Management of COPD Exacerbations

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Exacerbations of chronic obstructive pulmonary disease contribute to the high mortality rate associated with the disease. Randomized controlled trials have demonstrated the effectiveness of multiple interventions. The first step in outpatient management should be to increase the dosage of inhaled short-acting bronchodilators. Combining ipratropium and albuterol is beneficial in relieving dyspnea. Oral corticosteroids are likely beneficial, especially for patients with purulent sputum. The use of antibiotics reduces the risk of treatment failure and mortality in moderately or severely ill patients. Physicians should consider antibiotics for patients with purulent sputum and for patients who have inadequate symptom relief with bronchodilators and corticosteroids. The choice of antibiotic should be guided by local resistance patterns and the patient’s recent history of antibiotic use. Hospitalized patients with exacerbations should receive regular doses of short-acting bronchodilators, continuous supplemental oxygen, antibiotics, and systemic corticosteroids. Noninvasive positive pressure ventilation or invasive mechanical ventilation is indicated in patients with worsening acidosis or hypoxemia. (Am Fam Physician. 2010;81(5):607-613, 616. Copyright © 2010 American Academy of Family Physicians.)

Table 1. Classification of COPD Exacerbations by Severity

<table>
<thead>
<tr>
<th>Severity of exacerbation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Can be controlled with an increase in dosage of regular medications</td>
</tr>
<tr>
<td>Moderate</td>
<td>Requires treatment with systemic corticosteroids or antibiotics</td>
</tr>
<tr>
<td>Severe</td>
<td>Requires hospitalization or evaluation in the emergency department</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease.

Information from references 4 and 5.
COPD Exacerbations

Etiology
Infection of the tracheobronchial tree and air pollution (e.g., tobacco smoke, occupational exposures, ozone) are the most common identifiable causes of COPD exacerbations. One third of exacerbations have no identifiable cause. Other medical problems, such as congestive heart failure, nonpulmonary infections, pulmonary embolism, and pneumothorax, can also prompt a COPD exacerbation.

Initial Evaluation
The initial evaluation of patients with a suspected COPD exacerbation should include a history of baseline and current symptoms, such as limitations in activities of daily living. If available, previous chest radiographs, arterial blood gas measurements, and spirometry results can help establish the baseline lung function and illustrate a typical exacerbation. Because increasing confusion is a hallmark of respiratory compromise, the physical examination should include a mental status evaluation, as well as heart and lung examinations.

Recommended diagnostic evaluation of an exacerbation depends on its severity (Table 4). Pulse oximetry should be performed in all patients. Chest radiography, complete blood count, and metabolic panel should be performed if hospitalization is indicated. Consideration should be given to perform brain natriuretic peptide measurement if the patient is not responding to conventional exacerbation treatment.

Table 2. Symptoms of COPD Exacerbation

<table>
<thead>
<tr>
<th>Body system</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Chest tightness, Tachycardia</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Decreased exercise tolerance</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Confusion, Depression, Insomnia, Sleepiness</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Change in volume, color, or tenacity of sputum, Cough, Dyspnea, Tachypnea, Wheezing</td>
</tr>
<tr>
<td>Systemic</td>
<td>Fatigue, Fever, Malaise</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease. Information from references 6 through 8.

Table 3. Factors that Increase Risk of Severe COPD Exacerbations

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered mental status</td>
<td>At least three exacerbations in the previous 12 months</td>
</tr>
<tr>
<td>Body mass index</td>
<td>20 kg per m² or less</td>
</tr>
<tr>
<td>Marked increase in symptoms</td>
<td>or change in vital signs</td>
</tr>
<tr>
<td>Medical comorbidities</td>
<td>(especially cardiac ischemia, congestive heart failure, pneumonia, diabetes mellitus, or renal or hepatic failure)</td>
</tr>
<tr>
<td>Poor physical activity levels</td>
<td></td>
</tr>
<tr>
<td>Poor social support</td>
<td></td>
</tr>
<tr>
<td>Severe baseline COPD</td>
<td>FEV₁/FVC ratio less than 0.70 and FEV₁ less than 50 percent of predicted</td>
</tr>
<tr>
<td>Underutilization of home oxygen therapy</td>
<td></td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity. Information from references 5 through 7, and 9 through 11.

Table 4. Diagnostic Evaluation of Patients with Suspected COPD Exacerbation

<table>
<thead>
<tr>
<th>Test</th>
<th>Potential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform routinely</td>
<td></td>
</tr>
<tr>
<td>Pulse oximetry</td>
<td>Hypoxemia</td>
</tr>
<tr>
<td>Perform if hospitalized</td>
<td></td>
</tr>
<tr>
<td>Arterial blood gas measurement</td>
<td>Hypercarbia</td>
</tr>
<tr>
<td></td>
<td>Hypoxemia</td>
</tr>
<tr>
<td></td>
<td>Respiratory acidosis</td>
</tr>
<tr>
<td>Chest radiography</td>
<td>Alternate sources of dyspnea</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Anemia</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Metabolic panel</td>
<td>Cardiac ischemia</td>
</tr>
<tr>
<td>Brain natriuretic peptide measurement</td>
<td>CHF (one third of dyspnea in chronic lung disease may be attributable to CHF)</td>
</tr>
<tr>
<td>Cardiac enzyme measurement</td>
<td>Cardiac ischemia (myocardial infarction is underdiagnosed in patients with COPD)</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease. Information from references 5, 8, 9, 12, and 13.
radiography is appropriate in hospitalized patients and can guide treatment by revealing comorbid conditions such as congestive heart failure, pneumonia, and pleural effusion. A room air arterial blood gas (ABG) measurement should be obtained at the time of hospital admission to quantify hypercarbia and hypoxemia. Measurement of brain natriuretic peptide and serial cardiac enzyme levels should be considered in hospitalized patients, because cardiac ischemia and congestive heart failure are common comorbidities in patients with COPD.5,12,13

Other physical examination maneuvers, laboratory tests, and assessments of cardiac function have not been proven beneficial in the treatment of COPD exacerbations.9

**Indications for Hospitalization**

About 50 percent of COPD exacerbations are not reported to physicians, suggesting that many exacerbations are mild.14 The risk of death from an exacerbation increases with the development of respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support.3 Patients with symptoms of respiratory distress and those at risk of distress should be admitted to the hospital to provide access to critical care personnel and mechanical ventilation. Inpatient mortality for COPD exacerbations is 3 to 4 percent.9 Patients admitted to the intensive care unit have a 43 to 46 percent risk of death within one year after hospitalization.9

Nonambulatory patients should receive routine prophylaxis for deep venous thrombosis. Because COPD is a progressive and often fatal illness, physicians should consider discussing and documenting the patient’s wishes concerning end-of-life care.

**Oxygenation and Ventilation**

Oxygen supplementation should be titrated to an oxygen saturation level of at least 90 percent. High-flow oxygen devices deliver oxygen more reliably than nasal prongs, but nasal prongs may be better tolerated. Noninvasive positive pressure ventilation (NIPPV) is indicated if adequate oxygenation or ventilation cannot be achieved using a high-flow mask.15 Patients requiring NIPPV should be monitored continuously for decompensation.

If the patient cannot be adequately oxygenated, complications, such as pulmonary embolism or edema, should be considered.6 Carbon dioxide retention is possible in moderately and severely ill patients; therefore, ABG should be measured 30 to 60 minutes after initiating oxygen supplementation. Invasive mechanical ventilation is needed if the patient cannot tolerate NIPPV; has worsening hypoxemia, acidosis, confusion, or hypercapnia despite NIPPV; or has severe comorbid conditions, such as myocardial infarction or sepsis.6 Worsening hypercarbia and acidosis herald respiratory failure. A pH of less than 7.36 and an arterial partial pressure of carbon dioxide of more than 45 mm Hg indicate the need for mechanical ventilation.

**Therapeutic Options**

**SHORT-ACTING BRONCHODILATORS**

Inhaled short-acting bronchodilators include beta agonists (e.g., albuterol, levalbuterol [Xopenex]) and anticholinergics (e.g., ipratropium [Atrovent]). These agents improve dyspnea and exercise tolerance.6,9 The first step in treating a COPD exacerbation is increasing the dosage of albuterol delivered via metered dose inhaler or nebulizer.9 Levalbuterol is more expensive than albuterol but has similar benefits and adverse effects.16 If the patient is not already taking ipratropium, it can be added to the treatment regimen.7 Fixed-dose albuterol/ipratropium (Combivent) is available.

**CORTICOSTEROIDS**

Short courses of systemic corticosteroids increase the time to subsequent exacerbation, decrease the rate of treatment failure, shorten hospital stays, and improve hypoxemia and forced expiratory volume in one second (FEV1).1,6,7,9,17-20 Administration of oral corticosteroids early in an exacerbation decreases the need for hospitalization.21 A randomized controlled trial (RCT) of patients with COPD compared eight weeks of corticosteroids, two weeks of corticosteroids, and placebo; participants in the treatment groups had fewer treatment failures than those in the control group.17 Treatment failure rates were the same for long and short courses of corticosteroids.

High-dosage corticosteroid regimens (methylprednisolone [Solu-Medrol], 125 mg intravenously every six hours) and low-dosage regimens (prednisolone, 30 mg orally daily) decrease the length of hospitalization and improve FEV1, compared with placebo.17,19 An RCT comparing oral and intravenous prednisolone in equivalent dosages (60 mg daily) showed no difference in lengths of hospitalization and rates of early treatment failure.22

Because oral corticosteroids are bioavailable, inexpensive, and convenient, parenteral corticosteroids should be reserved for patients with poor intestinal absorption or comorbid conditions that prevent safe oral intake (e.g., decreased mental status, vomiting).5,6 Inhaled corticosteroids have no role in the management of an acute exacerbation.8
COPD Exacerbations

ANTIBIOTICS

One half of patients with COPD exacerbations have high concentrations of bacteria in their lower airways.\textsuperscript{5,23} Cultures often show multiple infectious agents, including Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, and viruses.\textsuperscript{6,23} The use of antibiotics in moderately or severely ill

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Outpatient management</th>
<th>Inpatient management</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic, broad spectrum (e.g., amoxicillin/clavulanate [Augmentin], macrolides, second- or third-generation cephalosporins, quinolones)</td>
<td>Consider if sputum is purulent or after treatment failure</td>
<td>Use if local microbial patterns show resistance to narrow-spectrum agents</td>
<td>Decreases risk of treatment failure and mortality compared with narrow-spectrum agents</td>
</tr>
<tr>
<td>Antibiotic, narrow spectrum (e.g., amoxicillin, ampicillin, trimethoprim/sulfamethoxazole [Bactrim, Septra], doxycycline, tetracycline)</td>
<td>Consider if sputum is purulent or after treatment failure</td>
<td>Use if local microbial patterns show minimal resistance to these agents and if patient has not taken antibiotics recently</td>
<td>Believed to decrease mortality risk, but has not been tested in placebo-controlled trials</td>
</tr>
<tr>
<td>Anticholinergic, short acting (e.g., ipratropium [Atrovent])</td>
<td>May add to beta agonist; if patient is already taking an anticholinergic, increase dosage</td>
<td>May add to beta agonist; if patient is already taking an anticholinergic, increase dosage</td>
<td>Improves dyspnea and exercise tolerance</td>
</tr>
<tr>
<td>Beta agonist, short acting (e.g., albuterol, levalbuterol [Xopenex])</td>
<td>Increase dosage</td>
<td>Increase dosage</td>
<td>Improves dyspnea and exercise tolerance</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Consider using oral corticosteroids in moderately ill patients, especially those with purulent sputum</td>
<td>Use oral corticosteroids if patient can tolerate; if not suitable for oral therapy, administer intravenously</td>
<td>Decreases risk of subsequent exacerbation, rate of treatment failures, and length of hospital stay</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>NA</td>
<td>Use if patient cannot tolerate NIPPV; has worsening hypoxemia, acidosis, confusion, or hypercapnia despite NIPPV; or has comorbid conditions such as myocardial infarction or sepsis</td>
<td>Decreases short-term mortality risk in severely ill patients</td>
</tr>
<tr>
<td>NIPPV</td>
<td>NA</td>
<td>Use in patients with worsening respiratory acidosis and hypoxemia when oxygenation via high-flow mask is inadequate</td>
<td>Improves respiratory acidosis and decreases respiratory rate, breathlessness, need for intubation, mortality, and length of hospital stay</td>
</tr>
<tr>
<td>Oxygen supplementation</td>
<td>NA</td>
<td>Use in patients with hypoxemia (PaO\textsubscript{2} less than 60 mm Hg)</td>
<td>Decreases mortality risk</td>
</tr>
</tbody>
</table>

\textsuperscript{COPD} = chronic obstructive pulmonary disease; FEV\textsubscript{1} = forced expiratory volume in one second; MDI = metered dose inhaler; NA = not applicable; NIPPV = noninvasive positive pressure ventilation; PaO\textsubscript{2} = arterial partial pressure of oxygen.

\textsuperscript{*}—Spacer can be used with MDI to improve delivery.

Information from references 5, 6, 8, 9, 18, and 25.
patients with COPD exacerbations reduces the risk of treatment failure and death. Antibiotics may also benefit patients with mild exacerbations and purulent sputum. The optimal choice of antibiotic and length of use are unclear. Increasing microbial resistance has prompted some physicians to treat exacerbations with broad-spectrum agents, such as second- or third-generation cephalosporins, macrolides, or quinolones. One meta-analysis showed a lower risk of treatment failure with broad-spectrum antibiotics compared with narrow-spectrum antibiotics (odds ratio = 0.51; 95% confidence interval, 0.34 to 0.75), but no change in mortality rates. Another meta-analysis showed no difference in clinical cure rates when broad-spectrum antibiotics were administered for at least five days versus less than five days. There is no comparable study of narrow-spectrum antibiotics. The decision to use antibiotics and the choice of antibiotic should be guided by the patient's symptoms (e.g., presence of purulent sputum), recent antibiotic use, and local microbial resistance patterns. Prophylactic, continuous use of antibiotics does not improve outcomes in patients with COPD.

### Table 5. Treatment Options for Acute COPD Exacerbations

<table>
<thead>
<tr>
<th>Disadvantages/common adverse effects</th>
<th>Typical dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic resistance, diarrhea, yeast vaginitis; side effects specific to the antibiotic prescribed</td>
<td>Amoxicillin/clavulanate: 875 mg orally twice daily or 500 mg orally three times daily for 5 days  Levofloxacin (Levaquin): 500 mg daily for 5 days</td>
</tr>
<tr>
<td>Antibiotic resistance, diarrhea, yeast vaginitis; side effects specific to the antibiotic prescribed</td>
<td>Amoxicillin: 500 mg orally three times daily for 3 to 14 days  Doxycycline: 100 mg orally twice daily for 3 to 14 days</td>
</tr>
<tr>
<td>Dry mouth, tremor, urinary retention</td>
<td>Ipratropium: 500 mcg by nebulizer every 4 hours as needed; alternatively, 2 puffs (18 mcg per puff) by MDI every 4 hours as needed*</td>
</tr>
<tr>
<td>Headache, nausea, palpitations, tremor, vomiting</td>
<td>Albuterol: 2.5 mg by nebulizer every 1 to 4 hours as needed, or 4 to 8 puffs (90 mcg per puff) by MDI every 1 to 4 hours as needed*</td>
</tr>
<tr>
<td>Gastrointestinal bleeding, heartburn, hyperglycemia, infection, psychomotor disturbance, steroid myopathy</td>
<td>Oral prednisone: 30 to 60 mg once daily  Intravenous methylprednisolone (Solu-Medrol): 60 to 125 mg 2 to 4 times daily</td>
</tr>
<tr>
<td>Aspiration, cardiovascular complications, need for sedation, pneumonia</td>
<td>Titrate to correct hypercarbia and hypoxemia</td>
</tr>
<tr>
<td>Expensive, poorly tolerated by some patients</td>
<td>Titrate to correct hypercarbia and hypoxemia</td>
</tr>
<tr>
<td>Hypercarbia</td>
<td>Titrate to Pao2 &gt; 60 mm Hg or oxygen saturation ≥ 90 percent</td>
</tr>
</tbody>
</table>

By defining the need for hospitalization and admission, patients can be discharged earlier, with a reduction in mortality rates. While asthma is not a disease that results in death, it can lead to severe symptoms. Similarly, COPD is not a disease that results in death, but it can lead to severe symptoms, including hypoxemia, which may result in death.

### OTHER TREATMENT OPTIONS

Parenteral methylxanthines, such as theophylline, are not routinely recommended for the treatment of COPD exacerbations. These agents are less effective and have more potentially adverse effects than inhaled bronchodilators.

Several therapies lack adequate evidence for routine use in the treatment of COPD exacerbations, including mucolytics (e.g., acetylcysteine [formerly Mucomyst]), nitric oxide, chest physiotherapy, antitussives, morphine, nedocromil, leukotriene modifiers, phosphodiesterase IV inhibitors (drug class not available in the United States), and immunomodulators (e.g., OM-85 BV, AM3 [neither drug available in the United States]). Table 5 summarizes the treatment options for acute COPD exacerbations.

### Preparation for Hospital Discharge

To qualify for discharge, a patient should have stable clinical symptoms and a stable or improving arterial partial pressure of oxygen of more than 60 mm Hg for at least 12 hours. The patient should not require albuterol more often than every four hours. If the patient is stable and can use a metered dose inhaler, there is no benefit to using nebulized bronchodilators. Patient education may improve the response to future exacerbations; suggested topics include a general overview of COPD, available medical treatments, nutrition, advance directives, and advice about when to seek medical help. In-home support, such as an oxygen concentrator, nebulizer, and home health nurse services, should be arranged before discharge.
Preventing Future Exacerbations

Smoking cessation, immunization against influenza and pneumonia, and pulmonary rehabilitation have been shown to improve function and reduce subsequent COPD exacerbations.6,7,30 Long-term oxygen therapy decreases the risk of hospitalization and shortens hospital stays in severely ill patients with COPD.7,31,32 The indications for long-acting inhaled bronchodilators and inhaled corticosteroids to improve symptoms and reduce the risk of exacerbations in patients with stable COPD are reviewed elsewhere.5,7,33-38

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REFERENCES

7. Snow V, Lascher S, Mottur-Pilson C, for the Joint Expert Panel on COPD of the American College of Chest Physicians and the American...


