INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States, accounting for approximately 110,000 deaths per year. COPD is a slowly progressive condition, with symptoms typically arising around age 50 to 60 years. As the U.S. population of current and former smokers ages, the prevalence of this disease is expected to climb [1]. More than 16 million adults in the United States currently have the disease. COPD accounts for 16,367,000 office visits, 500,000 hospitalizations, and direct health care costs of $18 billion annually [2].

The term COPD refers to a group of disorders characterized by permanent or minimally reversible expiratory airflow limitation, including chronic bronchitis and emphysema. Between 85% and 90% of all cases of COPD are caused by smoking; other causative factors include genetic factors (including alpha1-antitrypsin deficiency), passive smoking, occupational exposures, air pollution, and, possibly, hyperresponsive airways. Patients with chronic bronchitis have persistent airway inflammation that leads to dyspnea and a productive cough. Chronic bronchitis is clinically defined as the presence of a recurrent productive cough for 3 months of the year in 2 consecutive years [3]. Emphysema is a destructive process that involves the lung parenchyma. In emphysema, the elastic fibers of the alveoli and distal air spaces that provide the elastic recoil powering expiration are destroyed. In both the chronic bronchitis and emphysema variants of COPD, patients encounter a similar constellation of symptoms and a collection of derangements in respiratory function, including cough, sputum production, dyspnea, airflow limitation, and impaired gas exchange.

A common feature of COPD is the development of episodes of acute worsening of airway function. Often termed “flares” or acute exacerbations of COPD, these episodes are major causes of morbidity and mortality in this disease process. In the natural history of COPD, exacerbations occur more frequently as the disease progresses. In managing patients with acute exacerbations, physicians must first exclude other possible causes of the patient’s symptoms and then initiate multi-agent therapy to provide relief of symptoms.

CASE STUDY

Initial Presentation

A 58-year-old man presents to his primary care physician’s office with a complaint of increasing shortness of breath and dyspnea on exertion as well as wheezing and increased cough and sputum production, progressing over a 1-week period.

History

The patient does not report experiencing fever, chills, night sweats, weight loss, arthralgias or myalgias, or nausea or vomiting. He has no chest pain or pressure, orthopnea, or paroxysmal nocturnal dyspnea. His cough is more productive of sputum, but the sputum has not changed in quality. Prior to the start of his symptoms, he visited with a friend who had a cold. He does have rhinorrhea with clear drainage and nasal congestion.

The patient’s past medical history is significant for COPD diagnosed 5 years ago and for hypertension. His baseline oxygen saturation on room air measured by pulse oximetry (SpO2) is 91%, and baseline forced expiratory volume in 1 second (FEV1) is 35% of predicted. He currently is taking albuterol 2 puffs by metered dose inhaler (MDI) every 6 hours, ipratropium 2 puffs by MDI every 6 hours, and hydrochlorothiazide 50 mg daily. He is not on chronic oxygen therapy. The patient smoked 1 pack of cigarettes per day for 30 years but quit smoking 1 year ago. He is employed as a telephone installer.

Physical Examination

The patient has a temperature of 100.8°F, pulse of 91 bpm, respiratory rate of 22 breaths/min, and blood pressure of 146/73 mm Hg. Arterial oxygen saturation (SaO2) on room air is 84%, increasing to 92% with 1 L of supplemental oxygen by nasal cannula. His throat is mildly erythematous, and...
Accessory respiratory muscles are not being used. The patient experiences dyspnea only when speaking or walking. The lung examination is significant for decreased breath sounds throughout, with expiratory wheezing; fremitus and percussion are normal. Cardiac examination reveals tachycardia, with normal rhythm and no murmurs or gallops. There is no edema or clubbing of the extremities.

• What is the most likely cause of this patient’s symptoms?
• What evaluations are helpful in assessing a patient with COPD exacerbation?

Clinical Criteria
As mentioned, COPD exacerbations characterized by worsening airways function occur in the natural history of the disease. Acute exacerbations are usually diagnosed on a clinical basis. Although at present there are no established criteria to define an exacerbation, most criteria used by clinicians include some combination of 3 clinical findings: worsening of dyspnea, increased sputum purulence, and increased sputum volume. The most accepted system for describing and grading an exacerbation is the “Winnipeg criteria,” which grades the severity of an exacerbation based on the number of symptoms in a patient’s presentation [4] (Table 1). This system was used to define the severity of exacerbations in a trial of antibiotic therapy and is widely used in clinical research.

Diagnostic Testing
Diagnoses to be considered in the setting of a COPD exacerbation include pneumonia, pneumothorax, congestive heart failure, and deep vein thrombosis/pulmonary embolus. A number of laboratory assessments can be used to help rule out these disease entities and to determine the severity of the exacerbation (Table 2).

Chest Radiograph
The conditions most likely to present with a constellation of symptoms similar to those found in an exacerbation are congestive heart failure and pneumonia, both of which can be diagnosed from a chest radiograph. A chest radiograph done during a COPD exacerbation typically does not demonstrate changes from a baseline radiograph done when the patient is in stable condition. A retrospective study of chest radiograph abnormalities in 97 patients with COPD exacerbation found that 17 (17%) patients had abnormalities on radiograph, of which only 8 were significant (5 due to congestive heart failure and 3 due to pneumonia) [5]. The most significant predictors of a radiograph abnormality were an increased neutrophil count (> 8000/µL), history of congestive heart failure, and peripheral edema on physical examination. A second study that attempted to validate the predictors from the previous study found similar rates of radiographic abnormalities (16%) but was unable to validate the predictors with any statistical significance [6]. Both studies supported the use of a chest radiograph in evaluating patients with COPD exacerbations, showing that a radiograph can eliminate congestive heart failure or pneumonia as a cause of the symptoms and guide treatment.

Lung Function Tests
Spirometry showing reduced airflow is the key diagnostic study employed in the initial diagnosis and staging of COPD and subsequent monitoring of disease progression. Similarly, spirometry can be used during an acute exacerbation to stage severity of the exacerbation. However, when performed during an exacerbation, spirometry has not been shown to be helpful in making decisions regarding patient care. Investigators measuring the relationship between FEV₁ and arterial blood gas abnormalities in 70 patients with acute exacerbations presenting to an emergency department found a poor correlation between measured FEV₁ and arterial PaO₂ (r = 0.47, P > 0.05) [7]; FEV₁ showed a small but statistically significant correlation with pH (r = 0.36; P < 0.01). Another study involving 199 patients with acute exacerbation showed a good correlation between PEFR and FEV₁ (r = 0.84; P < 0.001) [8]; however, the difference in the measurements was greater than 10% in a small group of these patients, suggesting that the 2 measurements are not interchangeable and making the clinical relevance of the study findings uncertain. It must also be remembered that patients in respiratory distress are usually unable to perform lung function studies adequately.

Table 1. Winnipeg Criteria for Staging Acute Exacerbations of COPD

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Type of exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased sputum purulence</td>
<td>Type 1: All 3 symptoms present</td>
</tr>
<tr>
<td>Increased sputum volume</td>
<td>Type 2: 2 symptoms present</td>
</tr>
<tr>
<td>Increased dyspnea</td>
<td>Type 3: At least 1 symptom plus 1 of the following present:</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory infection in the past 5 days</td>
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<tr>
<td></td>
<td>Fever without other apparent cause</td>
</tr>
<tr>
<td></td>
<td>Increased wheezing</td>
</tr>
<tr>
<td></td>
<td>Increased cough</td>
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<tr>
<td></td>
<td>Respiratory or heart rate increased 20% above baseline</td>
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Sputum Examination
Most exacerbations are believed to be due to tracheobronchial infections. There is some controversy, however, regarding the infectious agents involved and their actual role in the exacerbation. Sputum collected from patients with mild to moderately severe chronic bronchitis has grown many bacteria on culture, including *Haemophilus influenzae* (22%), *Pseudomonas aeruginosa* (15%), *Streptococcus pneumoniae* (10%), and *Moraxella catarrhalis* (9%) [9]. *P. aeruginosa* has been found more frequently in patients with exacerbations requiring intensive care unit admission. The colonization of airways with nonpathogenic bacteria such as *Haemophilus parainfluenzae* accounted for up to one third of all isolates. Investigators suggest that up to 10% of all exacerbations are due to infection with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* [10–13]. There is also evidence that viruses (notably rhinovirus) may play an important role in the etiology of COPD exacerbations [13]. These studies suggest that sputum collection and Gram stain/culture should be considered in the routine management of COPD exacerbations as they can aid in both specific bacteriologic diagnosis and targeted antibacterial treatment.

**Laboratory Testing and Diagnosis**
A complete blood count reveals the following: white blood cell (WBC) count, 6100 cells/mm$^3$; hemoglobin, 10.6 g/dL; hematocrit, 32 mL/dL; platelets 263,000/mm$^3$; differential, 83% neutrophils, 7% lymphocytes, and 4% monocytes. Blood chemistries are significant for a BUN level of 17 mg/dL and a creatinine level of 1.0 mg/dL. FEV$_1$ shows a 25% decrease from baseline. Chest radiograph shows bilateral hyperinflated lungs, flattened diaphragms, and no apparent infiltrate or consolidation. Arterial blood gas measurements are as follows: pH, 7.34; PCO$_2$, 65 mm Hg; PO$_2$, 52 mm Hg; SaO$_2$, 84% on room air. Sputum Gram stain shows gram-negative rods and many WBCs.

The physician makes a diagnosis of a moderately severe COPD exacerbation as suggested by the presence of 3 Winnipeg criteria and decreased FEV$_1$. She admits the patient to the hospital because of worsening hypoxia and hypercarbia.

- **When should patients with COPD exacerbation be hospitalized?**

COPD exacerbations can be treated in both the outpatient and inpatient settings. The decision to admit a patient is usually based on clinical and laboratory criteria (Table 3). Treatment is aimed at decreasing symptoms and eradicating any causes (ie, infectious agents) of the exacerbation.

- **What is the approach to treatment of COPD exacerbations?**

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**Table 2. Evaluation of Suspected COPD Exacerbation**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Comment</th>
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<tbody>
<tr>
<td>History</td>
<td></td>
</tr>
<tr>
<td>Sputum volume*</td>
<td></td>
</tr>
<tr>
<td>Sputum characteristics (purulence)*</td>
<td></td>
</tr>
<tr>
<td>Level of dyspnea*</td>
<td></td>
</tr>
<tr>
<td>Constitutional symptoms (fever and fatigue)</td>
<td></td>
</tr>
<tr>
<td>Changes in exercise tolerance</td>
<td></td>
</tr>
<tr>
<td>Exposure to infectious agents</td>
<td></td>
</tr>
<tr>
<td>Diagnostic studies</td>
<td></td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Used to assess for pneumonia and congestive heart failure; also useful for diagnosis and treatment</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Used to assess for infectious causes</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td>Used to measure level of severity, including new or worsening hypoxia or hypercarbia; useful when deciding whether to admit patient and whether to institute assisted ventilation</td>
</tr>
<tr>
<td>Gram stain/culture (when sputum present)</td>
<td>Used for staging exacerbations; not useful for guiding therapy</td>
</tr>
<tr>
<td>Spirometry</td>
<td></td>
</tr>
<tr>
<td>Others: ventilation/perfusion scans, ultrasound, electrocardiogram, computed tomography scan</td>
<td>Useful only when specific disease suspicion is high</td>
</tr>
</tbody>
</table>

*Components of the Winnipeg criteria.
**COPD EXACERBATIONS**

**Table 3. Indications for Hospital Admission in Acute Exacerbation of COPD**

<table>
<thead>
<tr>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Poor response to outpatient management</td>
</tr>
<tr>
<td>Dyspnea that interferes with daily living (eating, walking)</td>
</tr>
<tr>
<td>High-risk comorbid conditions (pulmonary or nonpulmonary)</td>
</tr>
<tr>
<td>Altered mental status</td>
</tr>
<tr>
<td>New or worsening cor pulmonale</td>
</tr>
<tr>
<td>New or worsening hypercarbia/hypoxia</td>
</tr>
</tbody>
</table>


The mainstays of therapy are bronchodilators, corticosteroids, and antibiotics (Table 4). If the exacerbation progresses despite adequate treatment, patients can develop respiratory failure and hypoxia due to a combination of bronchoconstriction, collapse of airways during expiration, and air trapping. Treatment for these conditions includes supplemental oxygen and, traditionally, intubation and mechanical ventilation. Recently, noninvasive positive pressure ventilation (NPPV) increasingly has been used with success in this population.

### Bronchodilating Agents

Bronchoconstriction caused by airway inflammation and contraction of smooth muscle within the bronchial wall contributes to airflow obstruction and dyspnea in the COPD patient with an acute exacerbation. Bronchodilators alleviate this symptom by relaxing the smooth muscle and possibly reducing inflammation. The 2 classes of bronchodilators currently available—β<sub>2</sub> agonists and anticholinergics—bind to their respective receptors on smooth muscle and inhibit contraction, thus preventing bronchoconstriction. The results of randomized studies show that short-acting β<sub>2</sub> agonists and anticholinergic inhaled bronchodilators are equally effective, and both are superior to parenterally administered bronchodilators, including methylxanthines and sympathomimetic agents, in the care of patients with acute exacerbations of COPD [14–18]. Patients may benefit from the addition of a second bronchodilating agent once the maximal dose of the initial bronchodilator is reached [14,17]. These generalizations regarding use of bronchodilators are limited by the small number of analyzable trials published, substantial differences in inclusion and exclusion criteria between them, and variability in the drug dosages that were studied (many were substantially higher than the dosages conventionally used) [18].

### Corticosteroids

Several randomized controlled trials provide good evidence that the use of systemic corticosteroids may be of benefit [19–24]. In the largest study to date, 271 patients were randomized to receive either intravenous and then oral corticosteroids or placebo [24]. A 10% reduction in treatment failures was seen in the population taking the glucocorticoid compared with those taking placebo. The trial also showed no difference in outcome between patients on an 8-week and a 2-week drug-tapering regimen. Although the importance of treating with steroids has been studied, the optimal dose and duration of treatment remains uncertain.

### Antibiotics

Randomized, placebo-controlled studies and a recent meta-analysis of antibiotic treatment conclude that antibiotics are beneficial in the treatment of patients with acute exacerbations of COPD [4,25–35]. Three of the trials stratified patients by severity of disease [4,25,26]. Although they used different severity scales, in each case patients with more severe exacerbations were more likely to experience benefit than those less ill. This finding held up when studied in the context of the meta-analysis [35]. Thus, the data support the use of antibiotics in virtually all exacerbations of COPD. Antibiotic therapy initially should be targeted toward suspected organisms and then adjusted according to sputum culture results. Unfortunately, little evidence is available regarding the most effective duration of a course of antibiotics. Typical administration periods range from 3 to 14 days.

### Mucus Clearance

Data from randomized controlled trials involving 5 different mucolytic drugs showed that mucolytic agents are ineffective at shortening the course of patients with acute exacerbations

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**Table 4. Treatment for COPD Exacerbations**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose Details</th>
</tr>
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<tbody>
<tr>
<td><strong>Bronchodilators</strong></td>
<td></td>
</tr>
<tr>
<td>β&lt;sub&gt;2&lt;/sub&gt; agonists:</td>
<td>6 to 8 puffs by MDI every 1 to 2 hours OR 2.5 mg inhaled solution by nebulizer every 1 to 2 hours</td>
</tr>
<tr>
<td>Ipratropium:</td>
<td>6 to 8 puffs by MDI every 3 to 4 hours OR 0.5 mg inhaled solution by nebulizer every 3 to 4 hours</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone:</td>
<td>50 to 100 mg IV for first dose, then 40 to 60 mg every 6 to 8 hours OR 40 to 60 mg orally once daily to start</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
</tr>
<tr>
<td>Initial therapy is directed at most likely pathogen, and changes are guided by results of sputum culture</td>
<td></td>
</tr>
<tr>
<td><strong>Assisted ventilation</strong></td>
<td></td>
</tr>
<tr>
<td>Utilization is guided by presence of new or worsening hypoxia or hypercarbia</td>
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</tbody>
</table>

IV = intravenous; MDI = metered dose inhaler.
of COPD, although it is possible that these agents may improve symptoms [30,36–39]. Two trials of chest physiotherapy show that these strategies are ineffective in the treatment of patients with acute exacerbations of COPD [40,41].

Oxygen Therapy

The use of supplemental oxygen during COPD exacerbations is beneficial in patients with hypoxemia (PO2 < 55 mm Hg). Supplemental oxygen can alleviate vasoconstriction of pulmonary vasculature and improve oxygen delivery to tissues. However, hypercarbia and respiratory failure can develop when providing oxygen therapy to some hypoxemic patients. Mechanisms leading to these complications include depression of respiratory drive, ventilation-perfusion mismatch, and the Haldane effect (ie, oxygenated erythrocytes having a lower capacity for CO2 than deoxygenated erythrocytes). A study of proposed methods to identify patients at high risk to develop hypercapnic respiratory failure during supplemental oxygen therapy looked at 50 patients with COPD exacerbations [42]. Thirteen (26%) patients developed hypercarbia requiring mechanical ventilation. Arterial pH, PO2, and PCO2 were not predictive of respiratory failure. To date, no data have been published regarding the best method for titration of oxygen following an acute exacerbation of COPD. Based on data from the Nocturnal Oxygen Therapy Trial (NOTT), it can be estimated that 20% of patients requiring oxygen during an exacerbation will not require oxygen 3 weeks after hospital discharge [43].

Assisted Ventilation

Acute respiratory failure can be defined as potentially life-threatening hypoxia, hypercarbia, and respiratory acidosis. Combinations of abnormal ventilation patterns, severe airway obstruction (due to bronchospasm and secretion immobilization), and pulmonary edema produce the pathophysiologic disturbances of ventilation-perfusion mismatch, air trapping (intrinsic positive end-expiratory pressure [PEEP]), and increased work of breathing. For persons with COPD, this condition is considered “acute on chronic” respiratory failure since the pathophysiologic changes occur in the context of chronic gas exchange abnormalities. Management of acute respiratory failure is targeted at correcting the hypoxia, hypercarbia, and acidosis, while treating the cause of the exacerbation. Bronchodilators and corticosteroids are still the cornerstones of medical management.

Both traditional invasive mechanical ventilation and NPPV address the mechanical disturbances of acute respiratory failure. Positive pressure during inspiration facilitates ventilation by unloading ventilatory muscles; during expiration it reduces the breath initiation load imposed by intrinsic PEEP. Supplemental oxygen is used to correct hypoxia. Traditional invasive mechanical ventilation, however, is associated with more complications than NPPV, including nosocomial and ventilator-associated pneumonias, barotraumas, and hemodynamic changes such as decreased cardiac output [44]. For patients with more severe COPD at baseline, weaning from the ventilator can also be a very difficult process. NPPV has a lower complication rate than traditional mechanical ventilation [44], allows the concomitant use of conventional treatments (bronchodilators), and helps preserve patients’ nutrition and communication functioning.

In selected patients with acute exacerbations of COPD, NPPV can decrease the need for mechanical ventilation and improve survival. In 2 trials comparing NPPV with standard treatment, the need for intubation in the NPPV groups was significantly lower: 26% versus 74% in a study involving 85 patients [45], and 9% versus 67% in a study involving 23 patients [46]. Other studies have found similar outcomes [47,48]. A meta-analysis concluded that the risk of death was lower in patients who were randomized to receive NPPV (odds ratio [OR] = 0.22, 95% confidence interval [CI], 0.09 to 0.54), as was the risk of requiring invasive mechanical ventilation (OR = 0.12, 95% CI, 0.05 to 0.29) [49].

Treatment and Hospital Course

On admission to the hospital, the patient is treated with methylprednisolone, albuterol, and ipratropium. Supplemental oxygen is administered because of the patient’s hypoxia, and NPPV is instituted to treat his hypercarbia. The hypercarbia and hypoxia resolve with these therapies. Sputum cultures are positive for H. influenzae, and an appropriate antibiotic agent is administered intravenously for 3 days; the patient is then switched to an oral agent for a 7-day course.

Four days after admission, after his dyspnea has improved and he has been stable for 24 hours, the patient is discharged from the hospital. He completes the antibiotic regimen and a steroid taper as an outpatient. At a follow-up visit to his primary care physician 2 weeks after discharge, his respiratory status has returned to baseline.

Future Directions

A number of new modalities for the diagnosis and treatment of COPD are being investigated. Research has been directed at identifying biologic markers of infection and inflammation (eg, antioxidants, cytokines) in the blood and/or sputum. Future research in therapeutics for COPD may address the components of mucus formation and content; strategies for improving muscle strength and reducing muscle fatigue; therapies aimed at aborting the exacerbation cycle; and strategies aimed at preventing infectious exacerbations.

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References


