Chronic Obstructive Pulmonary Disease

**Patient population:** Adults with chronic obstructive pulmonary disease (COPD).

**Objectives:**
1. Provide a framework for management of chronic COPD and for the treatment of mild to moderate acute exacerbations
2. Improve symptoms, quality of life and lung function while reducing morbidity and mortality for patients with COPD.

**Key Points** (See Table 1 for overview of diagnosis and management of COPD.)

**COPD is underdiagnosed and misdiagnosed.** Routine population screening is not recommended [IIIID] but early case finding is encouraged. [ID] Appropriate comprehensive treatment can improve symptoms and quality of life. [IA]

**Diagnosis.**
- Consider COPD in any patient with dyspnea, chronic cough or sputum production, and/or a history of inhalational exposures known to be risk factors. [ID]
- Pulmonary function testing with post-bronchodilator assessment demonstrating a reduced FEV1/FVC ratio is required for diagnosis; severity of FEV1 decline (measured as % of predicted FEV1) establishes severity. [ID]

**Treatment.**
- **Smoking cessation** is the single most important intervention to slow the rate of lung function decline regardless of disease severity. [IA]
- **Chronic medication management** includes:
  - Bronchodilators (B2-agonists and anticholinergics) in stepwise progression based on disease severity (Tables 9 & 10) with the goal of improving symptoms. [IA]
  - Inhaled corticosteroids should be considered only for patients with severe disease (FEV1 < 50% predicted) and frequent (at least annual) exacerbations. [IA]
  - Supplemental oxygen if resting oxygen saturation ≤ 88% or PaO2 ≤ 55. [IA]
- **Acute exacerbation medication management** includes bronchodilators (B2-agonists and anticholinergics), antibiotics, and corticosteroid therapy based on clinical indications (Table 12). Empiric antibiotics are recommended for patients with increased sputum purulence plus either increased dyspnea or increased sputum volume. [IA] Sputum culture is not routinely recommended. [IIIC]
- **Pulmonary rehabilitation** should be considered for all patients with functional impairment. [IA]
- **Surgical therapy** options include bullectomy, lung volume reduction surgery, and lung transplantation. [IIIA] Total life expectancy should be incorporated into shared decision making regarding the potential benefits of surgery. [IIID] Pulmonary consultation is advised for consideration of surgical options. [ID]
- **Palliative care** should be discussed with patients desiring less aggressive therapy, avoidance of endotracheal intubation, or symptomatic care at the end of life. [ID]

*Strength of recommendation:*
- I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.

*Levels of evidence for the most significant recommendations*
- A= randomized controlled trials; B= controlled trials, no randomization; C= observational trials; D= opinion of expert panel

**Clinical Problem and Management Issues**

**Incidence.** COPD is the fourth-leading cause of death in the United States, accounting for over 120,000 deaths annually. The population burden for COPD continues to increase, with prevalence similar to diabetes and asthma. COPD also can have a long pre-symptomatic phase. Data from the National Health Interview and National Health and Nutrition Examination Surveys suggest that of the estimated 24 million Americans with COPD, half are undiagnosed.

(Text continues on page 9)
Table 1. Overview of Diagnosis and Management of Patients with COPD

**Diagnosis**

**Clinical suspicion.** Risk factors of exposure to smoking (≥ 10 pack-years) or inhalation irritants. Chronic cough, sputum production, or dyspnea. (See symptoms and signs in Table 2.)

**Pulmonary function test.** Required for diagnosis. Post-bronchodilator FEV1/FVC < 0.70 is required to demonstrate airflow obstruction that is not fully reversible.

**Alternative diagnoses.** If pulmonary function testing is negative or equivocal, consider alternative diagnoses (Tables 3 & 4) or consider referral to pulmonary specialist.

**Alpha-1 antitrypsin level.** Assess for deficiency in settings of clinical suspicion: age 45 or less, absence of other risk factors or severity of disease out of proportion to risk factors, prominent basilar lucency, family history, or bronchiectasis.

**Initial Assessment, Patient Education, Prevention, and Treatment**

**COPD severity staging.** Post-bronchodilator FEV1 determines stage (Table 5).

- For patients with severe disease (FEV1<50%), obtain oximetry on room air. Respiratory failure (O2 saturation ≤ 88%) indicates very severe disease (Table 11).
- For marginal resting room air oxygen saturation (89 – 93%), perform 6 minute walk test to assess for ambulatory desaturation (Table 11).
- BODE index assessment (see Table 6) may be used to determine prognosis for severe disease, but is usually deferred to referral specialists. (BODE = Body-mass index, Airflow obstruction [% of predicted FEV1], Dyspnea using the modified Medical Research Council dyspnea scale [Table 7], and Exercise capacity [distance walked in 6 minutes].)

**Patient education.** Provide educational overview of COPD pathology, causes, diagnosis, staging, exacerbation triggers, and treatment options (Table 8).

**Smoking cessation.** Encourage all smokers to quit, and assist them in quitting. (See UMHS Smoking Cessation guideline.)

**Inhaled irritant control.** Identify and review how to avoid triggers and exposures known to cause/aggravate COPD: smoking, second hand smoke, occupational fumes and chemicals, indoor air pollution (e.g., cooking with biomass fuels), outdoor air pollution, infection.

**Medical therapy.** Select bronchodilator and consider inhaled corticosteroid therapy based on COPD severity by stage and by current frequency of exacerbations (Table 9). Table 10 provides dose and cost information for medications.

**Oxygen therapy.** Initiate long term oxygen for patients with oxygen saturation ≤ 88% (Table 11).

**Chronic Disease Management**

**Vaccinate against influenza and pneumococcus.** Provide annual flu shots for all COPD patients. Provide pneumococcal vaccination. Provide a booster pneumococcal vaccine for patients age 65 and older if they received their first dose before age 65 and if more than five years have passed.

**Pulmonary rehabilitation.** Refer patients with functional limitations to pulmonary rehabilitation.

**Medical therapy.** Monitor patient adherence and correct usage. Prescribe long-acting bronchodilators for patients with frequent symptoms. For patients with exacerbations requiring systemic steroids or antibiotics within the past year and FEV1 ≤ 50% predicted, consider adding inhaled corticosteroid therapy (Table 9). Table 10 provides dose and cost information.

**Oxygen therapy.** Titrate long-term oxygen for patients with oxygen saturation ≤ 88% to achieve resting and exercise oxygen saturation ≥ 90% (Table 11).

**Inhaled irritant control.** Provide ongoing smoking cessation counseling and irritant control counseling. (See UMHS Smoking Cessation guideline.)

**Monitor comorbidities.** Consider increased risk for cardiovascular disease, depression, anxiety, and other smoking related diseases such as osteoporosis and cancer. Monitor blood sugar control for diabetic patients on inhaled corticosteroids. Monitor for glaucoma and cataracts for patients on inhaled corticosteroids.

**Refer to COPD specialist.** For patients with alpha-1-antitrypsin deficiency, severe disease (FEV1≤50%), supplemental oxygen dependence, severe exacerbation and/or frequent exacerbations, consider referral for co-management and consideration of surgical options.

**Advanced care planning.** Engage patients in shared decision making regarding goals of therapy and advanced directives.

(Continues on next page.)
Table 1. Overview of Diagnosis and Management of Patients with COPD (continued)

Acute Exacerbation Management

Assess exacerbation severity. Determine severity based on history, physical, and pulse oximetry.

Consider etiology. Assess clinically for risk of pneumonia, congestive heart failure, pulmonary embolism, or other causes of respiratory decline. Consider chest radiograph if clinically indicated.

Determine care setting. Consider hospitalization for patients with marked symptoms, severe underlying disease, significant complicating comorbidities, respiratory failure, uncertain diagnosis, or insufficient outpatient supports.

Medical therapy. Select bronchodilators, antibiotics, and corticosteroid therapy based on clinical indications with the goal of reducing the frequency of future exacerbations (Table 12).

Oxygen therapy. Titrate oxygen for patients with oxygen saturation < 88% to achieve resting and exercise oxygen saturation ≥ 90% (Table 11).

Follow-up. Consider repeat spirometry 4-6 weeks following exacerbation if symptoms have not returned to baseline. Re-evaluate necessity of oxygen therapy.

Table 2. Symptoms and Signs Suggesting COPD

<table>
<thead>
<tr>
<th>Dyspnea that is:</th>
<th>Sputum production:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive</td>
<td>Any pattern of chronic sputum production</td>
</tr>
<tr>
<td>Worse with exercise</td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td></td>
</tr>
<tr>
<td>Associated with chest heaviness or air hunger</td>
<td></td>
</tr>
<tr>
<td>Chronic cough:</td>
<td></td>
</tr>
<tr>
<td>May be intermittent</td>
<td></td>
</tr>
<tr>
<td>Morning pattern common</td>
<td></td>
</tr>
<tr>
<td>May be productive or unproductive</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure to risk factors:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco smoke (≥ 10 pack years)</td>
<td></td>
</tr>
<tr>
<td>Occupational dusts and chemicals</td>
<td></td>
</tr>
<tr>
<td>Smoke from home cooking and heating fuel</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Alternative Diagnoses for Chronic Cough and Dyspnea

<table>
<thead>
<tr>
<th>Asthma</th>
<th>Chronic Aspiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>Chronic Sinusitis or Rhinitis</td>
</tr>
<tr>
<td>Bronchiolitis Obliterans</td>
<td>Congestive Heart Failure</td>
</tr>
</tbody>
</table>

Table 4. Factors Differentiating Asthma and COPD

<table>
<thead>
<tr>
<th>Factors</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Onset</td>
<td>Usually &lt;30</td>
<td>Usually &gt;40</td>
</tr>
<tr>
<td>History of Atopy</td>
<td>Often</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Family History</td>
<td>Usually</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Lung Function with Therapy</td>
<td>Near Normal</td>
<td>Chronically &lt; normal</td>
</tr>
<tr>
<td>Bronchodilator Reversibility</td>
<td>Complete / Nearly so</td>
<td>Partial</td>
</tr>
<tr>
<td>Steroid Responsiveness</td>
<td>Strong</td>
<td>Usually weak</td>
</tr>
<tr>
<td>Leukotriene Modifier Responsiveness</td>
<td>Strong</td>
<td>Usually weak</td>
</tr>
<tr>
<td>Smoking History</td>
<td>Variable</td>
<td>Usually</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>Rare (extreme distress)</td>
<td>Common</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Rare</td>
<td>Not uncommon</td>
</tr>
<tr>
<td>Progressive Deterioration</td>
<td>Uncommon</td>
<td>Typical</td>
</tr>
<tr>
<td>Cough: Most Prominent</td>
<td>Nocturnal, exercise</td>
<td>Early morning</td>
</tr>
<tr>
<td>Purulent Sputum</td>
<td>Uncommon</td>
<td>Typical</td>
</tr>
<tr>
<td>IgE Elevated</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Antibiotics for Exacerbation</td>
<td>Poor efficacy</td>
<td>Good efficacy</td>
</tr>
</tbody>
</table>
### Table 5. COPD Severity Classifications

<table>
<thead>
<tr>
<th>Severity</th>
<th>FEV1 % predicted</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&gt;=80%</td>
<td>Individual may or may not be aware lung function is abnormal</td>
</tr>
<tr>
<td>Moderate</td>
<td>50-80%</td>
<td>Patients typically seek medical attention at this stage due to respiratory symptoms or an exacerbation</td>
</tr>
<tr>
<td>Severe</td>
<td>30-50%</td>
<td>Dyspnea, reduced exercise capacity, and repeated exacerbations impact quality of life</td>
</tr>
<tr>
<td>Very severe</td>
<td>&lt;30% or &lt;50% with deoxygenation</td>
<td>Quality of life significantly impaired; exacerbations may be life-threatening</td>
</tr>
</tbody>
</table>

### Table 6. BODE (Body-mass index, Obstruction, Dyspnea and Exercise) Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>&gt;21</td>
</tr>
<tr>
<td>FEV1% predicted</td>
<td>≥65</td>
</tr>
<tr>
<td>MMRC dyspnea scale score</td>
<td>0-1</td>
</tr>
<tr>
<td>6 minute walk distance (m)</td>
<td>≥350</td>
</tr>
</tbody>
</table>

Hazard risk for death from any cause per one-point increase in BODE score is 1.34 (NEJM 2004;350:1005-12).

### Table 7. MMRC (Modified Medical Research Council) Dyspnea Scale

Score equivalent to point value for highest level question to which a respondent answers “Yes.”

<table>
<thead>
<tr>
<th>Dyspnea Query</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?</td>
<td>0</td>
</tr>
<tr>
<td>Do you have to walk slower than people of your age on level ground because of shortness of breath?</td>
<td>1</td>
</tr>
<tr>
<td>Do you ever have to stop for breath when walking at your own pace on level ground?</td>
<td>2</td>
</tr>
<tr>
<td>Do you ever have to stop for breath when walking about 100 yards (or after a few minutes) on level ground?</td>
<td>3</td>
</tr>
<tr>
<td>Are you too short of breath to leave the house or short of breath on dressing or undressing?</td>
<td>4</td>
</tr>
</tbody>
</table>

### Table 8. Patient Education Overview

- **Mechanisms.** Inflammation, structural changes in the airways, and systemic effects
- **Triggers.** Exacerbation triggers (e.g., tobacco smoke, occupational dust and chemicals, indoor and outdoor air pollution) and trigger avoidance
- **Medications.** Dosing, schedule, rationale
- **Inhaler technique.** Correct administration technique and oral care for inhaled steroids
- **Smoking cessation.** Ask, advise, assess, assist, and arrange follow up (the “5 A’s”)
- **Signs.** Exacerbation warning signs (e.g., increased dyspnea, sputum production, or cough)
- **Acute exacerbation.** Recognition of an acute exacerbation and an initial action plan
- **End-of-Life.** Advanced directives and end-of-life treatment decisions
Table 9. Therapeutic Steps by Severity

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1/FVC &lt; 0.70</td>
<td>FEV1/FVC &lt; 0.70</td>
<td>FEV1/FVC &lt; 0.70</td>
<td>FEV1/FVC &lt; 0.70</td>
</tr>
<tr>
<td>FEV1 ≥ 80% predicted</td>
<td>FEV1 50-79% predicted</td>
<td>FEV1 30%-49% predicted</td>
<td>FEV1 &lt; 30% predicted (or &lt; 50% predicted and requiring oxygen)</td>
</tr>
</tbody>
</table>

- **Active reduction of risk factors:** smoking cessation, pneumovax, influenza vaccine
- **Short-acting bronchodilator when needed:** albuterol – first line agent; levalbuterol – second line agent, consider if patient has history of tachyarrhythmia or intolerant to albuterol
- **If symptomatic, pulmonary rehabilitation (regardless of disease severity)**

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add long-acting bronchodilator</td>
<td>Add inhaled glucocorticosteroid if repeated exacerbations: fluticasone or budesonide – first line agents (both also available as combination products: fluticasone / salmeterol and budesonide / formoterol)</td>
<td>Consider Long-term oxygen if oxygen saturation ≤ 88% or PaO2 ≤ 55 (see text for further discussion of indications)</td>
<td></td>
</tr>
<tr>
<td>Long-acting anti-cholinergic: tiotropium – first line long-acting agent</td>
<td>Long-acting beta-agonists: salmeterol or formoterol – consider adding to long acting cholinergic as a second line agent for additional symptomatic benefit, or consider first if patient intolerant to or has contraindication to long-acting anti-cholinergic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 10. Inhaled Medications Commonly Used in Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Name</th>
<th>Usual Adult Starting Dose</th>
<th>Solution for Nebulizer</th>
<th>Duration of Action</th>
<th>Cost (30 days) a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bronchodilators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>β₂-Agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td>ProAir HFA</td>
<td>2 puffs q 4-6 hrs PRN</td>
<td>2.5 mg q 6-8h PRN</td>
<td>4-6 h</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Proventil HFA</td>
<td>2 puffs q 4-6 hrs PRN</td>
<td>0.63 mg q 4-6 hrs PRN</td>
<td>4-6 h</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Ventolin HFA</td>
<td>2 puffs q 4-6 hrs PRN</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>Xopenex HFA b</td>
<td>2 puffs q 4-6 hrs PRN</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formoterol</td>
<td>Foradil Aerolizer</td>
<td>1 capsule bid</td>
<td></td>
<td>12+ h</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Perforomist</td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Brovana (R,R,formoterol)</td>
<td>1 capsule qd</td>
<td></td>
<td>24+ h</td>
<td>NA</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Serevent Diskus</td>
<td>1 puff bid</td>
<td></td>
<td>12+ h</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>Atrovent HFA</td>
<td>2 puffs qid (17 mcg/puff)</td>
<td></td>
<td>6-8 h</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiotropium bromide</td>
<td>Spiriva Handihaler</td>
<td>1 capsule qd (18 mcg/ capsule)</td>
<td></td>
<td>24+ h</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Combination short-acting β₂-Agonists + anticholinergic in one inhaler</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol/ipratropium</td>
<td>Combitvent c</td>
<td>2 puffs tid-qid (90/18mcg/puff)</td>
<td></td>
<td>6-8 h</td>
<td>NA</td>
</tr>
<tr>
<td>Duoneb</td>
<td></td>
<td>2.5/0.5 mg q 4 - 6h</td>
<td></td>
<td></td>
<td>$24</td>
</tr>
<tr>
<td><strong>Inhaled Corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>Pulmicort Flexhaler</td>
<td>1-2 puffs BID (180 mcg/puff)</td>
<td></td>
<td>12 h</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Pulmicort Respules</td>
<td></td>
<td></td>
<td>0.5-1.0 mg q 12h</td>
<td>NA</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Flovent HFA d</td>
<td>1-2 puffs BID (110-220 mcg/puff)</td>
<td></td>
<td>12 h</td>
<td>NA</td>
</tr>
<tr>
<td>Beclomethasone dipropionate HFA e</td>
<td>QVAR</td>
<td>1-2 puffs BID (110-220 mcg/puff)</td>
<td></td>
<td>12 h</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Combination Bronchodilators and Inhaled Corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formoterol/budesonide</td>
<td>Symbicort</td>
<td>4.5/160 2 puffs BID</td>
<td></td>
<td>12 h</td>
<td>NA</td>
</tr>
<tr>
<td>Fluticasone/salmeterol</td>
<td>Advair Diskus</td>
<td>250-500/50 1 puff BID</td>
<td></td>
<td>12 h</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Advair HFA e</td>
<td>115-230/21 2 puffs BID</td>
<td></td>
<td>12 h</td>
<td>NA</td>
</tr>
</tbody>
</table>

a Cost = Average wholesale price based -10% for brand products and Maximum Allowable Cost (MAC) + $3 for generics for average 30-day supply. Sources: AmerisourceBergen item catalog, 2/10, and Michigan Department of Community Health M.A.C. Manager, 2/10

b May cause less tremor and tachycardia compared to albuterol, but at a higher price and no difference in major clinical outcomes.

c Not recommend use as a first line agent due to inability to titrate the short acting beta agonist component to a lowest necessary dose while achieving a therapeutic anticholinergic dose.

d HFA steroid inhalers should always be used with a valved holding chamber type spacer.

e FDA indicated for asthma only. Included here because some payers approve only it as a covered inhaled corticosteroid.
Table 11. Indications for Intermittent or Continuous Use of Oxygen Therapy for Very Severe COPD

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Intermittent Use</th>
<th>Continuous Use b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Resting (\text{PaO}_2 \leq 55) mmHg or (\text{SaO}_2 \leq 88)%</td>
<td>Resting (\text{PaO}_2 56-59) mmHg ((\text{SaO}_2 89-90)%) with any one of the following:</td>
</tr>
<tr>
<td>Weak</td>
<td>Desaturation of (\text{PaO}_2 \leq 55) mmHg ((\text{SaO}_2 \leq 88)%), either:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>\• with activity</td>
<td>\• peripheral edema suggesting congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>\• at night</td>
<td>\• evidence of pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>(Resting (\text{PaO}_2 56-59) mmHg ((\text{SaO}_2 89-90)%)) with any one of the following:</td>
<td>\• polycythemia (hematocrit &gt; 55%)</td>
</tr>
</tbody>
</table>

a Criteria for Center for Medicare and Medicaid Services reimbursement.
b Administered for at least 15 hours per day, preferably longer.

Table 12. Acute Exacerbation: Commonly Used Pharmacologic Therapies and Doses

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Usual Adult Dose</th>
<th>Cost (30 days) a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short acting (\beta_2)-adrenergic agonists (SABA) – Inhaled</strong> [bronchodilator]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol MDI</td>
<td>ProAir (HFA)</td>
<td>4-8 puffs q 20 min x 4 hrs prn, then 4-8 puffs q 1-4 hrs prn (90 mcg/spray)</td>
<td>NA $26-43</td>
</tr>
<tr>
<td></td>
<td>Proventil (HFA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ventolin (HFA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol Nebulizer solution 0.5%</td>
<td>AccuNeb</td>
<td>2.5-5 mg q 20 min x 3 doses, then 5 – 10 mg q 1-4 hrs prn (5mg/mL)</td>
<td>$8 $46</td>
</tr>
<tr>
<td>Levalbuterol tartrate MDI</td>
<td>Xopenex (HFA)</td>
<td>2 puffs q 4-6 hrs prn (45 mcg/spray)</td>
<td>NA $50</td>
</tr>
<tr>
<td>Levalbuterol HCl Nebulizer solution</td>
<td>Xopenex</td>
<td>0.63 – 1.25 mg q 8hr prn (1.25 mg/0.5 mL)</td>
<td>$110 $126</td>
</tr>
<tr>
<td><strong>Short acting anticholinergic b – Inhaled</strong> [bronchodilator]. Can be used in addition to short acting (\beta_2)-adrenergic agonists (SABA), however efficacy is questionable.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium MDI</td>
<td>Atrovent (HFA)</td>
<td>2-4 puffs q 6 hrs prn (17 mcg/spray)</td>
<td>NA $128</td>
</tr>
<tr>
<td>Ipratropium Nebulizer solution</td>
<td></td>
<td>500 mcg q 6 hrs prn (500 mcg/2.5 mL)</td>
<td>$6-20 NA</td>
</tr>
<tr>
<td><strong>Oral Corticosteroids c [anti-inflammatory]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone: 1, 2.5, 5, 10, 20, 25 mg tabs; 1 mg/mL liquid</td>
<td></td>
<td>30-40 mg/day for 7-10 days. Regimens may vary in dosage strength and duration</td>
<td>$4-20 NA</td>
</tr>
<tr>
<td>Prednisolone: 5 mg tabs; 1 mg/mL, 3 mg/mL liquid</td>
<td></td>
<td>30-40 mg/day for 7-10 days. Regimens may vary in dosage strength and duration</td>
<td>$6-10 $30-50</td>
</tr>
</tbody>
</table>

(Table continues on next page)
Table 12. Acute Exacerbation: Pharmacologic Therapies and Doses (continued)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Usual Adult Dosing</th>
<th>Cost (30 days) a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics</strong> d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients without risk factors</strong> e</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Zithromax</td>
<td>500 mg PO on day 1, then 250 mg PO on days 2-5</td>
<td>$16-77</td>
</tr>
<tr>
<td>250, 500 mg tabs; 100, 200/5 mL liquid</td>
<td></td>
<td></td>
<td>$60-85</td>
</tr>
<tr>
<td><strong>Cephalosporins (2nd or 3rd generation)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefdinir</td>
<td>Omnicef</td>
<td>300 mg PO BID</td>
<td>$60-88</td>
</tr>
<tr>
<td>300 mg tabs; 125, 250/5mL liquid</td>
<td></td>
<td></td>
<td>$334-686</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>Vantin</td>
<td>200 mg PO BID</td>
<td>$102-466</td>
</tr>
<tr>
<td>100, 200 mg tabs; 100/5mL liquid</td>
<td></td>
<td></td>
<td>$522</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>Cefzil</td>
<td>500 mg PO BID</td>
<td>$150-177</td>
</tr>
<tr>
<td>250, 500 mg tabs; 250/5mL liquid</td>
<td></td>
<td></td>
<td>$436-520</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Vibramycin capsule</td>
<td>100 mg PO BID</td>
<td>$8</td>
</tr>
<tr>
<td>100 mg tabs</td>
<td></td>
<td></td>
<td>$355</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Vibramycin syrup</td>
<td>100 mg PO BID</td>
<td>$78</td>
</tr>
<tr>
<td>50/5 mL liquid</td>
<td></td>
<td></td>
<td>$348</td>
</tr>
<tr>
<td><strong>Trimethoprim/sulfamethoxazole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80/400, 160/800 mg tabs; 400/200/5 mL liquid</td>
<td>Bactrim</td>
<td>160/800 (DS tab) PO BID</td>
<td>$13-67 (all)</td>
</tr>
<tr>
<td></td>
<td>Sepra</td>
<td>160/800 (DS tab) PO BID</td>
<td>$120-140</td>
</tr>
<tr>
<td></td>
<td>Sulfatrim (liquid)</td>
<td>20 mL PO BID</td>
<td>(all)</td>
</tr>
<tr>
<td><strong>Patients with risk factors</strong> e (no particular order)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>Augmentin</td>
<td>500 mg PO q8 hrs or 875 mg PO q12 hrs</td>
<td>$60-92 (tab)</td>
</tr>
<tr>
<td>250/125, 500/125, 875/125 mg tabs; 200/28.5 /5mL, 400/57 /5mL liquid</td>
<td></td>
<td></td>
<td>$430-482</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>Levaquin</td>
<td>500 mg PO daily</td>
<td>NA</td>
</tr>
<tr>
<td>250, 500, 750 mg tabs; 25 mg/mL liquid</td>
<td></td>
<td></td>
<td>$436</td>
</tr>
<tr>
<td><strong>Patients at risk for infection with Pseudomonas aeruginosa</strong> f (no particular order)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>Levaquin</td>
<td>750 mg PO daily</td>
<td>NA</td>
</tr>
<tr>
<td>250, 500, 750 mg tabs; 25 mg/mL liquid</td>
<td></td>
<td></td>
<td>$817</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Cipro</td>
<td>500-750 mg PO BID</td>
<td>$25-36</td>
</tr>
<tr>
<td>100, 250, 500, 750 mg tabs</td>
<td></td>
<td></td>
<td>$323-484</td>
</tr>
</tbody>
</table>

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a Cost = Average wholesale price based -10% for brand products and Maximum Allowable Cost (MAC) + $3 for generics for average 30-day supply, Sources: AmerisourceBergen item catalog, 2/10, and Michigan Department of Community Health M.A.C. Manager, 2/10

b Tiotropium does not have acute bronchodilating properties. Ipratropium is preferred for acute exacerbations.

c Oral corticosteroids are not for general maintenance and should be weaned following exacerbation therapy.

d Antibiotics are recommended for patients with increased sputum purulence plus either increased sputum volume or increased dyspnea.

e Risk factors include: age > 65, FEV1 < 50% predicted, ≥ 3 exacerbations/year, and presence of comorbid diseases.

f Risk factors for Pseudomonas aeruginosa are:

- Recent hospitalization
- Frequent administration of antibiotics (4 courses over the past year)
- Severe COPD exacerbations
- Isolation of P. aeruginosa during a previous hospitalization or colonization during a stable period

g Use of fluoroquinolones should be reserved for use only when other options are not feasible, due to high rates of E coli resistance and propensity for collateral damage (resistance, C difficile infection).
Clinical Problem and Management Issues (continued)

Management issues. Both physicians and patients underrecognize the potential benefits of appropriate disease management for COPD. The lack of a large FEV1 response to bronchodilation may contribute to a sense of therapeutic nihilism. However, COPD is a chronic inflammatory disease with systemic manifestations that affect patient function, quality of life, rate of lung function decline and the development of comorbidities. FEV1 is not the sole measure of disease response. COPD is responsive to multiple treatments. With appropriate comprehensive treatment, patients with COPD may achieve improved quality of life and prognosis.

Rationale for Recommendations

Etiology/Prognosis

Etiology. The pulmonary manifestations of COPD are associated with an abnormal inflammatory response to noxious inhaled particles or gases. The most commonly associated noxious agent is cigarette smoke, and cigarette smoking is the single largest risk factor for COPD. Second hand smoke is a recognized risk factor, as are environmental and occupational air pollutants. Deficiency of alpha-1-antitrypsin is a treatable cause of abnormal inflammatory response; while uncommon, it can be an important etiologic factor in early onset and severe disease.

Prognosis. COPD is a chronic disease characterized by acute exacerbations. Airflow limitation is usually progressive, and life expectancy falls as disease progresses. In the United States, COPD is the fourth leading cause of death, and the number of deaths related to COPD are rising. While FEV1 is commonly used to assess disease severity, it is imperfect for prognostic prediction. A better predictor of survival is the multidimensional disease index known as BODE score (Table 6):

- Body mass index
- Obstruction of airflow as measured by FEV1
- Dyspnea as measured by the modified Medical Research Council scale (Table 7), and
- Exercise capacity measured by a timed 6-min walk distance

Screening for COPD

Although about half of the estimated 24 million people with COPD in the United States are undiagnosed, controversy exists regarding whether population-wide screening for COPD actually leads to improved outcomes or is ultimately cost effective. Screening in older populations may lead to overdiagnosis in “never” smokers. The United States Preventive Services Task Force recommends against population screening. While routine population screening cannot be recommended, early diagnostic case finding is encouraged for persons at risk.

Diagnosis of COPD and Diagnostic studies

Risk factors and clinical history. A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of inhalational exposures known to be risk factors for the disease including chronic tobacco smoke, occupational dusts and chemicals, and smoke from home cooking and heating fuels (see Table 2). Likelihood of a COPD diagnosis also increases with age.

Early diagnosis is encouraged, as the most effective therapy for COPD in terms of slowing lung function decline is smoking cessation. Also, case finding may improve smoking cessation rates.

Recent evidence suggests that explaining a patient’s pulmonary function to them in terms of relative “lung-age” enhances cessation rates.

Differential diagnosis considerations for patients with chronic cough and dyspnea can be found in Tables 3 and 4.

Symptoms and Signs on Physical Exam (Table 2). Dyspnea is the symptom that most frequently leads patients to seek medical attention and worsens with disease severity. With severe disease, dyspnea can be debilitating. Chronic cough often accompanied by sputum production may precede the onset of dyspnea. It frequently begins as an intermittent symptom, but later becomes persistent. Wheezing and chest tightness are nonspecific symptoms that may or may not be present. In patients with more severe disease, anorexia and anxiety may also develop.

The physical exam is typically unhelpful in the diagnosis of COPD. Early airflow limitation is typically detectable via spirometry before it is evident on physical exam. In patients with more severe disease, the physical exam may reveal decreased breath sounds, decreased air movement, wheezing, and rhonchi. Hyperinflation as indicated by a “barrel” chest, accessory muscle use and weight loss typically indicate more advanced disease.

Basic Testing

Spirometry. Spirometry is required to make a diagnosis of COPD. Spirometry is the diagnostic “gold standard” because it is the most reproducible, standardized, and objective way of measuring airflow limitation. Spirometry should be ordered with bronchodilator and the postbronchodilator values used to assess both the presence of airflow obstruction and severity. A post-bronchodilator FEV1/FVC <0.70 confirms the presence of airflow limitation that is not fully reversible. The severity of post-bronchodilator airflow obstruction is defined by the FEV1 (Table 5).

While bronchoreversibility (defined as an increase in FEV1 of ≥ 200 ml and ≥ 12% absolute value) is commonly associated with asthma as opposed to COPD, post-
bronzodilator FEV1 improvement of 12% can also be seen in COPD. In such cases of COPD with FEV1 bronchodilation response, the post-bronchodilator FEV1/FVC by definition remains <0.70 due to persistent airflow limitation. Therefore, FEV1 response to bronchodilator should not be solely relied upon to distinguish between the two diseases (see Table 4).

While diffusion capacity and lung volumes performed via plethysmography can aid in patient characterization, it is not required for making the diagnosis of COPD.

**Differentiating COPD and asthma.** Patients with COPD frequently complain of dyspnea, cough, and phlegm production. However, compatible symptoms are not enough to make a diagnosis of COPD. COPD is defined as the presence of fixed airflow obstruction. Data indicate that only one-third of patients in the US with a diagnosis of COPD have actually undergone confirmatory testing, suggesting that both underdiagnosis and misdiagnosis are common. Unfortunately, no one test can reliably distinguish asthma from COPD and some patients have both. However, a good clinical history along with spirometry can help distinguish most cases. Distinguishing between the two diseases is important because they differ in first-line therapies and chronic management. A set of clinical factors to help guide clinicians in distinguishing between asthma and COPD can be found in Table 4.

**Other Testing in COPD**

**Imaging.** Routine chest x-ray may suggest a diagnosis of COPD, particularly if it demonstrates hyperinflation. However, a chest x-ray should not be considered diagnostic of the disease. Generally COPD can be documented by spirometry before it is seen on chest x-ray.

The utility of chest CT in prognosticating and phenotyping patients with COPD is an area of active investigation. However, current evidence is not sufficient to recommend routine chest CT’s in early or moderate COPD. In patients with severe disease, high resolution CT is required to evaluate the appropriateness of therapies such as lung volume reduction surgery or transplant.

**Alpha-1 antitrypsin.** Controversy exists regarding who should be tested for alpha-1 antitrypsin deficiency. Some of the controversy derives from quality of data regarding efficacy of treatment with alpha-1-antitrypsin augmentation therapy. We recommend at a minimum following the GOLD (Global initiative for chronic Obstructive Lung Disease) Guidelines, with consideration for broader testing (e.g., recommendations of the American Thoracic Society / European Respiratory Society joint statement) based on clinician judgment, particularly in the presence of prominent basilar lucency, unexplained liver disease, and/or the absence of other risk factors.

The GOLD Guidelines recommend testing when COPD develops in patients of Caucasian descent under 45 years of age or with a strong family history of COPD.

The ATS/ERS joint statement recommends testing:
- Symptomatic adults with emphysema, COPD, or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators;
- Adolescents with persistent airflow obstruction; and
- Asymptomatic individuals with persistent airflow obstruction and no risk factors.

**O2 Saturation and ABG.** In patients with a room air resting oxygen saturation between 89-93%, a six minute walk test with oxygen saturation should be considered to rule out ambulatory desaturation. (See indications for supplemental oxygen therapy.)

**Comorbid Diseases**

Patients with COPD are frequently at increased risk for:
- cardiovascular disease, heart failure, hypertension
- diabetes
- osteoporosis
- cancer
- psychiatric disorders including anxiety and depression.

Cigarette smoking, an established risk factor for COPD, also places patients at risk for other diseases due to its systemic effects.

**Cardiovascular disease.** COPD itself is an independent risk factor for cardiovascular disease, even after controlling for smoking. The risk may be fueled by systemic inflammation. COPD patients are actually more likely to die of cardiovascular complications or cancer than respiratory failure. Fortunately, data from several studies suggest that beta-blockers necessary for cardiovascular conditions can be safely prescribed for most patients with COPD, particularly beta-1 cardioselective blockers (e.g. atenolol, metoprolol) or combined beta and alpha blockers (e.g. carvedilol).

Clinicians may have difficulty distinguishing between heart failure and COPD in certain clinical settings. Baseline BNP measurements may be elevated in COPD patients compared to those without COPD, but are not as high as measurements in patients with heart failure. Data suggest that in patients with COPD, a low BNP (less than 100) can be helpful in ruling out significant heart failure, while a very high BNP (greater than 500) can be helpful in ruling in heart failure. Values between 100 and 500 must be interpreted with caution and in context of the entire clinical picture. For further guidance regarding the management of heart failure, see the UMHS Heart Failure Clinical Guideline.

**Inhaled corticosteroids: diabetes, osteoporosis.** Inhaled corticosteroid use is associated with a small (approx 2 mg/dL) dose-dependent increase in serum glucose concentration only in diabetics. For further guidance regarding diabetes management, see the UMHS Diabetes Clinical Guideline.
While inhaled corticosteroids may carry theoretic risk for decreasing bone mineral density (BMD), several studies following BMD over 3 years indicate the risk is likely minimal. For further guidance regarding osteoporosis management, see the UMHS Osteoporosis Clinical Guideline.

Psychiatric disorders. Psychiatric disorders may be two to three times more prevalent in COPD patients than the general population. These include depression and anxiety. Studies also indicate that women, in particular, experience greater symptoms, worse quality of life, more depression and more anxiety than their male counterparts with COPD. Efforts should be made to identify and treat psychiatric disorders in COPD patients. For further guidance regarding depression management, see the UMHS Depression Clinical Guideline.

General Management of COPD

Patient Education

Multiple nonpharmacologic care interventions have been shown to achieve improved quality of life for patients with COPD. Therefore, tailored and patient-focused education is generally recommended. Education regarding smoking cessation has the greatest capacity to influence the natural history of COPD. Education also improves patient response to exacerbations. Prospective end-of-life discussions help patients understand advanced directives and therapies at end-of-life. Specific recommended patient education content is noted in Table 8.

Disease management involves partnering with nurses and respiratory therapists to assist in patient education and compliance. Patients enrolled in pulmonary rehabilitation at the University of Michigan receive instruction in self management skills that support chronic disease management.

Preventive Care

Preventive care focuses on avoiding irritants that can aggravate COPD. The most common “triggers” are smoking, second hand smoke, occupational fumes and chemicals, indoor air pollution (e.g., cooking with biomass fuels), outdoor air pollution, and infection.

Smoking Cessation. Smoking cessation is the single most important intervention to slow the rate of lung decline and reduce respiratory symptoms regardless of the severity of the patient’s disease. The benefit of smoking cessation on the natural history of COPD is greater the earlier in the disease that cessation is achieved.

Smoking cessation should be encouraged at each visit. The combination of pharmacologic and psychosocial treatment for smoking cessation has been shown to be superior to psychosocial treatment alone in patients with COPD. Smoking cessation counseling is a billable diagnosis for patients with COPD. For further guidance on smoking cessation, see the UMHS Smoking Cessation Guideline.

Second hand smoke. Directly measured second hand smoke (SHS) exposure appears to have an adverse impact on health outcomes in COPD, independent of personal smoking. SHS is a modifiable risk factor. Clinicians should assess SHS exposure in their patients and counsel its avoidance. In public health terms, the effects of SHS exposure on this vulnerable subpopulation provide a further rationale for laws prohibiting public smoking.

Occupational fumes. Nineteen percent of COPD cases are attributed to occupational pulmonary irritant exposure. Therefore, limiting exposure to industrial fumes and dust is advised. Limiting exposure can help slow progression of disease and improve symptoms. Occupational exposures include organic and inorganic dusts, chemical agents, and fumes. In men with early COPD, each year of continued occupational fume exposure has been found to be associated with a 0.25% reduction in post-bronchodilator FEV1% predicted.

Particulates (air pollution). Patients with COPD should be counseled to monitor the pollution index and stay indoors when pollution is high. Staying indoors when air quality is poor may help reduce symptoms. Emergency room visits have been shown to increase among patients with COPD following days of high air pollution.

Patients should be counseled to avoid indoor air pollution as well. Use of biomass fuels, such as wood, crop material, and garbage, for indoor cooking is a significant risk factor for COPD, especially in developing countries.

Vaccination. Patients with COPD are at increased risk for complications from pulmonary infections (e.g., hospitalization, increased use of antibiotics). Therefore, the CDC Advisory Committee of Immunization Practices recommends all patients receive pneumococcal polysaccharide vaccine and yearly influenza vaccine.

Pneumococcal polysaccharide vaccination is performed through an initial dose given to all COPD patients. If the initial dose is given at an age < 65, a second dose should be administered when the individual is ≥ 65 years old and ≥ 5 years have passed since the initial vaccination. Pneumococcal vaccine has not been shown in randomized controlled trials to have significant impact on morbidity or mortality in patients with COPD. However, the vaccine remains recommended based on consensus expert opinion.

Yearly influenza vaccination has been shown to reduce exacerbations and influenza-related respiratory infections. Influenza vaccine reduces serious illness and death from influenza in COPD patients by approximately 50%.

Medications for Chronic Care

Medications commonly used in COPD include bronchodilators (both short and long acting B2-Agonists
and anti-cholinergics) and anti-inflammatory agents (inhaled glucocorticoids). Guidelines for inhaler management by disease stage are presented in Table 9. More detailed dosing and cost information by drug is presented in Table 10. While medical therapy improves functional status, no existing medications for COPD have been shown to modify long-term decline in lung function and oxygen is the only treatment proven to impact mortality.

**B2-agonists and anti-cholinergics.** Both of these agents are bronchodilators. Despite limited change in spirometric measures, treatment with bronchodilators still provides clinical benefit. In COPD, long-acting bronchodilators can prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. They are indicated in the treatment of any COPD patient who is symptomatic. All categories of bronchodilators have been shown to increase exercise capacity in COPD. Current evidence suggests long-acting anti-cholinergics should be considered first line agents for baseline bronchodilator control. Combining different types of bronchodilators may increase the degree of bronchodilation with equivalent or fewer side effects.

Recently several safety concerns have been raised with both long-acting B2-agonists and anti-cholinergics.

- **Long-acting B2-agonists (LABA).** An FDA advisory panel recently reviewed long-acting beta-agonists and recommended that long-acting beta-agonists not be used as single-agent therapy in asthma (see UMHS Asthma guideline). While long-acting beta agonists may increase blood pressure and heart rate, data for COPD patients from the TORCH study (a three-year, placebo controlled trial in COPD of fluticasone propionate and salmeterol combination versus fluticasone alone, salmeterol alone, or placebo) found no increased risk of all-cause death or cardiovascular death in the salmeterol group. Thus, for patients with COPD, long-acting beta-agonists may still be used without an inhaled corticosteroid. These data further underscore the importance of distinguishing asthma from COPD.

- **Anticholinergics.** A recent meta-analysis suggested that inhaled anticholinergics (ipratropium and tiotropium) are associated with significantly increased risk of cardiovascular death, MI, or stroke among patients with COPD. However, since then, data from the UPLIFT study (a four-year, placebo controlled trial of tiotropium) found no significant increase in myocardial infarction or stroke in the tiotropium treated group. The clinician should be aware that anticholinergic drugs may also worsen symptoms and signs associated with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction and should be used with caution in patients with any of these conditions.

**Inhaled glucocorticosteroids (ICS).** Treatment with these anti-inflammatory agents can improve symptoms and health status and decrease the frequency of exacerbations. They are indicated in patients with an FEV1≤50% and frequent (at least annual) exacerbations. ICS should not be used as monotherapy or first-line therapy in COPD. However, ICS can provide additive benefit to bronchodilators in reducing the frequency of exacerbations and improving health status. Withdrawal from treatment with ICS can lead to short term increase in exacerbations in some patients.

An increase in the frequency of pneumonia, particularly in patients ≥ 65, has also been reported. The frequency of reported pneumonia appears to be approximately double in several studies comparing inhaled corticosteroid/LABA combinations versus placebo in COPD. However, in the largest published mortality study in COPD, no increase in pulmonary related deaths were noted in the ICS/LABA combination therapy group as compared to placebo. In patients with COPD being treated with ICS, particularly those over 65, the clinician should be aware of the possible increased risk of pneumonia and maintain a lower threshold for considering a diagnosis of pneumonia when patients present with increased symptoms.

Inhaled corticosteroids may also increase a patient’s risk for cataracts or glaucoma. Regular eye exams should be considered for patients using these medications. Patients should also be warned about the possibility of ICS related thrush and vocal changes. Rinsing the mouth after use of ICS should be encouraged. Decrease in bone density is a theoretic risk of this class of medication although there is little long-term data in this patient population.

Interestingly, a recent head-to-head trial of tiotropium versus salmeterol-fluticasone in COPD demonstrated similar reductions in exacerbation rates although improvements in health status were greater and deaths fewer in the salmeterol/fluticasone treated patients. The clinical implications of these data, however, are not yet clear; we recommend adding an ICS only in patients with severe disease and frequent (at least annual) exacerbations.

**Oral glucocorticosteroids** are not generally indicated for chronic use. (See Acute Exacerbation.)

**Theophylline** is effective for symptom control in COPD. However, due to its narrow therapeutic window and side effect profile, inhaled bronchodilators are preferred. All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations.

**Antibiotics.** The use of routine prophylactic antibiotics can not currently be recommended, although the utility of daily macrolide antibiotics in particular has recently received attention and is currently being investigated.

**Leukotriene modifiers.** These agents have not been adequately tested in COPD and can not be recommended at this time.

**Oxygen Therapy**

The primary goal of oxygen therapy is to maintain vital organ function by ensuring adequate oxygen delivery. This is achieved by increasing the baseline PaO2 to at least 60
mmHg (or SaO2 to at least 90%) at rest. In patients with very severe COPD, long term oxygen therapy has been shown to improve the following outcomes:

- mortality
- quality of life
- cardiovascular morbidity (i.e. pulmonary hypertension)
- depression
- cognitive function
- exercise capacity
- frequency of hospitalization

Virtually no adverse affects occur with long term oxygen therapy.

**Indications for oxygen therapy.** Oxygen saturation of ≤ 88% is considered respiratory failure in need of oxygen therapy. Patients with marginal oxygenation saturation, 89-93%, should be further evaluated for possible oxygen treatment according to clinical indications. Indications for intermittent and continuous oxygen use are summarized in Table 11.

For intermittent use, no data show symptomatic benefit from short bursts of oxygen therapy before or after exercise, although some patients may recognize an improvement in dyspnea following activity. Despite this, CMS (Center for Medicare and Medicaid Services) will reimburse intermittent oxygen use for the criteria shown in Table 11.

**Pulmonary Rehabilitation**

Pulmonary rehabilitation should be considered in any patient with COPD who experiences significant dyspnea or exercise limitation, regardless of severity of airflow limitation. (Note that Medicare typically reimburses rehabilitation only for patients who have a diagnosis of COPD and also meet the following criteria: FEV1% predicted ≤ 65%, FVC% predicted ≤ 65%, or DLCO % predicted ≤ 65%. Medicare patients who continue to smoke must also be enrolled in a smoking cessation program.)

Pulmonary rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of disease. Pulmonary rehabilitation programs typically involve a comprehensive patient assessment, aerobic exercise training, strength training, education, and psychosocial support. Randomized controlled trials demonstrate that exercise pulmonary rehabilitation in COPD patients can relieve dyspnea and improve health-related quality of life. Controlled trials suggest that pulmonary rehabilitation may reduce the number of hospital days and health-care utilization in patients with COPD.

**Follow Up Care**

**Frequency.** No clear consensus exists on frequency of office visits for chronic COPD care. In general, we recommend that initial chronic care visits occur at least semi-annually. Visits may revert to annual assessments for currently nonsmoking patients with mild disease who are stable on treatment (i.e. with only rare exacerbations). Frequency of follow-up can be guided based on:

- worsening of symptoms not associated with an exacerbation
- frequency of acute exacerbations
- smoking status
- adherence to treatment plan
- social support systems
- presence of other comorbid chronic diseases

**Factors to reassess.** At follow-up visits reassess:

- pulmonary irritant exposure risks
- symptoms: severity, control, new, stable or worsening (e.g., sputum production, dyspnea, cough, activities of daily living)
- exacerbation history and possible causes
- smoking cessation, if applicable
- current medications, dosages, adherence, and proper use
- vaccinations

**Spirometry.** Rather than routinely repeating spirometry, we recommend monitoring symptoms and functional status to guide spirometry use at routine follow up visits. No clear consensus exists on the appropriate frequency of spirometry to guide therapy after the initial diagnosis of COPD. Systematic reviews found insufficient evidence for using spirometry to guide therapy. Once therapy is initiated, evidence-based reviews do not support annual spirometry to monitor disease status for otherwise stable patients. When patients report symptomatic change or experience a significant acute exacerbation, follow-up spirometry may be warranted to detect clinically significant functional changes that may alter clinical therapeutic options.

**Medications.** Steps for increasing medical therapy based on increased severity are summarized in Table 9 and as described above under Medications for Chronic Care. If patients remain symptomatic at subsequent follow-up visits, combination pharmacotherapy should be considered.

**Oxygen therapy.** Patients with worsening symptoms, particularly if most recent FEV1 is <50% predicted or room air oxygen saturation is 89-93%, should undergo a 6 minute walk test followed by assessment of oxygen saturation. Patients currently using oxygen should be reassessed for resting hypoxemia (oxygen saturation ≤ 88%). If room air oxygenation has improved on therapy, oxygen may be discontinued. All patients prescribed oxygen must be recertified every 12 months for Medicare and Medicaid reimbursement, however retesting of PaO2 or SaO2 is not required.

**Pulmonary rehabilitation.** If not already initiated, pulmonary rehabilitation should be considered in all
patients with significant dyspnea or exercise limitation. See Pulmonary Rehabilitation section above.

After hospitalization for acute exacerbation. Patients should be reassessed following hospital discharge for acute COPD exacerbation. The assessment should include:

- spirometry (significant declines in lung function can occur with exacerbations)
- ability to cope in their home environment
- inhaler technique and understanding of treatment regimen.
- need for oxygen

Acute Exacerbation

No single definition of acute COPD exacerbation is universally accepted. It can reasonably be described as an acute change in a patient’s baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variability and is sufficient to warrant a change in medication in a patient with underlying COPD.

A commonly used operational classification of COPD acute exacerbation severity is:

- Level I: treated at home
- Level II: requires hospitalization
- Level III: leads to respiratory failure

This guideline will focus on Level I exacerbations, which can be treated as an outpatient.

Causes and differential diagnosis. Causes of acute exacerbation include:

- Infection (both viral and bacterial)
- Environmental conditions
- Air pollution
- Lack of compliance with long-term oxygen therapy
- Unknown (~1/3 of cases)

When performing a differential diagnosis of acute exacerbation of COPD, alternate diagnoses need to be considered including:

- Pneumonia
- Congestive heart failure
- Pneumothorax
- Pleural effusion
- Pulmonary embolism
- Cardiac arrhythmia

Assessment. The outpatient assessment for an acute exacerbation of COPD starts with the clinical history and physical examination. Obtaining an oxygen saturation via pulse oximetry is recommended. Ordering a chest radiograph is generally not recommended, however may be reasonable for patients >65 years of age, exposure to inhaled steroids, or the presence of fever.

There is limited utility in obtaining a sputum gram stain & culture. An exception may be patients who have recently been on antibiotics. Spirometry, arterial blood gas, and electrocardiogram are generally not recommended.

Pharmacotherapy of Acute Exacerbation

Outpatient management of acute exacerbation involves treatment with bronchodilators, systemic corticosteroids, and antibiotics. Specific drugs and dosing are described in Table 12.

Bronchodilators. Bronchodilators are considered first-line therapy since they improve respiratory symptoms and FEV1. The dose and/or frequency of short-acting β2-agonists, either inhaler or nebulizer, should be increased. An inhaled anticholinergic (ipratropium) can be added if not already used, although the effectiveness of combination therapy in the setting of acute exacerbation is questionable. Clinical response does not appear to differ between bronchodilator delivery via MDI with a spacer or by nebulizer.

Systemic corticosteroids. Corticosteroids can reduce recovery time, improve lung function (FEV1), and improve hypoxemia (PaO2). Prednisone 30-40mg PO daily is recommended for 10-14 days, particularly in patients with an FEV1 % predicted < 50%. Discontinue corticosteroids following exacerbation therapy.

Antibiotics. Antibiotics are recommended for patients with:

- increased sputum purulence
- plus either
  - increased dyspnea or
  - increased sputum volume.

Antibiotic choice should be selected for presumptive therapy based on local resistance patterns. Sputum cultures are generally not recommended unless the patient has recently been taking antibiotics. For patients who meet the above criteria for antibiotics, the selection of a specific antibiotic depends on risk factors and unusual circumstances (see Table 12).

Indications for hospitalization. The following are reasons for emergency department evaluation or hospital admission:

- Marked increase in symptoms such as dyspnea at rest
- Severe underlying COPD
- Frequent exacerbations
- Significant comorbidities (e.g., older age, pneumonia, congestive heart failure, diabetes mellitus, renal or liver failure)
- Worsening hypoxemia or hypercapnia
- Changes in mental status
- Inadequate response to outpatient therapy
- Uncertain diagnosis
- Insufficient home support

Other Management Approaches

Surgical treatment: lung volume reduction surgery, lung transplantation. Surgical therapeutic options include bullectomy and lung volume reduction surgery (LVRS). Bullectomy may be considered for patients with localized
giant bullae that are associated with compression of adjacent lung. Lung volume reduction surgery may be considered for patients with bilateral upper lobe disease and reduced exercise capacity as measured by formal cardiopulmonary exercise testing despite maximal medical therapy and pulmonary rehabilitation. Data demonstrate improved exercise capacity, dyspnea, and quality of life at 24 months; survival outcomes were favorable for those with upper lobe emphysema and reduced exercise capacity. Cost-effectiveness of this approach is not demonstrated for even the most favorable NETT subgroup (i.e. COPD patients with upper lobe emphysema and reduced exercise capacity) unless outcomes are expected to remain favorable for 10 years. Therefore, total life expectancy should be incorporated into shared decision making regarding the potential benefits of surgery.

Lung transplantation may be considered for patients with BODE index 7 to 10 without comorbid conditions that would otherwise limit the expected lifespan. Consideration of transplantation potential requires co-management with a pulmonary specialist for detailed assessment of baseline pulmonary physiology and potential contraindications.

**Complementary and alternative medicine.** While complementary and alternative medical therapies have been proposed for the treatment of COPD, little evidence of significant clinical benefit exists. For example, yoga training as a strategy to reduce dyspnea in COPD has been investigated with some evidence to suggest it may reduce dyspnea. While usual advice regarding healthy diet is generally endorsed, specific nutrient supplements have no proven benefit. Creatine supplementation has not been shown to demonstrate additive exercise capacity or muscle mass benefit for patients engaged in pulmonary rehabilitation. Pulmonary function demonstrated statistically significant worsening immediately following osteopathic manipulative treatment, as measured by FEV1 and residual volume.

**Palliative care.** Severe COPD increases risk of respiratory failure and is a leading cause of death. Given the progressive nature of the disease, clinicians are strongly encouraged to engage patients in shared decision making regarding goals of therapy, including advanced care planning and advance directives. A palliative focus for care should be discussed with patients desiring less aggressive therapy, avoidance of endotracheal intubation, or comfort care measures (symptomatic care) at the end of life. Therapies with proven effectiveness for management of dyspnea at the end of life include opioids and oxygen.

**Referral to COPD Specialist**

Consider referral to a pulmonologist/COPD specialist if:
- Concurrent cardiac disease, suspected asthma, or another pulmonary disease complicates diagnosis or management;
- Alpha-1-antitrypsin deficiency is diagnosed or strongly considered;
- Upper airway obstruction is suspected (e.g. upper airway wheezing or stridor, with consideration of otolaryngology referral v. pulmonary referral);
- Symptoms do not respond to optimal therapy or are out of proportion to obstructive findings;
- Supplementary oxygen therapy is required;
- Severe or frequent (at least one per year) exacerbations or pneumonia complicate management;
- Lung volume reduction surgery or lung transplantation is considered (BODE of 7-10, giant bullae, or earlier referral for monitoring and preparation if FEV1 <50% and likely to be a future candidate);
- Intensive care pulmonary hospitalization or mechanical ventilation is required.

**Literature Search and Recommendations**

The team began the search of literature by accepting the results of the literature searches performed for fairly recent systematic reviews (see “annotated references for full citation):

(Received literature through Dec. 2006.)

**Chronic COPD Management** Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. Annals of Internal Medicine, 2007; 14(9):633-638.  
(Received diagnosis and management (except below), through May 2005.)

(Received inhaled therapies, pulmonary rehabilitation, disease management, and supplemental oxygen, through March 2007.)

(Received literature through Nov. 2006)

To update those searches with more recent literature and to examine literature on other topics, a systematic search of literature on Medline was performed. The major search term was chronic obstructive pulmonary disease. The searches were for either guidelines or controlled trials for literature on human adults in the English language. Within these parameters individual searches were performed for the following topics starting with the indicated dates:

A. Etiology: Smoking, particulate inhalation exposures, alpha-1-antitrypsin deficiency, life expectancy based on FEV1/BODE [1/07]
B. Screening: Questionnaires, pulmonary function testing/spirometry, [1/03]
C. Diagnosis: History (risk factors, symptoms), physical exam [6/05]
D. Diagnostic studies: PFTs, alpha-1-antitrypsin level, chest X-ray, 6 minute walk test, chest CT [6/05]
E. Diagnostic classification: GOLD classes, MRC or MMRC dyspnea scale, BODE index [6/05]
F. Definition and diagnosis: Acute exacerbation [12/06]
G. Other “diagnosis” not included in C–F above [6/05]
H. Comorbid diseases (increased risk) [6/05]
I. Prevention: Smoking cessation, vaccination (influenza, pneumococ) [1/07]
J. Prevention: Irritant avoidance [1/03]
K. Pharmacologic treatment: Bronchodilators, inhaled corticosteroids [4/07]
L. Treatment: Supplemental oxygen [4/07]
M. Treatment: Pulmonary rehabilitation [4/07]
N. Treatment: Complementary and alternative medicine [1/03]
O. Treatment: Mental health, psychosocial support [1/03]
P. Treatment: Acute exacerbation – outpatient management, hospitalization [12/06]
Q. Referral to pulmonary sub-specialist [4/07]
R. Surgical treatment: Lung volume reduction surgery, lung transplantation [4/07]
S. Treatment: Follow up care, monitoring, chronic disease management [1/03]
T. Treatment: Palliative care [1/03]
U. Other “treatment” not in I–T above [12/06]
V. Other not in A–U above [12/06]

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle.

Conclusions were based on prospective randomized controlled trials if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size. The “strength of recommendation” for key aspects of care was determined by expert opinion.

Related National Guidelines

This guideline is generally consistent with the:

Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

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Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Emergency Medicine, Family Medicine, General Medicine, Geriatric Medicine, Obstetrics & Gynecology (Women’s Health), and Pulmonary & Critical Care Medicine. The Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers endorsed the final version.

Annotated References

This update focuses on chronic COPD.

This review article focuses on the role of infection in COPD

This systematic review provides recommendations for this screening in primary care.


This article focuses on the practical application of recommendations for care.


The first reference provides the guideline for management of stable COPD and the second reference provides detail on the methods and literature used to develop the guideline.


This review summarizes evidence and recommendations for management of acute exacerbations.