Chronic Obstructive Pulmonary Disease (COPD)

Clinical Practice Guidelines

Reviewed/Approved by the National Guideline Directors: August 11, 2016

Next Review/Approval: August, 2018

Developed by the National COPD Guideline Development Team

Disclaimer
This guideline is informational only. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient’s needs on an individual basis.

Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.
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Chronic Obstructive Pulmonary Disease (COPD) Clinical Practice Guidelines

Purpose
This guideline was developed by the KP National COPD Guideline Development Team (GDT) (Appendix A) to assist primary care physicians and other health care professionals in the outpatient diagnosis and management of stable COPD and COPD exacerbations.

Background
This evidence-based guideline is a new national COPD KP guideline created in 2016. It is based primarily on the 2014 Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease, and the 2015 American College of Chest Physician (ACCP)/Canadian Thoracic Society (CTS) Guidelines for the Prevention of Acute Exacerbation of Chronic Obstructive Pulmonary Disease, all with harmonization to the 2011 American College of Physician (ACP) Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease Guidelines. Additionally, the screening recommendation is adopted from the United States Preventive Services Task Force, and the staging of severity of disease is based on The Global Initiative for Chronic Obstructive Lung Disease (GOLD) international consensus statement that continues to be the standard for clinical trials.

GOLD defines COPD as “a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.”

COPD exacerbation has been defined as “an event in the natural course of the disease characterized by a baseline change in the patient’s dyspnea, cough and/or sputum that is beyond the normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.”

Methods
KP National Guideline Program follows a methodology that incorporates well-established scientific frameworks to critically appraise evidence and evaluate external guidelines.

In developing these recommendations, the GDT considered recommendations from the 2014 Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease, the 2015 American College of Chest Physician (ACCP)/Canadian Thoracic Society (CTS) Guidelines for the Prevention of Acute Exacerbation of Chronic Obstructive Pulmonary Disease, the 2011 American College of Physician (ACP) Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease Guidelines, the United States Preventive Services Task Force, and the GOLD international consensus statement that continues to be the standard for clinical trials. The GDT’s decisions and justification are outlined in Appendix B1.

Recommendations are accompanied by language that clinicians should use to weigh the strength of the recommendation against the individual patient situation. The KP National Guideline methodology, updated most recently in 2016, streamlines ratings to strong, weak, or no recommendation (i.e., when evidence is reviewed but is inadequate to drive a recommendation for or against an intervention). The current KP guidelines evolved from multiple rating systems. Appendix B2 provides a crosswalk to compare language between current KP guidelines, the ACCP, ACP, VA/DoD, and the USPSTF.
The GDTs develop guideline recommendations using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria, which considers the balance between desirable and undesirable effects, quality of evidence, patient values and preferences, and resource use. When the GDT changes a previous KP guideline, adapts an external guideline with some modifications, or reviews new evidence to inform its recommendation, the GRADE framework provides transparency into those decisions. Appendix C summarizes GDT deliberations from the GRADE process. KP recommendations that were unchanged and external guidelines that were adopted verbatim are not subject to GRADE assessment.

Additional evidence review work that was completed to inform the development of these recommendations can be found in Appendix D. This includes an assessment of the quality of the recommendations for KP adoption using the Appraisal of Guidelines Research and Evaluation (AGREE II) tool and A Measurement Tool to Assess systematic Reviews (AMSTAR).

Recommendations

Topic: Screening
- Do not screen for chronic obstructive pulmonary disease (COPD) in asymptomatic adults. (Strong Recommendation)

Topic: Diagnosis and Classification
- Use spirometry with post-bronchodilator testing to confirm all initial diagnoses of chronic obstructive pulmonary disease (COPD). This is an adapted recommendation. (Strong Recommendation)
- Offer prevention and risk reduction efforts, including smoking cessation and vaccination. (Strong Recommendation)
- Consider using the GOLD COPD classification to determine severity of airflow limitation (mild, moderate, severe, very severe) based on post-bronchodilator spirometry measurement and symptoms. This is an adapted recommendation. (Weak Recommendation)
- For patients presenting with early onset COPD or a family history of early onset COPD, consider testing for alpha-1 antitrypsin (AAT) deficiency. (Weak Recommendation)
- Refer patients with AAT deficiency to a pulmonologist for management of treatment. (Strong Recommendation)

Topic: Pharmacologic Treatment for Stable COPD
- Prescribe inhaled short-acting beta 2-agonists (SABAs) to patients with confirmed COPD for rescue therapy as needed. (Strong Recommendation)
- Consider using spacers for patients who have difficulty actuating and coordinating drug delivery with metered-dose inhalers (MDIs). (Weak Recommendation)
- Offer long-acting bronchodilators (i.e. LAMA or LABA) to patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). (Strong Recommendation)
• Consider offering inhaled long-acting antimuscarinic agents (LAMA) as first-line maintenance therapy in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). (Weak Recommendation)

• Prescribe inhaled inhaled long-acting antimuscarinic agents (LAMA) as first-line therapy for patients with confirmed, stable COPD who have respiratory symptoms (e.g., dyspnea, cough) and severe airflow obstruction (i.e., post-bronchodilator FEV1 < 50%) or a history of COPD exacerbations. (Strong Recommendation)
  o Discontinue short-acting antimuscarinic agents (SAMA) if/when starting long-acting (LAMA) antimuscarinic agents. (Clinical Consideration)

• Do not use inhaled long-acting beta 2-agonists (LABAs) without an ICS in patients with COPD who may have concomitant asthma. (Strong Recommendation)

• Do not offer an inhaled corticosteroid (ICS) in symptomatic patients with confirmed, stable COPD as a first-line monotherapy. (Strong Recommendation)

• Do not use inhaled long-acting beta 2-agonists (LABAs) without an ICS in patients with COPD who may have concomitant asthma. (Strong Recommendation)

• In patients with confirmed, stable COPD who are on inhaled LAMAs (e.g., tiotropium) or inhaled LABAs alone and have persistent dyspnea on monotherapy, use combination therapy with both classes of drugs. (Strong Recommendation)

• In patients with confirmed, stable COPD who are on combination therapy with LAMAs (e.g., tiotropium) and LABAs and have persistent dyspnea or COPD exacerbations, consider adding ICS as a third medication. (Weak Recommendation)

• Consider not withholding cardio-selective beta-blockers in patients with confirmed COPD who have a cardiovascular indication for beta-blockers. (Weak Recommendation)

**Topic: Nonpharmacologic Treatment for Stable COPD**

• Offer pulmonary rehabilitation to stable patients with exercise limitation despite pharmacologic treatment and to patients who have recently been hospitalized for an acute exacerbation. (Strong Recommendation)

• Prescribe pulmonary rehabilitation for symptomatic patients with an FEV1 < 50% predicted or who have recently been hospitalized for an acute exacerbation. (Strong Recommendation)

• Consider pulmonary rehabilitation for symptomatic or exercise-limited patients with an FEV1 > 50% predicted. (Weak Recommendation)
• Offer long-term oxygen therapy (LTOT) to patients with chronic stable resting severe hypoxemia (partial pressure of oxygen in arterial blood [PaO2] < 55 mm Hg and/or peripheral capillary oxygen saturation [SaO2] ≤ 88%) or chronic stable resting moderate hypoxemia (PaO2 of 56-59 mm Hg or SaO2 > 88% and ≤ 90%) with signs of tissue hypoxia (hematocrit >55%, pulmonary hypertension, or cor pulmonale).

(Strong Recommendation)

**Topic: Prevention of Acute Exacerbation**

• Do not give oral or intravenous systemic corticosteroids beyond the first 30 days following an acute exacerbation of COPD for the sole purpose of preventing hospitalization due to subsequent exacerbations. *This is an adapted recommendation.*

(Strong Recommendation)

• For COPD patients on optimal inhaled regimens with moderate to severe chronic obstructive pulmonary disease and a history of acute exacerbations, consider using long term macrolide therapy, oral theophylline, roflumilast, or oral N-acetylcysteine in consultation with pulmonary specialists. *This is an adapted recommendation.*

(Weak Recommendation)

**Topic: Treatment of Acute Exacerbation**

• Prescribe antibiotics for patients with COPD exacerbations who have increased dyspnea and increased sputum purulence (change in sputum color) or volume.

(Strong Recommendation)

• For acute COPD exacerbations, prescribe a course of systemic corticosteroids (oral preferred) of 30-40 mg prednisone equivalent daily for 5-7 days.

(Strong Recommendation)

• Use early non-invasive ventilation (NIV) in patients with acute COPD exacerbations to reduce intubation, mortality, and length of hospital stay.

(Strong Recommendation)

The complete guidelines from the VA/DoD\(^1\), ACCP/CTS\(^2\), ACP\(^3\), USPSTF\(^4,5\) and GOLD\(^6\) can be accessed below:

**VA/DOD**


**ACCP/CTS**


**ACP**


**USPSTF**


**GOLD**

Appendix A: National COPD Guideline Development Team

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Click here for more information on the Kaiser Permanente National Guideline Program Process and Methodology for Systematic Development of Clinical Practice Recommendations.
## Appendix B1: Crosswalk of KP Recommendations

<table>
<thead>
<tr>
<th>2016 KP Recommendation</th>
<th>Source Recommendation(s)*</th>
<th>KP GDT Decision</th>
<th>Justification</th>
</tr>
</thead>
</table>

### Topic: Screening

*Do not screen for chronic obstructive pulmonary disease (COPD) in asymptomatic adults.*  
*(Strong Recommendation)*

<table>
<thead>
<tr>
<th>2016 KP Recommendation</th>
<th>Source Recommendation(s)*</th>
<th>KP GDT Decision</th>
<th>Justification</th>
</tr>
</thead>
</table>

*The 2016 USPSTF recommends against screening for chronic obstructive pulmonary disease (COPD) in asymptomatic adults.*  
*(Grade D)*

Adopt 2016 USPSTF as is  
See evidence review *(App. D)*. Approved by GDT with no additional changes needed.

### Topic: Diagnosis & Classification

**Use spirometry with post-bronchodilator testing to confirm all initial diagnoses of chronic obstructive pulmonary disease (COPD).**  
*(Strong Recommendation)*

<table>
<thead>
<tr>
<th>2016 KP Recommendation</th>
<th>Source Recommendation(s)*</th>
<th>KP GDT Decision</th>
<th>Justification</th>
</tr>
</thead>
</table>

*The 2014 VA/DoD recommends that spirometry, demonstrating airflow obstruction (post-bronchodilator forced expiratory volume in one second/forced vital capacity [FEV1/FVC] <70%, with age adjustment for more elderly individuals), be used to confirm all initial diagnoses of chronic obstructive pulmonary disease (COPD).*  
*(Strong Recommendation)*

Adapted with minor changes  
See GRADE assessment *(App. C)* and evidence review *(App. D)* which avoids proscriptive use of age-adjusted cutoff and allows cut-off based off fixed ratio <0.7

**Offer prevention and risk reduction efforts, including smoking cessation and vaccination.**  
*(Strong Recommendation)*

<table>
<thead>
<tr>
<th>2016 KP Recommendation</th>
<th>Source Recommendation(s)*</th>
<th>KP GDT Decision</th>
<th>Justification</th>
</tr>
</thead>
</table>

*The 2014 VA/DoD recommends offering prevention and risk reduction efforts including smoking cessation and vaccination.*  
*(Strong Recommendation)*

Adopt 2014 VA/DoD as is  
Approved by GDT with no additional changes needed.

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* Various recommendation rating and evidence grading systems are used; see Appendix B2 for a crosswalk with KP recommendation ratings.
### 2016 KP Recommendation

<table>
<thead>
<tr>
<th>Topic: Stable COPD - Pharmacologic Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescribe inhaled short-acting beta 2-agonists (SABAs) to patients with confirmed COPD for rescue therapy as needed.</strong> (Strong Recommendation)</td>
</tr>
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<td><strong>Consider using spacers for patients who have difficulty actuating and coordinating drug delivery with metered-dose inhalers (MDIs).</strong> (Weak Recommendation)</td>
</tr>
<tr>
<td>2016 KP Recommendation</td>
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<tr>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Offer long-acting bronchodilators (i.e. LAMA or LABA) to patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). (Strong Recommendation)</td>
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<td>Consider offering inhaled long-acting antimuscarinic agents (LAMA) as first-line maintenance therapy in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). (Weak Recommendation)</td>
</tr>
<tr>
<td>Prescribe inhaled long-acting antimuscarinic agents (LAMA) as first-line therapy for patients with confirmed, stable COPD who have respiratory symptoms (e.g., dyspnea, cough) and severe airflow obstruction (i.e., post bronchodilator FEV1 &lt;50%) or a history of COPD exacerbations. (Strong Recommendation)</td>
</tr>
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<td>Discontinue short-acting antimuscarinic agents (SAMA) if/when starting long-acting (LAMA) antimuscarinic agents.</td>
</tr>
<tr>
<td>Do not offer an inhaled corticosteroid (ICS) in symptomatic patients with confirmed, stable COPD as a first-line monotherapy. (Strong Recommendation)</td>
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<tr>
<td>2016 KP Recommendation</td>
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<td>Do not use inhaled long-acting beta 2-agonists (LABAs) without an ICS in patients with COPD who may have concomitant asthma. (Strong Recommendation)</td>
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<td>In patients with confirmed, stable COPD who are on inhaled LAMAs (e.g. tiotropium) or inhaled LABAs alone and have persistent dyspnea on monotherapy, use combination therapy with both classes of drugs. (Strong Recommendation)</td>
</tr>
<tr>
<td>In patients with confirmed, stable COPD who are on combination therapy with LAMAs (e.g. tiotropium) and LABAs and have persistent dyspnea or COPD exacerbations, consider adding ICS as a third medication. (Weak Recommendation)</td>
</tr>
<tr>
<td>Consider not withholding cardio-selective beta-blockers in patients with confirmed COPD who have a cardiovascular indication for beta-blockers. (Weak Recommendation)</td>
</tr>
</tbody>
</table>

**Topic: Stable COPD - Nonpharmacologic Treatment**

<p>| Offer pulmonary rehabilitation to stable patients with exercise limitation despite pharmacologic treatment and to patients who have recently been hospitalized for an acute exacerbation. (Strong Recommendation) | The 2014 VA/DoD recommends offering pulmonary rehabilitation to stable patients with exercise limitation despite pharmacologic treatment and to patients who have recently been hospitalized for an acute exacerbation. (Strong Recommendation) | Combined with 2011 ACP recommendation below. | Approved by GDT with no additional changes needed. |</p>
<table>
<thead>
<tr>
<th>2016 KP Recommendation</th>
<th>Source Recommendation(s)*</th>
<th>KP GDT Decision</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer pulmonary rehabilitation for symptomatic patients with an FEV1&lt;50% predicted or who have recently been hospitalized for an acute exacerbation. (Strong Recommendation)</td>
<td>The 2011 ACP, ACCP, ATS, and ERS recommends that clinicians should prescribe pulmonary rehabilitation for symptomatic patients with an FEV1 &lt; 50% predicted (Grade: strong recommendation, moderate-quality evidence). Clinicians may consider pulmonary rehabilitation for symptomatic or exercise-limited patients with an FEV1&gt;50% predicted. (Grade: weak recommendation, moderate-quality evidence).</td>
<td>Adapt 2011 ACP, ACCP, ATS, and ERS to include 2014 VA/DoD and 2015 ACCP populations</td>
<td>Approved by GDT with no additional changes needed.</td>
</tr>
<tr>
<td>Consider pulmonary rehabilitation for symptomatic or exercise-limited patients with an FEV1&gt;50% predicted. (Weak Recommendation)</td>
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<tr>
<td>Offer long-term oxygen therapy (LTOT) to patients with chronic stable resting severe hypoxemia (partial pressure of oxygen in arterial blood [PaO2] &lt;55 mm Hg and/or peripheral capillary oxygen saturation [SaO2] ≤88%) or chronic stable resting moderate hypoxemia (PaO2 of 56-59 mm Hg or SaO2 &gt;88% and ≤90%) with signs of tissue hypoxia (hematocrit &gt;55%, pulmonary hypertension, or cor pulmonale). (Strong Recommendation)</td>
<td>The 2014 VA/DoD recommends providing long-term oxygen therapy (LTOT) to patients with chronic stable resting severe hypoxemia (partial pressure of oxygen in arterial blood [PaO2] &lt;55 mm Hg and/or peripheral capillary oxygen saturation [SaO2] ≤88%) or chronic stable resting moderate hypoxemia (PaO2 of 56-59 mm Hg or SaO2 &gt;88% and ≤90%) with signs of tissue hypoxia (hematocrit &gt;55%, pulmonary hypertension, or cor pulmonale).</td>
<td>Adopt 2014 VA/DoD as is</td>
<td>Approved by GDT with no additional changes needed.</td>
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<tr>
<td><strong>Topic: Acute Exacerbation - Prevention</strong></td>
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<tr>
<td>Do not give oral or intravenous systemic corticosteroids beyond the first 30 days following an acute exacerbation of COPD for the sole purpose of preventing hospitalization due to subsequent exacerbations. (Strong Recommendation)</td>
<td>The 2015 ACCP recommends that for patients with an acute exacerbation of COPD in the outpatient or inpatient setting, systemic corticosteroids not be given orally or intravenously for the sole purpose of preventing hospitalization due to subsequent acute exacerbations of COPD beyond the first 30-days following the initial acute exacerbation of COPD. (Grade 1A)</td>
<td>Adapted with minor changes</td>
<td>See GRADE assessment (App. C) and evidence review (App. D)</td>
</tr>
<tr>
<td>2016 KP Recommendation</td>
<td>Source Recommendation(s)*</td>
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<tr>
<td>For COPD patients on optimal inhaled regimens with moderate to severe chronic obstructive pulmonary disease and a history of acute exacerbations, consider using long term macrolide therapy, oral theophylline, roflumilast, or oral N-acetylcysteine in consultation with pulmonary specialists (Weak Recommendation)</td>
<td>The 2015 ACCP suggests the use of a long term macrolide to prevent acute exacerbations of COPD, for patients with moderate to severe COPD who have a history of one or more moderate or severe COPD exacerbations in the previous year despite optimal maintenance inhaler therapy. (Grade 2A)</td>
<td>Adapt with modifications/rationale table to create one single recommendation</td>
<td>See GRADE assessment (<a href="#">App. C</a>) and evidence review (<a href="#">App. D</a>).</td>
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<td></td>
<td>The 2015 ACCP suggests the use of roflumilast to prevent acute exacerbations of COPD, for patients with moderate to severe COPD with chronic bronchitis and a history of at least one exacerbation in the previous year. (Grade 2A)</td>
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<td>The 2015 ACCP suggests treatment with oral slow-release theophylline twice daily to prevent acute exacerbations of COPD, for stable patients with chronic obstructive pulmonary disease. (Grade 2B)</td>
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<td>The 2015 ACCP suggests treatment with oral N-acetylcysteine to prevent acute exacerbations of COPD, for patients with moderate to severe chronic obstructive pulmonary disease and a history of two or more exacerbations in the previous two years. (Grade 2B)</td>
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</tbody>
</table>

**Topic: Acute Exacerbation - Treatment**

| Prescribe antibiotics for patients with COPD exacerbations who have increased dyspnea and increased sputum purulence (change in sputum color) or volume. (Strong Recommendation) | The 2014 VA/DoD recommends antibiotic use for patients with COPD exacerbations who have increased dyspnea and increased sputum purulence (change in sputum color) or volume. (Strong Recommendation) | Adopt 2014 VA/DoD as is | Approved by GDT with no additional changes needed. |
For acute COPD exacerbations, prescribe a course of systemic corticosteroids (oral preferred) of 30-40 mg prednisone equivalent daily for 5-7 days.

(Strong Recommendation)

The 2014 VA/DoD recommends a course of systemic corticosteroids (oral preferred) of 30-40 mg prednisone equivalent daily for 5-7 days for acute COPD exacerbations.

(Strong Recommendation)

Adopt 2014 VA/DoD as is

Newer evidence identified that reinforces the strength of the evidence for the duration of steroids recommended in acute exacerbation: Walters et al. 2014[13]. See evidence review (App. D). Approved by GDT with no additional changes needed.

Use early non-invasive ventilation (NIV) in patients with acute COPD exacerbations to reduce intubation, mortality, and length of hospital stay.

(Strong Recommendation)

The 2014 VA/DoD recommends the early use of non-invasive ventilation (NIV) in patients with acute COPD exacerbations to reduce intubation, mortality, and length of hospital stay.

(Strong Recommendation)

Adopt 2014 VA/DoD as is

Approved by GDT with no additional changes needed.
## Appendix B2: Crosswalk of Recommendation Ratings

<table>
<thead>
<tr>
<th>ACCP² Grading System</th>
<th>ACP³ Grading System</th>
<th>USPSTF⁴,⁵ Grading System</th>
<th>Kaiser Permanente⁹ and VA/DoD¹ Grading System</th>
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<tbody>
<tr>
<td>Grade</td>
<td>Strength of</td>
<td>Grade</td>
<td>Strength of</td>
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<td>recommendation</td>
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<td>recommendation</td>
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<tr>
<td>Strong recommendation, High-quality evidence (1A)</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Strong recommendation, High-quality evidence</td>
<td>Benefits clearly outweigh risks and burden clearly outweigh benefits</td>
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<tr>
<td></td>
<td>Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.</td>
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<tr>
<td>Strong recommendation, Moderate-quality evidence (1B)</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Strong recommendation, Moderate-quality evidence</td>
<td>Benefits clearly outweigh risks and burden clearly outweigh benefits</td>
</tr>
<tr>
<td>Grade</td>
<td>ACCP² Grading System</td>
<td>ACP³ Grading System</td>
<td>USPSTF⁴,⁵ Grading System</td>
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<td></td>
<td>Strength of</td>
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<td>recommendation</td>
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<td>recommendation</td>
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<td>Recommendation can</td>
<td>Strong recommendation</td>
<td>Benefits clearly</td>
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<td></td>
<td>apply to most patients</td>
<td>or vice versa</td>
<td>outweigh risks and</td>
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<td>in most circumstances.</td>
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<td>burden or risks</td>
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<td>Higher quality research</td>
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<td>and burden clearly</td>
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<td>may well have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
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<td></td>
<td>Evidence for at least one critical outcome from observational studies, case series, or from randomized, controlled trials with serious flaws or indirect evidence.</td>
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<td></td>
<td>Recommendation can apply to most patients in many circumstances.</td>
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<td></td>
<td>Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.</td>
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<tr>
<td>Strong recommendation, Low or very low quality evidence (1C)</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Strong recommendation, Low-quality evidence</td>
<td>Benefits clearly outweigh risks and burden or risks and burden clearly outweigh benefits</td>
</tr>
<tr>
<td>Grade</td>
<td>ACCP² Grading System</td>
<td>ACP³ Grading System</td>
<td>USPSTF⁴,⁵ Grading System</td>
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<td>-----------------------------------------</td>
<td>--------------------------------------------------</td>
<td>-------------------------------------------------</td>
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<tr>
<td>Weak recommendation, High-quality evidence (2A)</td>
<td>Benefits closely balanced with risks and burden Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies. The best action may differ depending on circumstances or patients’ or societal values. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
<td>Weak recommendation, High-quality evidence Benefits finely balanced with risks and burden</td>
<td>Grade C The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.</td>
</tr>
<tr>
<td>Weak recommendation, Moderate-quality evidence (2B)</td>
<td>Benefits closely balanced with risks and burden Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies. The best action may differ depending on circumstances</td>
<td>Weak recommendation, Moderate-quality evidence Benefits finely balanced with risks and burden</td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td>Strength of recommendation</td>
<td>Grade</td>
<td>Strength of recommendation</td>
</tr>
<tr>
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<td>----------------------------</td>
</tr>
<tr>
<td>ACCP&lt;sup&gt;2&lt;/sup&gt; Grading System</td>
<td></td>
<td>ACP&lt;sup&gt;3&lt;/sup&gt; Grading System</td>
<td></td>
</tr>
<tr>
<td>or patients' or societal values. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate. Research may well have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
<td>Weak recommendation, Low or very low quality evidence (2C)</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced</td>
<td></td>
</tr>
<tr>
<td>Evidence for at least one critical outcome from observational studies, case series, or from randomized, controlled trials with serious flaws or indirect evidence. Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.</td>
<td>Weak recommendation, Low-quality evidence</td>
<td>Benefits finely balanced with risks and burden</td>
<td></td>
</tr>
<tr>
<td>ACCP² Grading System</td>
<td>ACP³ Grading System</td>
<td>USPSTF⁴,⁵ Grading System</td>
<td>Kaiser Permanente⁹ and VA/DoD¹ Grading System</td>
</tr>
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<td>----------------------</td>
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<td>---------------------------------------------</td>
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<tr>
<td>Grade</td>
<td>Strength of</td>
<td>Grade</td>
<td>Grade</td>
</tr>
<tr>
<td></td>
<td>recommendation</td>
<td></td>
<td>Intended action</td>
</tr>
<tr>
<td>Consensus-based</td>
<td>Uncertainty due to</td>
<td>Insufficient evidence to</td>
<td>No recommendation</td>
</tr>
<tr>
<td>(CB)</td>
<td>lack of evidence but</td>
<td>determine net benefits</td>
<td>for or against</td>
</tr>
<tr>
<td></td>
<td>expert opinion that</td>
<td>or risks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>benefits outweigh</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>risk and burdens or</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>vice versa</td>
<td></td>
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<tr>
<td></td>
<td>Insufficient evidence for a graded recommendation</td>
<td></td>
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<tr>
<td></td>
<td>Future research may well have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Grade I Statement</td>
<td>No recommendation for or against</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recommendation language: No recommendation for or against
# Appendix C: Rationale for KP-Modified Recommendation

## Topic: Spirometry testing with post-bronchodilator testing for confirmation of initial diagnoses of chronic obstructive pulmonary disease (COPD)

<table>
<thead>
<tr>
<th><strong>Recommendation</strong></th>
<th>Use spirometry, with post-bronchodilator testing to confirm all initial diagnoses of chronic obstructive pulmonary disease (COPD). (Strong Recommendation)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basis of Recommendation</strong></td>
<td>Spirometry with post-bronchodilator testing to confirm all initial diagnoses of chronic obstructive pulmonary disease is needed to meet diagnostic criteria for COPD. A HEDIS measure additionally exists to hold health care delivery systems accountable to this standard. Although age adjustments may be beneficial for more elderly patients as delineated in the VA DoD(^1) recommendations and others, community standard for diagnostic spirometry in the United States generally relies on a simple requirement that fixed obstructive physiology be identified, characterized by a post-bronchodilator FEV1/FVC less than 0.70. Although age adjustments such as using statistically derived lower limit of normal cutoffs to define obstructive physiology may improve diagnostic accuracy at the extremes of age, we did not feel that sufficient evidence supported requiring adjustments to be dictated by these guidelines.</td>
</tr>
<tr>
<td><strong>GRADE criteria</strong></td>
<td>GRADE assessment</td>
</tr>
<tr>
<td><strong>Balance of desirable and undesirable effects</strong></td>
<td>Generally, in a typical adult population at time of diagnosis with a medium age in the 5th to 6th decades, age adjusted cutoffs have not emerged as having significant advantage over the fixed ratio for diagnostic accuracy. Added technical resources and expert consensus across institutions and providers who interpret spirometry cannot be justified without clear evidence that age adjustment in requisite. However, individual providers or clinical groups would not be prevented from employing evidence based strategies to age adjust.</td>
</tr>
<tr>
<td><strong>Quality of Evidence</strong></td>
<td>Evidence was of low quality to support age adjustments with mixed results suggesting benefit only at the age extremes. No evidence has tested the various cutoff strategies for effectiveness of improving valued disease management outcomes.</td>
</tr>
<tr>
<td><strong>Values and Preferences</strong></td>
<td>The GDT places a high value on making accurate diagnoses of COPD. The GDT rationale in favor of not using a prescriptive cutoff for spirometric diagnosis is consistent with the current practice and standards at KP delivery sites and nationally in the medical community. Individual providers or clinical groups would not be prevented from employing evidence based strategies to age adjust, but a consistent method across a delivery region is desirable to avoid conflicting interpretations or clinical confusion. Variability of values and preferences is estimated to be low.</td>
</tr>
<tr>
<td><strong>Resource implications</strong></td>
<td>Low to moderate as some of the options for employing age adjustments may be currently available in existing spirometric equipment.</td>
</tr>
</tbody>
</table>
**Topic: Staging for COPD**

Consider using the GOLD COPD classification to determine severity of airflow limitation (mild, moderate, severe, very severe) based on post-bronchodilator spirometry measurement and symptoms. (Weak Recommendation)

<table>
<thead>
<tr>
<th>Mild</th>
<th>FEV₁ ≥ 80% predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>FEV₁ ≥ 50% predicted but &lt; 80% predicted</td>
</tr>
<tr>
<td>Severe</td>
<td>FEV₁ ≥ 30% predicted but &lt; 50% predicted</td>
</tr>
<tr>
<td>Very severe</td>
<td>FEV₁ &lt; 30% predicted</td>
</tr>
</tbody>
</table>

Although the primary adapted guideline that KP used (VA¹) made the following 2 statements:

1. We have no recommendations regarding utilization of existing clinical classification systems at this time.
2. We suggest classification of patients with COPD into two groups:
   a. Patients who experience frequent exacerbations (two or more/year, defined as prescription of corticosteroids, prescription of antibiotics, hospitalization, or emergency department [ED] visit); and
   b. Patients without frequent exacerbations

We suggest that the GOLD⁶ clinical classification system based on severity of airflow limitation (mild, moderate, severe, very severe) as determined by post-bronchodilator spirometry measurement be used to help guide clinical decisions and shared decision-making as a simple starting point on which to explore the balance of benefits and harms for therapy. The GOLD⁶ classification is used in the ACCP Guideline² (many treatment oriented guidelines rely on moderate / severe classification and comment further for those with exacerbation in prior year) as well as the ACP³ which uses FEV₁ <60% in pharmaceutical recommendations based on the increased strength of evidence in clinical trials for those with this degree of severity.

Although GOLD⁶ also offers a more complex combined assessment based on the balance of symptom and exacerbation history, data is lacking that this more complex staging system aids in shared decision-making or clinical management. The link provides more data on this approach and in time it may become a more favored approach to the clinical care. Specialized clinics and care management teams may find certain components helpful in management of more severe disease.

---

**GRADE criteria**  
**GRADE assessment**

**Balance of desirable and undesirable effects**

Generally, most spirometers produce age, height, race, gender percent predicted values allowing simple categorization into GOLD stages; presently many spirometers do not compute an age adjusted or LLN value. Although more comprehensive data may in time prove to be beneficial in management, no current evidence based strategies are based on the more complex staging systems.
<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Evidence was of low quality to support age adjustments with mixed results suggesting benefit only at the age extremes. No evidence has tested the various staging strategies for effectiveness of improving valued disease management outcomes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values and Preferences</td>
<td>The GDT places a high value on making accurate diagnoses of COPD. The GDT rationale in favor of suggesting use of GOLD staging is based on its consistency with the current practice and standards at KP delivery sites and nationally in the medical community. Individual providers or clinical groups would not be prevented from employing evidence based strategies to age adjust or add symptoms to patient management decisions. Variability of values and preferences is estimated to be low.</td>
</tr>
<tr>
<td>Resource implications</td>
<td>Low as spirometers meet criteria to support the simple GOLD staging.</td>
</tr>
</tbody>
</table>
## Topic: Avoiding long term systemic corticosteroid use for the purpose of exacerbation prevention.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Do not give oral or intravenous systemic corticosteroids beyond the first 30 days following an acute exacerbation of COPD for the sole purpose of preventing hospitalization due to subsequent exacerbations. (Strong Recommendation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basis of Recommendation</td>
<td>Although evidence supports the use of systemic corticosteroids in treatment of acute exacerbation, the use of systemic corticosteroids to treat an acute exacerbation has not been shown to reduce acute exacerbations beyond the 30-day window. Furthermore, as summarized by the ACCP/CTS recommendation, there is no evidence to support the use of chronic corticosteroids to reduce exacerbations of COPD and the risks of hyperglycemia, weight gain, infection, osteoporosis, and adrenal suppression far outweigh any benefits (ACCP(^2)). As the ACCP/CTS sought primarily to answer the key question only of exacerbation prevention, the original language of the recommendation was worded to avoid any suggestion against the use of steroids for acute therapy. Incorporating this guideline into our more comprehensive set of recommendations, the GDT felt that adapting the wording to focus on the strong negative recommendation against long term systemic steroids was more efficacious and harmonious with other adopted and adapted recommendations.</td>
</tr>
</tbody>
</table>

## GRADE criteria

### GRADE assessment

| Balance of desirable and undesirable effects | Consistent with the ACCP/CTS systematic review\(^2\), there is no evidence to support the use of chronic corticosteroids to reduce exacerbations of COPD and the risks of hyperglycemia, weight gain, infection, osteoporosis, and adrenal suppression far outweigh any benefits. |
| Quality of Evidence | Evidence was of moderate to high quality to support the negative recommendation (Grade 2B) against long term systemic steroid use. |
| Values and Preferences | The GDT places a high value on prevention of acute exacerbations in COPD and avoidance of undue side effects for agents that are not effective or recommended for prevention. |
| Resource implications | Low as recommendation against inappropriate therapy and can prevent undue complications. Uncertainty: Low based on strength of evidence. |
### Topic: Use of macrolide therapy, oral theophylline, roflumilast, or oral N-acetylcysteine for the prevention of acute exacerbations

#### Recommendations
Consider using long term macrolide therapy, oral theophylline, roflumilast, or oral N-acetylcysteine in consultation with pulmonary specialists for COPD patients on optimal inhaled regimens with moderate to severe chronic obstructive pulmonary disease and a history of acute exacerbations. (Weak Recommendation)

#### Basis of Recommendation
Although some evidence exists to consider the use of these agents, strong recommendation are not indicated and a myriad of considerations that include co-morbidity, patient preferences, side effect profile, cost to patients, adherence, and drug characteristics should be brought to the shared decision-making in selection of additional agents. We agree with the VA that specialty consultation is generally indicated when considering these agents. See below:

The primary adapted guideline that KP used (VA DoD) made the following 4 statements:

1. We suggest against offering roflumilast in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. (Weak Against)
2. We suggest against offering chronic macrolides in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. (Weak Against), and
3. There is insufficient evidence to recommend for or against the use of N-acetylcysteine (NAC) preparations available in the US in patients with confirmed, stable COPD
4. We suggest against offering theophylline in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist.

#### Balance of desirable and undesirable effects
Generally, in a typical COPD population inhaled regimens are the preferable long-term management approach. For those patient with ongoing symptoms and exacerbations, consideration of using long term macrolide therapy, oral theophylline, roflumilast, or oral N-acetylcysteine is best done in consultation with pulmonary specialists.

#### GRADE criteria

<table>
<thead>
<tr>
<th>GRADE criteria</th>
<th>GRADE assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Evidence</td>
<td>Evidence was of low to moderate quality to support consideration of these agents; insufficient evidence was available to consider population wide balance of side effects against clinical advantage in chronic COPD management.</td>
</tr>
<tr>
<td>Values and Preferences</td>
<td>The GDT places a high value on prevention of acute exacerbations in COPD. Although evidence is modest, there are anticipated advantages of using these agents and of the benefit of specialty consultation for patients with such severe and uncontrolled disease.</td>
</tr>
<tr>
<td>Resource implications</td>
<td>Low to moderate as some agents are very low cost but consultative pulmonary services are a limited resources. Uncertainty: Moderate as net benefits are unknown and outcome studies of comparative effectiveness are lacking.</td>
</tr>
</tbody>
</table>
Appendix D: Systematic Review

Executive Summary
The COPD National Guideline Lead Team conducted a review of existing KP regional guidelines and potential high-quality existing guidelines on COPD available for adaptation or adoption. The Lead Team determined that the Va/DoD\textsuperscript{1} best addressed the needs of the NGP and proceeded to analyze the quality and content of this guideline for comprehensiveness and adoption to the KP NGP. Additional guidelines relevant to the management of patients with current high quality systematic reviews were also identified and attempts to harmonize and supplement the VA/DoD\textsuperscript{1} was made by the Lead Team. The final product of the KP guideline is based primarily on the Va/DoD\textsuperscript{1} with harmonization to the ACP guideline\textsuperscript{3}; USPSTF for screening\textsuperscript{4}, and the ACCP/CTS\textsuperscript{2} for prevention of acute exacerbation, additionally the staging of severity of disease is based on the GOLD\textsuperscript{6} international consensus statement that continues to be the standard for clinical trials.

Clinical Questions
Following are the Key Questions adopted and adapted from the existing non-KP guidelines.

Key Questions to be Systematically Reviewed

SCREENING (Source: USPSTF\textsuperscript{4,5})

1. Does screening for COPD with prebronchodilator screening spirometry in asymptomatic adults age 40 years and older improve HrQOL or reduce morbidity or mortality?
   a. Does the effect of screening among asymptomatic adults vary across strategy (i.e., selective subgroups [age, presence of certain comorbid conditions, sex, race/ethnicity, smoking history, or others] vs. general population)?

2. Do prescreening questionnaires reliably identify high-risk asymptomatic adults who are more likely to test positive on screening for COPD?

3. What is the test performance of screening pulmonary function tests (e.g., prebronchodilator screening spirometry, peak flow [PEF] meter) in predicting diagnosis of COPD in asymptomatic adults, based on confirmation with postbronchodilator spirometry to identify fixed airflow obstruction?

4. What are the adverse effects of screening for COPD with prescreening questionnaires or screening pulmonary function tests?

5. Does identifying asymptomatic adults with fixed airflow obstruction through screening improve the delivery and uptake of targeted preventive services?
   a. Does screening for COPD increase smoking cessation rates among asymptomatic adults compared to usual care?
   b. Does screening for COPD increase relevant immunization rates among asymptomatic adults compared to usual care?

6. What are the adverse effects of COPD screening, including the impact of targeted preventive services in this population (e.g., false reassurance for screen-negative smokers)?

7. Does treatment of asymptomatic adults identified with mild to moderate COPD through screening improve HrQOL or reduce morbidity or mortality?

8. What are the adverse effects of COPD treatment in this population?

DIAGNOSIS and CLASSIFICATION (Source: VA/DoD\textsuperscript{1}, GOLD\textsuperscript{6})

1. In patients with COPD, what is the evidence that using spirometry (including the value of bronchodilator responsiveness), symptom severity, risk of exacerbations (e.g., annual exacerbation rate, time to first exacerbation), and comorbidities, alone or in combination, improves diagnosis, clinical classification (including pre-operative assessments), treatment planning, and clinician adherence to treatment protocols? (VA/DoD\textsuperscript{1} KQ1)
2. In COPD patients, what diagnostic tests are effective in distinguishing between COPD exacerbation and other causes of acute symptoms including cardiovascular disease in primary care and ER settings? (VA/DoD¹ KQ8)

**STABLE COPD - PHARMACOLOGIC TREATMENT** (Source: VA/DoD¹, ACP³)

1. In patients with COPD, what is the evidence that stepped therapy with the following drug classes, or combinations, improves outcomes?
   a. long-acting beta agonists (LABA)
   b. short-acting beta agonists (SABA) prn (as needed)
   c. SABA regularly administered
   d. short-acting anticholinergics
   e. long-acting anticholinergics
   f. inhaled corticosteroids
   g. phosphodiesterase 4 inhibitors
   h. chronic macrolides (e.g., azithromycin; chronic usage is defined as longer than 3 weeks)
   i. theophylline
   j. N-acetylcysteine

2. What is the evidence that certain subpopulations (e.g. COPD patients over 65 years) have increased benefits or risks from stepped therapy? (VA/DoD¹ KQ5)

3. In patients with COPD, who have other clinical indication(s) for beta-blocker treatment, what is the evidence of benefits and/or harms with use of these agents? (VA/DoD¹ KQ9)

**STABLE COPD - NONPHARMACOLOGIC TREATMENT** (Source: VA/DoD¹, ACP³)

1. In patients with severe COPD on optimized pharmacologic therapy, does a pulmonary rehabilitation program or chronic disease management lead to better outcomes and decreased health care utilization than routine care without rehabilitation? Pulmonary rehabilitation includes:
   a. physical rehabilitation
   b. psychological assessment and support
   c. nutrition and dietary assessment and support
   d. O2 assessment and support

2. What does the evidence show are the most effective interventions, or combination of interventions? (VA/DoD¹ KQ3)

3. What management strategies are effective for treating COPD? (ACP³, Q3)
   a. mono- and combination inhaled therapies (anticholinergics, long-acting β-agonists, or corticosteroids;)
   b. pulmonary rehabilitation programs; or
   c. supplemental long-term oxygen therapy (evidence not updated).

**ACUTE EXACERBATION – PREVENTION** (Source: ACCP²)

1. In patients greater than 40 years of age who are previous or current smokers diagnosed with COPD, does oral therapy prevent/decrease acute exacerbation of COPD? (ACCP², Pico 3)

**ACUTE EXACERBATION - TREATMENT** (Source: VA/DoD¹)
1. In patients with COPD and exacerbations, what is the evidence that short-term antibiotics are more effective than placebo in obtaining improved outcomes?
   a. Is there evidence that one antibiotic or one class of antibiotics is safer or more effective than another antibiotic or class of antibiotics?
   b. Is there evidence that self-initiated versus physician initiated antibiotics are more effective in improving outcomes for COPD patients experiencing an exacerbation?
   c. Is there evidence that procalcitonin testing is more effective in distinguishing between acute exacerbations of COPD due to bacterial infections, viral infections and noninfectious causes?
   d. Can procalcitonin testing be used to determine when antibiotics should be initiated and the duration of therapy? (VA/DoD1 KQ4)

2. In patients with COPD and acute exacerbations, what is best evidence for dosage and duration of steroid therapy to improve health outcomes? Does tapering systemic steroids lead to better outcomes than not tapering oral steroids in COPD patients treated for an acute exacerbation? (VA/DoD1 KQ7)

3. For patients hospitalized with acute COPD exacerbation, what is the evidence that use of non-invasive ventilation (NIV) improves health outcomes when compared to regular care? (VA/DoD1 KQ6)

Evidence Synthesis

**Topic: Screening**

*Diagnosis and Classification: Diagnosis (From the USPSTF Evidence Review)*

Although age adjustments may be beneficial for more elderly patients, current guidelines and the community standard for diagnostic spirometry in the United States generally relies on the requirement that fixed obstructive physiology be identified, characterized by a post-bronchodilator FEV1/FVC less than 0.70 (GOLD6). Severity of obstruction is further characterized by the post-bronchodilator FEV1 percent predicted, a ratio of volume exhaled in the first second over one predicted by any of a number of reference equations based on age, gender, race, and height. Although the fixed ratio of FEV1/FVC less than 0.70 is an easily operationalized standard for diagnostic confirmation of obstructive physiology, it has been demonstrated that due to normal aging processes the fixed ratio results in underestimation of airflow obstruction among young adults and an overdiagnosis of obstruction in the elderly. An alternative approach has been proposed using a statistically derived lower limit of normal (LLN) FEV1/FVC criteria for a threshold determination of obstruction usually defined by the lower fifth percentile or defined by more complex statistical variations against some healthy reference population. While the LLN is anticipated to be physiologically more accurate and some epidemiological study supports clinical utility in individuals younger than 45 to 50 years of age or over 70 years of age, experts disagree on the utility of the LLN and the preferred methodology of this measure. Misidentification of obstruction using LLN is generally limited to approximately 5 to 15 percent if individuals at the age extremes. Generally, in a typical adult population at time of diagnosis with a medium age in the 5th to 6th decades, the LLN has not emerged as having significant advantage over the fixed ratio for diagnostic accuracy.

**Topic: Diagnosis and Classification: Staging for COPD**

For aiding clinical decision-making, we suggest considering the use of GOLD6 COPD classification of severity of airflow limitation (mild, moderate, severe, very severe) based on spirometry measurement and symptoms (GOLD6 Table 4). Additional information on COPD assessment can be found in the GOLD report6.

<table>
<thead>
<tr>
<th>Classification</th>
<th>FEV1 (%) Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>≥ 80%</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥ 50% but &lt; 80%</td>
</tr>
<tr>
<td>Severe</td>
<td>≥ 30% but &lt; 50%</td>
</tr>
<tr>
<td>Very severe</td>
<td>&lt; 30%</td>
</tr>
</tbody>
</table>

The classification of severity in patients are as follows:
Although the primary adapted guideline that KP used (VA') made the following 2 statements:

1. We have no recommendations regarding utilization of existing clinical classification systems at this time.
2. We suggest classification of patients with COPD into two groups:
   a. Patients who experience frequent exacerbations (two or more/year, defined as prescription of corticosteroids, prescription of antibiotics, hospitalization, or emergency department [ED] visit); and
   b. Patients without frequent exacerbations,

we suggest that the GOLD\textsuperscript{6} clinical classification system based on severity of airflow limitation (mild, moderate, severe, very severe) as determined by post-bronchodilator spirometry measurement be used to help guide clinical decisions and shared decision-making as a simple starting point on which to explore the balance of benefits and harms for therapy. The GOLD\textsuperscript{6} classification is used in the ACCP Guideline\textsuperscript{2} (many treatment oriented guidelines rely on moderate / severe classification and comment further for those with exacerbation in prior year) as well as the ACP\textsuperscript{3} which uses FEV\textsubscript{1} < 60% in pharmaceutical recommendations based on the increased strength of evidence in clinical trials for those with this degree of severity.

Although GOLD\textsuperscript{6} also offers a more complex combined assessment based on the balance of symptom and exacerbation history, data is lacking that this more complex staging system aids in shared decision-making or clinical management. The link provides more data on this approach and in time it may become a more favored approach to the clinical care. Specialized clinics and care management teams may find certain components helpful in management of more severe disease.

**Topic: Prevention of Acute Exacerbation**

The ACCP\textsuperscript{2} made a number of recommendations for additional therapies beyond standard inhaled management for which the evidence base provides some advantage for these agents in prevention of subsequent exacerbations. Four separate recommendations with caveats as to the better quality evidence are articulated as follows:

For patients with moderate to severe COPD, who have a history of one or more moderate or severe COPD exacerbations in the previous year despite optimal maintenance inhaler therapy, we suggest the use of a long term macrolide to prevent acute exacerbations of COPD. (Grade 2A)

For stable patients with chronic obstructive pulmonary disease, we suggest treatment with oral slow-release theophylline twice daily to prevent acute exacerbations of COPD. (Grade 2B)

For patients with moderate to severe chronic obstructive pulmonary disease and a history of two or more exacerbations in the previous two years, we suggest treatment with oral N-acetylcysteine to prevent acute exacerbations of COPD. (Grade 2B)

For patients with moderate to severe COPD with chronic bronchitis and a history of at least one exacerbation in the previous year, we suggest the use of roflumilast to prevent acute exacerbations of COPD (Grade 2A).

The primary adapted guideline that KP used (VA DoD') made the following 4 statements:

1. We suggest against offering roflumilast in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. (Weak Against)
2. We suggest against offering chronic macrolides in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. (Weak Against), and
3. There is insufficient evidence to recommend for or against the use of N-acetylcysteine (NAC) preparations available in the US in patients with confirmed, stable COPD
4. We suggest against offering theophylline in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist.

The ACCP® evidence summary is based on more recent data indicating some utility for patients with these 4 agents. We suggest that for COPD patients on optimal inhaled regimens with moderate to severe chronic obstructive pulmonary disease and a history of acute exacerbations that practitioners in consultation with pulmonary specialists consider offering long term macrolide therapy, oral theophylline, roflumilast, or oral N-acetylcysteine to prevent acute exacerbations of COPD.

**Topic: Treatment of Acute Exacerbation**

We adopted the VA DoD¹ recommendations as timely and performed at a high standard of evidence synthesis. With respect to the recommendation for a limited course of systemic steroids, we identified an updated systematic review that met high quality standards by an AMSTAR evaluation. The 2014 systematic review performed from the Cochrane group reinforced the strength of the evidence for the duration of steroids recommended in acute exacerbation. The following summary comes from Walters, 2014¹³ updated Cochrane SR that was not included in the evidence base of the VA CPG.

**Objectives**

To compare the efficacy of short-duration (seven or fewer days) and conventional longer-duration (longer than seven days) systemic corticosteroid treatment of adults with acute exacerbations of COPD.

**Main results**

Eight studies with 582 participants met the inclusion criteria, of which five studies conducted in hospitals with 519 participants (range 28 to 296) contributed to the meta-analysis. Mean ages of study participants were 65 to 73 years, the proportion of male participants varied (58% to 84%) and COPD was classified as severe or very severe. Corticosteroid treatment was given at equivalent daily doses for three to seven days for short-duration treatment and for 10 to 15 days for longer-duration treatment. Five studies administered oral prednisolone (30 mg in four, tapered in one), and two studies provided intravenous corticosteroid treatment. Studies contributing to the meta-analysis were at low risk of selection, performance, detection, and attrition bias. In four studies we did not find a difference in risk of treatment failure between short-duration and longer-duration systemic corticosteroid treatment (n = 457; odds ratio (OR) 0.72, 95% confidence interval (CI) 0.36 to 1.46), which was equivalent to 22 fewer per 1000 for short-duration treatment (95% CI 51 fewer to 34 more). No difference in risk of relapse (a new event) was observed between short-duration and longer-duration systemic corticosteroid treatment (n = 457; OR 1.04, 95% CI 0.70 to 1.56), which was equivalent to nine fewer per 1000 for short-duration treatment (95% CI 68 fewer to 100 more). Time to the next COPD exacerbation did not differ in one large study that was powered to detect non-inferiority and compared five days versus 14 days of systemic corticosteroid treatment (n = 311; hazard ratio 0.95, 95% CI 0.66 to 1.37). In five studies no difference in the likelihood of an adverse event was found between short-duration and longer-duration systemic corticosteroid treatment (n = 503; OR 0.89, 95% CI 0.46 to 1.69, or nine fewer per 1000 (95% CI 44 fewer to 51 more)). Length of hospital stay (n = 421; mean difference (MD) -0.61 days, 95% CI -1.51 to 0.28) and lung function at the end of treatment (n = 185; MD FEV1 -0.04 L; 95% CI -0.19 to 0.10) did not differ between short-duration and longer-duration treatment.

**Authors’ conclusions**

Information from a new large study has increased our confidence that five days of oral corticosteroids is likely to be sufficient for treatment of adults with acute exacerbations of COPD, and this review suggests that the likelihood is low that shorter courses of systemic corticosteroids
(of around five days) lead to worse outcomes than are seen with longer (10 to 14 days) courses. We graded most available evidence as moderate in quality because of imprecision; further research may have an important impact on our confidence in the estimates of effect or may change the estimates. The studies in this review did not include people with mild or moderate COPD; further studies comparing short-duration systemic corticosteroid versus conventional longer-duration systemic corticosteroid for treatment of adults with acute exacerbations of COPD are required.

AMSTAR Summary

In developing the 2016 COPD clinical practice guideline, the Lead Team identified a Cochrane systematic review\(^1\) that was deemed to be of acceptable quality and relevant to a specific clinical question of steroid duration; the 2014 systematic review updates and affirms the strength of the evidence for the duration of steroids recommended in acute exacerbation. The studies analyzed in the existing systematic review examine relevant populations, interventions, comparisons and outcomes as delineated in the clinical question posed by the VA DoD\(^1\). The evidence analyst and methodologist evaluated the review using the online modification of the AMSTAR\(^1\) systematic review assessment checklist and found it to be of high quality.

The AMSTAR checklist consists of 11 questions that rate the quality of systematic reviews. Responders can choose between the following choices when answering each question: ‘yes’, ‘no’, ‘can’t answer’, and ‘not applicable’. A ‘yes’ response indicates that the systematic review has met the criteria for high quality as it relates to a specific quality domain.

All 11 questions for the Cochrane systematic review received a ‘yes’ rating indicating that it was of overall high quality. Specifically, for this systematic review, there was an a priori design, duplicate study selection and data extraction methods, and a comprehensive literature search. In addition, quality assessments were done on each study included in the systematic review using the GRADE methodology.

Walters 2014 AMSTAR Summary

AGREE II Summary

The AGREE (Appraisal of Guidelines Research and Evaluation)\(^1\) II tool is used to assess the methodological quality of existing clinical practice guidelines being considered for adoption into the NGP portfolio. This evidence-based guideline summary is based primarily on the 2014 Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease\(^1\), the 2015 American College of Chest Physician (ACCP)/Canadian Thoracic Society (CTS) Guidelines for the Prevention of Acute Exacerbation of Chronic Obstructive Pulmonary Disease\(^2\), and the earlier 2011 American College of Physician (ACP) Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease Guidelines\(^3\). The evidence analyst and methodologist evaluated the 3 identified guidelines using the online AGREE II assessment checklist and found all to be of high quality and without clear concerns for biased recommendations. The VA/DoD, ACCP, and USPSTF guidelines scored an overall quality of 7/7; the older ACP guideline scored a 4/7 mostly downgraded for lack of comprehensive descriptions of the methods used for the evidence summary (although performed by AHRQ whose standards from the Evidence Based Practice centers are usually of highest quality) and for limited consideration of implementation such as facilitators and barriers to its application. Lastly, we relied on USPSTF recommendation\(^4,5\) for the most up to date recommendation for screening (that affirms earlier statements recommending against screening by the ACP\(^3\) and VA/DoD\(^1\)).

2014 VA/DoD AGREE II Appraisal
2011 ACP AGREE II Appraisal
2015 ACCP AGREE II Appraisal
2016 USPSTF AGREE II Appraisal
AHRQ Analytic Framework for Screening for COPD

*Source: Screening for Chronic Obstructive Pulmonary Disease: A Systematic Evidence Review for the U.S. Preventive Services Task Force. April 2016*
Analytical Framework for Treatment of Stable COPD and Prevention of Exacerbations and Adverse Effects of Both
(Based on 2014 VA-DoD CPG')

KQ #1: In patients with COPD, does treatment improve outcomes?

KQ1A:
- a. long-acting beta agonists (LABA)
- b. short-acting beta agonists (SABA) prn (as needed)
- c. SABA regularly administered
- d. short-acting anticholinergics
- e. long-acting anticholinergics
- f. inhaled corticosteroids
- g. phosphodiesterase 4 inhibitors
- h. chronic macrolides (e.g., azithromycin; chronic usage is defined as longer than 3 weeks)
- i. theophylline
- j. N-acetylcysteine

KQ1B: Pulmonary Rehab

KQ1C: Supplemental Oxygen Therapy

CQ1: What is the evidence that certain subpopulations (e.g. COPD patients over 65 years, higher severity, more symptomatic, more exacerbations) have increased benefits or risks from treatment?

KQ #2: What are the adverse effects of treatment?

KQ #3: In patients with COPD, does the delivery of preventive services (smoking cessation, vaccinations) improve outcomes?

KQ #4: What are the adverse effects of preventive services?
References


