistent or worsening hypoxemia despite supplemental O<sub>2</sub> or severe or worsening of respiratory acidosis (pH ≤ 7.30).</li> <li>• Required assisted mechanical ventilation, whether through means of tracheal intubation or noninvasive techniques.</li> </ul> <p><b>Hospital management</b></p> <p>Indications for hospitalization of patients with COPD (adapted and modified from American Thoracic Society guidelines):</p> <ol style="list-style-type: none"> <li>1. Patient has acute exacerbation plus one or more of the following: <ul style="list-style-type: none"> <li>• Inadequate response of symptoms to outpatient management.</li> <li>• Inability to walk between rooms (patient previously mobile).</li> <li>• Inability to eat or sleep due to dyspnea.</li> <li>• Conclusion by family and/or physician that patient cannot manage at home and supplementary home care resources are not immediately available.</li> <li>• A high-risk comorbid condition, pulmonary (e.g., pneumonia) or non pulmonary.</li> <li>• Prolonged, progressive symptoms before emergency department visit.</li> <li>• Altered mentation.</li> <li>• Worsening hypoxemia.</li> <li>• New or worsening hypercarbia.</li> </ul> </li> <li>2. Patient has new or worsening cor pulmonale unresponsive to outpatient management.</li> <li>3. A planned invasive surgical or diagnostic procedure requires analgesics or sedatives that may worsen pulmonary function.</li> <li>4. Comorbid conditions (e.g., steroid myopathy or vertebral compression fractures) have worsened pulmonary function.</li> </ol> <p>Other indications for hospitalization may apply to patients undergoing pulmonary rehabilitation.</p>
<p><b>ACP-ASIM/ACCP (2001)</b></p>	<p>No recommendations offered.</p> <p><i>Note: This guideline considers only inpatient management.</i></p>
<p><b>WHO/NHLBI</b></p>	<p><b>Home management:</b></p>

<p><b>(2001)</b></p>	<p>There is increasing interest in home care for end-stage COPD patients, although economic studies of home care services have yielded mixed results. A major outstanding issue is when to treat an exacerbation at home and when to hospitalize the patient.</p> <p><b>Hospital management:</b> Hospital assessment/admission should be considered for all patients who fit the criteria below:</p> <ul style="list-style-type: none"> <li>• Marked increase in intensity of symptoms, such as sudden development of resting dyspnea</li> <li>• Severe background COPD</li> <li>• Onset of new physical signs (e.g., cyanosis, peripheral edema)</li> <li>• Failure of exacerbation to respond to initial medical management</li> <li>• Significant comorbidities</li> <li>• Newly occurring arrhythmias</li> <li>• Diagnostic uncertainty</li> <li>• Older age</li> <li>• Insufficient home support</li> </ul> <p>Some patients need immediate admission to an ICU. ICU admission should be considered for all patients who fit the criteria below:</p> <ul style="list-style-type: none"> <li>• Severe dyspnea that responds inadequately to initial emergency therapy.</li> <li>• Confusion, lethargy, coma.</li> <li>• Persistent or worsening hypoxemia (PaO<sub>2</sub> &lt;6.7 kPa, 50 mm Hg), and/or severe/worsening hypercapnia (PaCO<sub>2</sub> &gt;9.3 kPa, 70 mm Hg), and/or severe/worsening respiratory acidosis (pH &lt;7.30) despite supplemental oxygen and noninvasive positive-pressure ventilation (NIPPV)</li> </ul> <p>Admission of patients with severe COPD exacerbations to intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment are available to identify and manage acute respiratory failure successfully.</p>
<p><b><i>Management of Acute Exacerbation Pharmacologic Treatment</i></b></p>	
	<p><b>Short-acting beta<sub>2</sub> agonists</b></p>
<p><b>VHA/DOD (1999)</b></p>	<p><b>Outpatient or inpatient management:</b> Selective beta<sub>2</sub>-adrenergic agonists (albuterol, metaproterenol, terbutaline) are first-line agents:</p> <ol style="list-style-type: none"> <li>1. Aerosolization using a low-volume nebulizer is generally the first mode used when the patient is severely dyspneic.</li> </ol>

	<ol style="list-style-type: none"> <li>2. After the patient has stabilized and can use the metered-dose inhaler (MDI), there is no difference between using an MDI with a spacer and nebulized aerosolization.</li> <li>3. An optimal dosing schedule of beta<sub>2</sub>-agonists cannot be suggested.</li> <li>4. Beta<sub>2</sub>-agonists should be titrated to maximal effect.</li> <li>5. Monitor closely for adverse effects (including ECG monitoring) of the larger-than-usual doses that are sometimes necessary to relieve airway obstruction.</li> </ol> <p>Selective beta<sub>2</sub>-agonists are less likely to cause tachycardia.</p> <p>Nebulizer aerosolization is used when the patient is severely dyspneic and can neither effectively breathe nor coordinate for effective MDI use. After the patient has stabilized and can use the MDI, there is no difference between using an MDI with a spacer compared with nebulized aerosolization. The patients skill with MDI should be evaluated by demonstration.</p>
<p><b>ACP-ASIM/ACCP (2001)</b></p>	<p>Inhaled short-acting beta<sub>2</sub>-agonists, such as albuterol, and anticholinergic bronchodilators, such as ipratropium, are equally efficacious in patients with acute exacerbations of COPD. They are also superior to all parenterally administered bronchodilators, including methylxanthines and sympathomimetic agents.</p> <p>There is no difference between using MDI plus spacer versus nebulization delivery systems. The choice of delivery system can be made on a patient to patient basis.</p>
<p><b>WHO/NHLBI (2001)</b></p>	<p><b>Home management:</b> Home management of COPD exacerbations involves increasing the dose and/or frequency of existing bronchodilator therapy. If not already used, an anticholinergic can be added until the symptoms improve. In more severe cases, high-dose nebulizer therapy can be given on an as-needed basis for several days and if a suitable nebulizer is available. However, long-term use of nebulizer therapy after an acute episode is not routinely recommended.</p> <p><b>Hospital management:</b> Short-acting inhaled beta<sub>2</sub>-agonists are usually the preferred bronchodilators for treatment of acute exacerbations of COPD. If a prompt response to these drugs does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the effectiveness of this combination is rather controversial.</p>
	<p><b>Inhaled anticholinergics</b></p>
<p><b>VHA/DOD (1999)</b></p>	<p><b>Outpatient or inpatient management:</b> Anticholinergic agents may be valuable as additive or single agents particularly if the patient is intolerant of beta<sub>2</sub>-agonist or</p>

	<p>has side effects, has significant coronary artery disease or severe left ventricular dysfunction.</p> <p>High-dose ipratropium bromide, although possibly effective, has not been studied in acute exacerbation of COPD. If the decision to use ipratropium is made, the following dose is suggested: 500 micrograms every six hours by nebulizer, or six to eight puffs every four hours by MDI with spacer.</p>
<b>ACP-ASIM/ACCP (2001)</b>	Inhaled anticholinergic bronchodilators or inhaled short-acting beta <sub>2</sub> -agonists are beneficial in the treatment of patients presenting to the hospital with acute exacerbation of COPD. Since the inhaled anticholinergic bronchodilators have fewer and more benign side effects, consider these agents first.
<b>WHO/NHLBI (2001)</b>	No recommendations offered for anticholinergics as monotherapy.
	<b>Combination therapy with inhaled anticholinergics and short-acting beta<sub>2</sub> agonists</b>
<b>VHA/DOD (1999)</b>	<p><b>Outpatient management:</b></p> <p>While the effect of ipratropium or a beta<sub>2</sub>-agonist are comparable in COPD exacerbation, the evidence that addition of ipratropium to a beta<sub>2</sub>-agonist regimen improves outcomes in moderate COPD exacerbation is not proven. However, since some patients may benefit from the combination, and the toxicity of ipratropium is low, it is reasonable to add ipratropium to a beta<sub>2</sub>-agonist regimen. This is especially the case in unmonitored patients in whom there may be concern about toxicity from high-dose SAIBA.</p>
<b>ACP-ASIM/ACCP (2001)</b>	Only after the initial bronchodilator is at maximum dose is the addition of a second inhaled bronchodilator beneficial.
<b>WHO/NHLBI (2001)</b>	If a prompt response to beta <sub>2</sub> -agonists does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the effectiveness of this combination is rather controversial.
	<b>Methylxanthines</b>
<b>VHA/DOD (1999)</b>	<p><b>Outpatient management:</b></p> <p>Limited evaluation of COPD exacerbation has not demonstrated a definitive role for introduction of theophylline in acute COPD exacerbations. Theophylline is unlikely to be indicated in moderate COPD exacerbations. If the patient is already taking theophylline, it would be prudent to measure a plasma theophylline concentration and, if low (less than 5 micrograms/ml), additional dosing can be given to achieve</p>

	<p>therapeutic levels (5 to 12 micrograms/ml).</p> <p><b>Inpatient management:</b>  There is inadequate evidence in the literature to recommend the routine use of theophylline or amce to exclude a benefit for selected patients. Toxicity occurs frequently in hospitalized patients and is associated with a prolonged stay. Clinicians who choose to use this agent must be thoroughly familiar with its metabolism, drug interactions, and toxicity.</p>
<b>ACP-ASIM/ACCP (2001)</b>	<p>In the treatment of patients with acute exacerbation of COPD methylxanthine bronchodilators are not a beneficial therapeutic option. The toxicity profile of the methylxanthine agents makes them potentially harmful.</p>
<b>WHO/NHLBI (2001)</b>	<p><b>Hospital management:</b>  Despite its widespread clinical use, aminophyllines role in the treatment of exacerbations of COPD remains controversial. Most studies of aminophylline have demonstrated minor improvements in lung volumes but also worsening of gas exchange and hypoxemia. In more severe exacerbations, addition of an oral or intravenous methylxanthine to the treatment can be considered. However, close monitoring of serum theophylline is recommended to avoid the side effects of these drugs.</p>
	<b>Corticosteroids</b>
<b>VHA/DOD (1999)</b>	<p><b>Outpatient management:</b>  Certain patients should be considered for systemic corticosteroid treatment. Indications for steroids in COPD exacerbation represent consensus based on expert opinion. Patient groups to consider include the following:</p> <ul style="list-style-type: none"> <li>• On oral steroid or on inhaled steroids.</li> <li>• Who recently stopped oral steroids.</li> <li>• Who previously responded to oral steroids.</li> <li>• With oxygen saturation less than 90%.</li> <li>• With peak expiratory flow less than 110 L/min.</li> <li>• Not responding to initial bronchodilator therapy.</li> </ul> <p>A typical oral dose is 0.6-0.8 mg/kg prednisone per day. Once the patient is stabilized, the dose should be tapered carefully, monitoring for relapse of the exacerbation. The goal should be to wean the patient off steroids. This may not be possible in some patients who should then be treated with the smallest effective dose ideally every other day.</p> <p><b>Inpatient management:</b>  Steroids should be given early in patients with acute exacerbation of COPD particularly in patients with severe underlying lung function and those with severe exacerbation.</p>

	<p>Studies demonstrating the benefits of corticosteroids in acute exacerbation involved a small number of patients and show small improvement in lung function. The recommend dose equivalents of at least 0.5 mg/kg of methylprednisolone every 6 hours for at least 3 days.</p>
<b>ACP-ASIM/ACCP (2001)</b>	<p>In the treatment of patients presenting to the hospital with moderate or severe acute exacerbation of COPD, systemic corticosteroids given for up to 2 weeks are beneficial in patients who are not receiving long-term therapy with oral steroids.</p> <p>Inhaled steroids are not appropriate in the treatment of acute exacerbation of COPD.</p>
<b>WHO/NHLBI (2001)</b>	<p><b>Home management:</b> Systemic glucocorticosteroids are beneficial in the management of acute exacerbations of COPD. They shorten recovery time and help to restore lung function more quickly. They should be considered in addition to bronchodilators if the patients baseline FEV<sub>1</sub> is less than 50% predicted. A dose of 40 mg of prednisolone per day for 10 days is recommended.</p> <p><b>Hospital management:</b> Oral or intravenous glucocorticosteroids are recommended as an addition to bronchodilator therapy, (plus eventually antibiotics and oxygen therapy) in the hospital management of acute exacerbations of COPD. The exact dose that should be given is not known, but high doses are associated with a significant risk of side effects. 30 to 40 mg of oral prednisolone daily for 10 to 14 days is a reasonable compromise between efficacy and safety Prolonged treatment does not result in a greater efficacy and increases the risk of side effects.</p>
	<b>Antibiotics</b>
<b>VHA/DOD (1999)</b>	<p><b>Outpatient management:</b> In patients with evidence of respiratory infection, a white cell count and chest x-ray may be considered. Evidence of respiratory infection with a clear chest X-ray suggests that the exacerbation of COPD is due to purulent bronchitis. Antibiotic therapy should be considered. Patients with a clinical presentation and chest radiograph consistent with pneumonia should be considered for admission. Drug interaction should be considered if patient is undertreatment with theophylline.</p> <p><b>Inpatient management:</b> Many patients with acute exacerbation do well without antibiotic treatment. However, for patients whose exacerbation is associated with changes in sputum (quality, volume, color) or fever, antibiotics are a reasonable treatment option. Patients who are older than 60 years or have severe underlying lung function are more likely to benefit from the use of antibiotics. Usually, the older, less expensive antibiotics, such as</p>

	<p>amoxicillin, trimethoprim-sulfamethoxazole, and doxycycline, will suffice. However, the choice may be affected by the history of exacerbation in the individual patient and by the pattern of microbial resistance found in the community. It is important to keep the possibility of drug interactions in mind when selecting antibiotics. This should be a consideration for any patient on theophylline.</p>
<b>ACP-ASIM/ACCP (2001)</b>	<p>In patients with severe exacerbations of COPD, initial narrow-spectrum antibiotics are reasonable first-line agents. The superiority of newer, more broad-spectrum antibiotics has not been established.</p> <p>Randomized, placebo-controlled trials favored amoxicillin, trimethoprim-sulfamethoxazole, and tetracycline. Most of these studies were done before the emergence of multidrug-resistant organisms, particularly <i>Streptococcus pneumoniae</i>. To date, however, no randomized, placebo-controlled trials have proved the superiority of newer broad-spectrum antibiotics in acute exacerbations of COPD. The trials also did not include nursing home residents or recently hospitalized patients.</p>
<b>WHO/NHLBI (2001)</b>	<p><b>Home or hospital management:</b> Antibiotics are only effective when patients with worsening dyspnea and cough also have increased sputum volume and purulence (Evidence B). The choice of agents should reflect local patterns of antibiotic sensitivity among <i>Streptococcus pneumoniae</i>, <i>Haemophilis influenzae</i>, and <i>Moraxella catarrhalis</i>.</p>
<p><b>Management of Acute Exacerbation Non-pharmacologic Treatment</b></p>	
	<b>Oxygen</b>
<b>VHA/DOD (1999)</b>	<p><b>Outpatient management:</b> If ambulatory facilities are available, oxygen should be given to keep O<sub>2</sub> saturation ≥ 90 percent while the patient receives more aggressive bronchodilator therapy. In some centers this may require Emergency Department management. Blood gases should be obtained to guide oxygen therapy in patients with known hypercapnea or where the status of CO<sub>2</sub> retention is unknown.</p> <p>Patients who are stabilized after aggressive drug therapy but continue to have hypoxemia may require outpatient oxygen therapy at least on a temporary basis. Blood gases should be checked or oximetry performed in one month or soon thereafter when the patient is stable to determine the need for continued long-term oxygen therapy.</p> <p><b>Inpatient management:</b> The goal of oxygen therapy is to optimize oxygenation and</p>

	<p>minimize respiratory acidosis, if present. Thus, all patients presenting with acute exacerbation of COPD should receive oxygen by Venturi mask (24 to 35 percent), which delivers a precise oxygen concentration, until the PaCO<sub>2</sub> is determined. The lowest fraction of inspired oxygen (FiO<sub>2</sub>) resulting in an SaO<sub>2</sub> of 90 percent is optimal. The nasal cannula is to be avoided initially because of its inability to deliver a precise FiO<sub>2</sub>. Arterial blood gases should be obtained initially and SaO<sub>2</sub> should be monitored continuously. If a ventilator is used in the emergency room, the initial FiO<sub>2</sub> setting should be 1.0.</p>
<p><b>ACP-ASIM/ACCP (2001)</b></p>	<p>Oxygen, with caution, in hypoxemic patients is a beneficial therapeutic option in the treatment of patients presenting to the hospital with moderate or severe acute exacerbations of COPD.</p> <p>Ample evidence shows that oxygen therapy provides important benefits to inpatients with acute exacerbations of COPD and hypoxemia. The major concern with the administration of this therapy is the risk for resultant hypercarbia and respiratory failure. In three observational studies, most patients with acute exacerbations of COPD developed hypercarbia after oxygen administration (FiO<sub>2</sub> ranged from 24% to 28%). These studies seem to suggest that the relationship between pH and PO<sub>2</sub> at presentation is a good predictor of the risk for hypercarbia and subsequent failure.</p>
<p><b>WHO/NHLBI (2001)</b></p>	<p><b>Hospital management:</b> Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Adequate levels of oxygenation (PaO<sub>2</sub> &gt; 8.0 kPa, 60 mm Hg, or SaO<sub>2</sub> &gt; 90%) are easy to achieve in uncomplicated exacerbations, but CO<sub>2</sub> retention can occur insidiously with little change in symptoms. Once oxygen is started, arterial blood gases should be checked 30 minutes later to ensure satisfactory oxygenation without CO<sub>2</sub> retention or acidosis. Venturi masks are more accurate sources of controlled oxygen than are nasal prongs but are more likely to be removed by the patient.</p>
<p><b>Mechanical ventilation and endotracheal intubation</b></p>	
<p><b>VHA/DOD (1999)</b></p>	<p><b>Inpatient management:</b> Decision to initiate mechanical ventilation and tracheal intubation can be made prior to obtaining arterial blood gases. Advance directives should be considered prior to initiating these supportive measures.</p> <p>Indications for mechanical ventilation (invasive or noninvasive/bilevel positive airway pressure) include:</p> <ul style="list-style-type: none"> <li>• Severe respiratory or combined respiratory and metabolic acidosis.</li> <li>• Sustained respiratory rate ≥ 40 per minute.</li> <li>• Abnormal breathing pattern suggestive of increased</li> </ul>

	<p>respiratory workload and/or respiratory muscle fatigue.</p> <ul style="list-style-type: none"> <li>• Depressed mental status.</li> <li>• Severe hypoxemia.</li> </ul> <p>Indications for tracheal intubation include:</p> <ul style="list-style-type: none"> <li>• Suspected airway obstruction.</li> <li>• Depressed mental status.</li> <li>• High risk of gastropulmonary reflux and aspiration.</li> <li>• Difficulty managing secretions.</li> </ul>
<p><b>ACP-ASIM/ACCP (2001)</b></p>	<p>In the treatment of patients presenting to the hospital with moderate or severe acute exacerbation of COPD, noninvasive positive-pressure ventilation (NIPPV) administered under the supervision of a trained physician is a beneficial therapeutic option.</p> <p>NIPPV is frequently used in the inpatient management of patients with acute exacerbations of COPD. It not only improves ventilation and decreases PCO<sub>2</sub> levels but, in many instances, is also a means of avoiding intubation. In five randomized, controlled trials and five observational studies, NPPV was a beneficial support strategy and decreased the likelihood of respiratory failure requiring invasive mechanical ventilation. Some data show that NPPV might improve survival of patients with acute exacerbations of COPD. These conclusions, however, are weakened by issues of study design, such as unclear selection criteria for patients receiving therapy, and the uncertain number of patients who were screened but excluded from the trials. Further studies are needed to provide information on which patients would benefit most from this intervention.</p>
<p><b>WHO/NHLBI (2001)</b></p>	<p><b>Hospital management:</b>  <u>Noninvasive intermittent positive pressure ventilation (NIPPV)</u>  NIPPV has been studied in many uncontrolled and five randomized controlled trials in acute respiratory failure. The studies show consistently positive results with success rates of 80-85%. Taken together they provide evidence that NIPPV increases pH, reduces PaCO<sub>2</sub>, reduces the severity of breathlessness in the first 4 hours of treatment, and decreases the length of hospital stay. More importantly, mortality - or its surrogate, intubation rate - is reduced by this intervention. However, NIPPV is not appropriate for all patients.</p> <p>Selection and Exclusion Criteria for NIPPV:  <i>Selection criteria (at least 2 should be present)</i></p> <ul style="list-style-type: none"> <li>• Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion.</li> <li>• Moderate to severe acidosis (pH 7.30 - 7.35) and</li> </ul>

	<p>hypercapnia (Pa CO<sub>2</sub> &gt; 6.0 - 8.0 kPa, 45 - 60 mmHg).</p> <ul style="list-style-type: none"> <li>• Respiratory frequency 25 breaths per minute.</li> </ul> <p><i>Exclusion criteria (any may be present)</i></p> <ul style="list-style-type: none"> <li>• Respiratory arrest.</li> <li>• Cardiovascular instability (hypotension, arrhythmias, myocardial infarction).</li> <li>• Somnolence, impaired mental status, uncooperative patient.</li> <li>• High aspiration risk; viscous or copious secretions.</li> <li>• Recent facial or gastroesophageal surgery.</li> <li>• Craniofacial trauma, fixed nasopharyngeal abnormalities.</li> <li>• Burns.</li> <li>• Extreme obesity.</li> </ul> <p><u>Invasive Mechanical Ventilation</u>  Patients who show impending acute respiratory failure and those with life-threatening acid-base status abnormalities and/or altered mental status despite aggressive pharmacologic therapy are likely to be the best candidates for invasive (conventional) mechanical ventilation. The three ventilatory modes most widely used are assisted-control ventilation, and pressure support ventilation alone or in combination with intermittent mandatory ventilation.</p> <p><i>Indications for Invasive Mechanical Ventilation:</i></p> <ul style="list-style-type: none"> <li>• Severe dyspnea with use of accessory muscles and paradoxical abdominal motion.</li> <li>• Respiratory frequency &gt;35 breaths per minute.</li> <li>• Life-threatening hypoxemia (PaO<sub>2</sub> &lt;5.3 kPa, 40 mmHg or PaO<sub>2</sub>/FiO<sub>2</sub>* &lt;200 mmHg).</li> <li>• Severe acidosis (pH &lt;7.25) and hypercapnia (PaCO<sub>2</sub> &gt;8.0 kPa, 60 mmHg).</li> <li>• Respiratory arrest.</li> <li>• Somnolence, impaired mental status.</li> <li>• Cardiovascular complications (hypotension, shock, heart failure).</li> <li>• Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion).</li> <li>• NIPPV failure (or exclusion criteria [see above]).</li> </ul> <p>* FiO<sub>2</sub>: Fractional concentration of oxygen in dry inspired gas</p>
<p><b>Management of Acute Exacerbation Hospital Discharge and Follow-up</b></p>	
	<p><b>Discharge Criteria</b></p>

<p><b>VHA/DOD (1999)</b></p>	<p><b>Outpatient management:</b></p> <p>The following should be considered in evaluating the possibility of discharge:</p> <ol style="list-style-type: none"> <li>1. Patient clinical condition has improved. Evidence of improvement of COPD exacerbation includes: <ul style="list-style-type: none"> <li>• Decrease in cough, sputum production or dyspnea.</li> <li>• Decrease in respiratory rate.</li> <li>• Decrease in heart rate.</li> <li>• Increase in function and endurance.</li> </ul> </li> <li>2. Patient has adequate support system at home.</li> <li>3. Patient is able to continue necessary therapy at home (e.g., oxygen supply).</li> </ol> <p><b>Inpatient management:</b></p> <p>Discharge criteria for patients with acute exacerbation of COPD (adapted and modified from American Thoracic Society guidelines):</p> <ol style="list-style-type: none"> <li>1. Features of the severe exacerbation are resolved.</li> <li>2. Anticipated need for inhaled bronchodilators is not more frequent than every 4 hours and the patient is on oral medication.</li> <li>3. Reversible component of airway obstruction, if present, is under stable control.</li> <li>4. Patient or caregiver understands appropriate use of medications.</li> <li>5. Follow-up and home care arrangements have been completed (e.g., visiting nurse, oxygen delivery, meal provisions).</li> <li>6. Patient, family, and physicians are confident that the patient can manage successfully.</li> </ol>
<p><b>ACP- ASIM/ACCP (2001)</b></p>	<p>No recommendations offered.</p>
<p><b>WHO/NHLBI (2001)</b></p>	<p>Insufficient clinical data exist to establish the optimal duration of hospitalization for acute exacerbations of COPD. Consensus and limited data support the discharge criteria listed below:</p> <ul style="list-style-type: none"> <li>• Inhaled beta<sub>2</sub>-agonst therapy is required no more frequently than every 4 hrs.</li> <li>• Patient, if previously ambulatory, is able to walk across room.</li> <li>• Patient is able to eat and sleep without frequent awakening by dyspnea.</li> <li>• Patient has been clinically stable for 12-24 hrs.</li> </ul>

	<ul style="list-style-type: none"> <li>• Arterial blood gases have been stable for 12-24 hrs.</li> <li>• Patient (or home caregiver) fully understands correct use of medications.</li> <li>• Follow-up and home care arrangements have been completed (e.g., visiting nurse, oxygen delivery, meal provisions).</li> <li>• Patient, family, and physician are confident patient can manage successfully.</li> </ul>
	<b>Follow-up</b>
<b>VHA/DOD (1999)</b>	<p><b>Outpatient management:</b></p> <ol style="list-style-type: none"> <li>1. Once the patient is stabilized, with improvement in the level of function, reduce intensity of the bronchodilator regimen down to the usual level of treatment over the course of a few days.</li> <li>2. Tapering of corticosteroids depends on the prior history of use and tapering, but often is done over one to two weeks. This can be done in consultation with the primary care provider.</li> <li>3. The provider should see the patient soon to ensure that the course of action is appropriate and for consideration of any further therapy such as smoking cessation, or changes in pharmacotherapy in view of the recent exacerbation.</li> </ol>
<b>ACP-ASIM/ACCP (2001)</b>	No recommendations offered.
<b>WHO/NHLBI (2001)</b>	<p>Items to include in a follow-up assessment 4 to 6 weeks after discharge from the hospital are listed below:</p> <ul style="list-style-type: none"> <li>• Ability to cope in usual environment.</li> <li>• Measurement of FEV<sub>1</sub>.</li> <li>• Reassessment of inhaler technique.</li> <li>• Understanding of recommended treatment regimen.</li> <li>• Need for long-term oxygen therapy and/or home nebulizer (for patients with severe COPD).</li> </ul> <p>Thereafter, follow-up is the same as for stable COPD, including supervising smoking cessation, monitoring the effectiveness of each drug treatment, and monitoring changes in spirometric parameters.</p> <p>If hypoxemia developed during the exacerbation, arterial blood gases should be rechecked at discharge and at the follow-up visit. If the patient remains hypoxemic, long-term oxygen therapy should be instituted. Decisions about continuous domiciliary oxygen based on the severity of the acute</p>

	hypoxemia during an exacerbation are frequently misleading.
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<b>TABLE 3: BENEFITS AND HARMS</b>	
	<b>BENEFITS</b>
<b>VHA/DOD (1999)</b>	<p><i>Overall</i></p> <ul style="list-style-type: none"> <li>• Effective treatment of COPD may result in improvement of clinical outcomes.</li> </ul> <p><i>Specific</i></p> <ul style="list-style-type: none"> <li>• <i>Pharmacotherapy.</i> Appropriate use of medications for asthma or COPD may alleviate symptoms, increase exercise tolerance, improve pulmonary function, and improve quality of life.</li> <li>• <i>Antibiotic treatment in the patient with acute exacerbation of COPD and evidence of respiratory infection.</i> A recent meta-analysis of nine randomized, placebo-controlled studies suggest a small benefit from antibiotic treatment. Antibiotic therapy may be of greater importance in preventing deterioration rather than expediting improvement in outpatients with COPD exacerbation. Mild COPD exacerbations may not benefit from antibiotics.</li> </ul>
<b>ACP-ASIM/ACCP (2001)</b>	<p><i>Overall</i></p> <ul style="list-style-type: none"> <li>• To improve the care that patients receive by identifying efficacious and inefficacious treatment strategies.</li> <li>• To reduce the number and severity of annual exacerbations.</li> </ul> <p><i>Specific</i></p> <ul style="list-style-type: none"> <li>• Noninvasive positive-pressure ventilation (NPPV) is a beneficial support strategy that decreases risk for invasive mechanical ventilation and possibly improves survival in selected hospitalized patients with respiratory failure</li> </ul>
<b>WHO/NHLBI (2001)</b>	<p><i>Overall</i></p> <ul style="list-style-type: none"> <li>• COPD prevention</li> <li>• The goals of effective COPD management are to: <ul style="list-style-type: none"> <li>• Prevent disease progression</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>• Relieve symptoms</li> <li>• Improve exercise tolerance</li> <li>• Improve health status</li> <li>• Prevent and treat complications</li> <li>• Prevent and treat exacerbations</li> <li>• Reduce mortality</li> </ul>
	<b>HARMS</b>
<p><b>VHA/DOD (1999)</b></p>	<p><i>Short-acting inhaled beta<sub>2</sub>-agonists (SAIBA)</i>  Inhaled beta<sub>2</sub>-agonists may cause tremor, increased heart rate, insomnia, restlessness, hypokalemia, or a paradoxical reduction in arterial oxygenation.</p> <p><i>Inhaled anticholinergic agent (i.e., ipratropium)</i>  Inhaled ipratropium may cause dry mouth or increased heart rate, or exacerbate glaucoma, benign prostatic hypertrophy or other conditions potentially worsened by the drugs anti-cholinergic activity.</p> <p><i>Steroids, oral and inhaled</i>  Adverse effects of oral corticosteroids are numerous and include: hypertension, hyperglycemia, weight gain, immunosuppression, skin thinning, personality, purpura, mental status changes, depression, glaucoma, cataracts, and adrenal suppression. Patients requiring long-term steroids should be evaluated for risk of osteoporosis and preventive measures instituted, such as calcium and vitamin D supplements, weight-bearing exercise and hormone replacement therapy if appropriate.</p> <p>Adverse effects of inhaled corticosteroids include oral candidiasis, hoarseness, and possible adrenal suppression at high doses.</p> <p><i>Theophylline</i>  Theophylline has a narrow therapeutic index, with the potential for dose related adverse reactions that include insomnia, anxiety, nausea, vomiting, tremor, arrhythmias, delirium, seizures, and death.</p> <p>Attempts to withdraw theophylline, even at lower levels, should be done cautiously, since deterioration in pulmonary function and exercise performance may occur.</p>
<p><b>ACP-ASIM/ACCP (2001)</b></p>	<p><i>Bronchodilators.</i> Adverse effects of bronchodilators vary. The side effects of ipratropium bromide are generally fewer and milder. Three randomized, controlled trials did not report any adverse effects with ipratropium bromide. Other effects include increased incidence of tremors and dry mouth and urinary retention when used in combination with albuterol. The adverse effects of albuterol include tremors, headache, nausea, vomiting, and palpitations. Adverse cardiovascular effects, such as changes in</p>

	<p>heart rate, blood pressure, and electrocardiography tracings, are also possible but rare. Adverse effects associated with theophylline include nausea, vomiting, headache, arrhythmias, and seizures. The effects are more significant among patients with higher levels of theophylline.</p> <p><i>Corticosteroids.</i> Hyperglycemia was the most common adverse effect associated with systemic corticosteroids for acute exacerbation of COPD. In the Systemic Corticosteroids in Chronic Obstructive Pulmonary Disease Exacerbations (SCCOPE) trial, two thirds of hyperglycemic episodes requiring treatment occurred in patients who were known to have diabetes mellitus. Nearly all episodes occurred in the first 30 days.</p> <p><i>Oxygen Therapy.</i> The major concern for most clinicians administering oxygen therapy to patients with acute exacerbations of COPD is that oxygen supplementation will lead to hypercarbia and subsequent respiratory failure.</p>
<p><b>WHO/NHLBI (2001)</b></p>	<p><i>Beta<sub>2</sub>-agonists.</i> Stimulation of beta<sub>2</sub>-receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in very susceptible patients, although this appears to be a remarkably rare event with inhaled therapy. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of beta<sub>2</sub>-agonists, whatever the route of administration, and this limits the dose that can be tolerated.</p> <p>Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics, and oxygen consumption can be increased under resting conditions, these metabolic effects show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO<sub>2</sub> occur after administration of both short- and long-acting beta<sub>2</sub>-agonists, but the clinical significance of these changes is doubtful. Despite the concerns raised some years ago, further detailed study has found no association between beta<sub>2</sub>-agonist use and an accelerated loss of lung function or increased mortality in COPD.</p> <p><i>Anticholinergics.</i> Anticholinergic drugs, such as ipratropium bromide, are poorly absorbed, which limits the troublesome systemic effects seen with atropine. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal relationship. A bitter, metallic taste is reported by some patients using ipratropium.</p> <p><i>Methylxanthines.</i> Toxicity is dose related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given. Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include the development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal</p>

	<p>convulsions (which can occur irrespective of prior epileptic history). More common and less dramatic side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum theophylline. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental).</p> <p><i>Oral Glucocorticosteroids.</i> A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced COPD.</p> <p><i>Invasive Mechanical Ventilation.</i> Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation.</p>
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**GUIDELINE CONTENT COMPARISON**

Veterans Health Administration/Department of Veterans Affairs (VHA/DOD), American College of Physicians-American Society of Internal Medicine/American College of Chest Physicians (ACP-ASIM/ACCP), and World Health Organization/National Heart, Lung, and Blood Institute (WHO/NHLBI) present recommendations for management of acute exacerbations of chronic obstructive pulmonary disease (COPD) and provide explicit reasoning behind their judgments. Both VHA/DOD and WHO/NHLBI identify the type of supporting evidence for selected recommendations. The reader is directed to the original guidelines for the evidence grades for specific recommendations. Although ACP-ASIM/ACCP does not specifically state the type of supporting evidence for individual recommendations, their guideline considered the best available evidence for each subtopic selected for analysis.

As mentioned in the introduction above, the scope and format of the guidelines vary. The VHA/DOD guideline (with accompanying clinical algorithms) is expressed in 10 modules, divided into two major sections: outpatient management and inpatient (emergency room and hospital ward) interventions. The guideline addresses diagnosis, assessment, pharmacotherapy, and non-pharmacologic therapy (e.g. oxygen therapy and mechanical ventilation) in patients with stable disease and in patients with acute exacerbation of COPD. The VHA/DOD guideline also provides recommendations for management of air travel and insomnia in COPD and for preoperative evaluation and management.

The ACP-ASIM/ACCP guideline, on the other hand, applies only to acute exacerbations of COPD in the emergency department or inpatient setting. This guideline presents the available evidence on risk stratification for relapse and 6-month mortality rates, diagnostic testing for acute exacerbations of COPD, and current treatment options (both pharmacologic and non-pharmacologic) for acute exacerbations.

The WHO/NHLBI guideline differs from the other guidelines in its global perspective and in its emphasis on prevention strategies. This guideline presents a COPD management plan with four components: (1) assessment and monitoring of disease, (2) reduction of risk factors, (3) management of stable COPD, and (4) management of exacerbations. The WHO/NHLBI guideline also differs from the other two guidelines in including recommendations for pulmonary rehabilitation and surgical treatment of COPD.

## **Areas of Agreement**

### *Definition of Acute Exacerbation*

Although there is some difference among the guidelines in the specific symptoms noted for acute exacerbation of COPD, all three guidelines recognize worsening dyspnea, increase in sputum purulence, and increase in sputum volume as cardinal symptoms of acute exacerbation.

### *Assessing severity of exacerbation*

ACP-ASIM/ACCP acknowledges in its guideline that there is no standardized, clinically validated system for staging the severity of acute exacerbation of COPD. Thus, the severity is assessed by changes in the severity of symptoms, especially dyspnea and sputum color and volume. Both VHA/DOD and WHO/NHLBI state that loss of alertness is an indication of severe exacerbation requiring hospitalization.

### *Chest X-ray and Electrocardiography (ECG)*

All three guidelines recommend chest x-ray in the initial evaluation of patients with suspected acute exacerbation. Both VHA/DOD and WHO/NHLBI also recommend ECG.

### *Measurement of arterial blood gases*

The three guideline groups are in agreement that arterial blood gas analysis is important both to assess severity of acute exacerbations and to gauge the need for oxygen therapy or ventilatory support.

### *Indications for hospital management*

Both VHA/DOD and WHO/NHLBI agree that certain patients require immediate hospitalization or even admission to intensive care units (ICUs). Criteria for ICU management include severe dyspnea that does not respond to initial emergency room management; severe confusion, lethargy, or coma; persistent or worsening hypoxemia, or need for assisted mechanical ventilation. Hospital admission is indicated for significant worsening of symptoms, failure of outpatient management, significant comorbidities, and inadequate home support.

### *Combination therapy with inhaled anticholinergics and short-acting beta<sub>2</sub> agonists*

All three guidelines recommend combination therapy with inhaled anticholinergic and short-acting beta<sub>2</sub> agonists if a patient fails to respond to initial single-agent therapy. The guidelines also acknowledge that the evidence for the effectiveness of this combination remains controversial. Both VHA/DOD and WHO/NHLBI recommend the use of short-acting inhaled beta<sub>2</sub>-adrenergic agonists as first-line agents for the treatment of patients with acute exacerbation of COPD. ACP-ASIM/ACCP recommends inhaled

anticholinergic bronchodilators be considered first since these agents have fewer and more benign side effects than inhaled short-acting beta<sub>2</sub> agonists.

#### *Use of methylxanthines*

The guidelines are in general agreement that methylxanthines (theophylline, aminophylline) cannot be routinely recommended in patients with acute exacerbation of COPD because of their potential toxicity. Monitoring of serum theophylline levels is recommended if clinicians choose to use these agents.

#### *Use of systemic corticosteroids*

VHA/DOD, ACP-ASIM/ACCP, and WHO/NHLBI agree that systemic corticosteroids are beneficial in hospitalized patients with acute exacerbation. All three organizations provide guidance on duration of steroid treatment. For inpatient management of acute COPD exacerbations, VHA/DOD recommends treatment with corticosteroids for at least three days. ACP-ASIM states that systemic corticosteroids be given for up to two weeks in patients who are not receiving long-term therapy with oral steroids. WHO/NHLBI states that a ten to fourteen day course of oral prednisolone is reasonable. VHA/DOD and WHO/NHLBI also recommended systemic steroids for outpatient management. Steroids should be given in addition to bronchodilator therapy.

#### *Use of antibiotics*

There is general agreement among all three guidelines that antibiotics are beneficial in patients with severe exacerbation, i.e. those with increased sputum volume and purulence. Benefits of antibiotics are less clear in patients without severe exacerbation. VHA/DOD and ACP-ASIM/ACCP both recommend use of older antibiotics such as amoxicillin, trimethoprim-sulfamethoxazole, and tetracyclines for treatment, although VHA/DOD acknowledges the need to address community patterns of resistance as well as individual patient history. WHO/NHLBI states that the choice of antibiotic should reflect local patterns of sensitivity to common respiratory pathogens.

#### *Oxygen therapy*

The guidelines are unanimous in their recommendations for oxygen therapy in all patients with acute exacerbation and hypoxemia. They also recommend blood gas monitoring to guard against hypercarbia and subsequent respiratory failure.

#### *Mechanical ventilation*

Noninvasive mechanical ventilation is recommended by all three guidelines for patients with severe exacerbations to prevent respiratory failure. Use of noninvasive methods can reduce the need for intubation. WHO/NHLBI also provides explicit indications for the use of invasive mechanical ventilation.

#### *Discharge criteria*

VHA/DOD and WHO/NHLBI are in general agreement on the discharge criteria for patients with acute exacerbation of COPD. These include stability of the patient's condition, need for bronchodilators not more frequent than every 4 hours, and follow-up and home care arrangements completed. ACP-ASIM/ACCP does not offer any recommendations regarding discharge criteria for patients with acute exacerbation of COPD.

### **Areas of Differences**

#### *Use of bronchodilators*

There is some disagreement among the guidelines on the choice of first-line bronchodilators for patients with acute exacerbation. All three groups agree that both short-acting beta<sub>2</sub>-agonists and anticholinergics are effective bronchodilators; however, ACP-ASIM/ACCP recommends that inhaled anticholinergics be used first because of their more benign side effect profile. VHA/DOD and WHO/NHLBI, on the other hand, recommend short-acting inhaled beta<sub>2</sub> agonists. VHA/DOD recommends the use of inhaled anticholinergic agents as either additive or single agents, whereas WHO/NHLBI does not offer any recommendations for the use of anticholinergic monotherapy for patients with acute exacerbation of COPD.

#### *Measurement of airflow limitation — spirometry*

Guidelines differ in their recommendations for use of spirometry in diagnosing acute exacerbation. ACP-ASIM/ACCP states that spirometry should not be used in patients with acute exacerbation. This recommendation is based on observational studies showing that spirometry performed at presentation or during treatment was not useful in judging severity or guiding management of patients during acute exacerbation. Furthermore, FEV<sub>1</sub> showed no significant correlation with PO<sub>2</sub> and only a weak correlation with PCO<sub>2</sub>. Both VHA/DOD and WHO/NHLBI, on the other hand, state that spirometry can be useful in diagnosing acute exacerbation. VHA/DOD bases its recommendations for optional spirometry on standards developed by the American Thoracic Society and European Respiratory Society. Nevertheless, WHO/NHLBI acknowledges that even simple lung function tests can be difficult for sick patients, and VHA/DOD acknowledges that there is not a good relationship between spirometry and blood gases in acute exacerbations.

*Updates in Progress:* The organizations that are represented in this Synthesis are not in the process of updating their guidelines.

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