VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendations.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

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Prepared by:

The Management of Chronic Obstructive Pulmonary Disease Working Group

With support from:

The Office of Quality, Safety and Value, VA, Washington, DC
&
Office of Evidence Based Practice, US Army Medical Command

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Background

Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) comprises a combination of chronic and slowly progressive respiratory disorders including emphysema and chronic bronchitis. Clinically, COPD can be described as a significant airflow limitation, as measured by reduced maximal expiratory flow during forced exhalation. [1] A key characteristic of COPD is the incomplete reversibility of airway obstruction, which differs from other conditions such as asthma, in which airway obstruction is commonly reversible with bronchodilators. [1]

Pathology

While COPD is primarily a respiratory condition, it is associated with systemic inflammation and manifestations. [2,3] COPD results from an inflammatory process in the distal airways possibly linked to oxidative stress. [1] Pathologic changes occur in the large and small airways and in the terminal respiratory unit. These distal airways narrow in response to the inflammation. There are a number of additional pathophysiological changes as well, including hyperinflation and impaired gas exchanges, among others. [1]

Etiology

In most cases, COPD results from prolonged exposure to lung irritants. In the United States (US), for most patients, exposure to smoking is the key causal factor in the development of COPD. [1,4] Smoking has been causally associated with COPD, and more than 80% of cases of COPD in the US may have developed as a result of smoking. [4] Smoking is also a risk factor for COPD complications, such as pneumonia. [4] Smokers who give up cigarettes experience a significant slowing of decline in lung function, but typically no reversal of the established damage. [1]

Smoking is more common among military personnel than among civilians, especially in those who have been deployed. [4] The Department of Veterans Affairs (VA) spends billions of dollars a year to treat patients with COPD, a majority of which is spent to treat cases caused by smoking. [4]

Other risk factors for COPD include environmental and occupational air pollution, secondhand smoke, history of childhood respiratory infections, and genetic predisposition. [1] More unusual causes of COPD include alpha-1 antitrypsin (AAT) deficiency and other rare genetic conditions.

Epidemiology and Impact

COPD has a considerable public health impact on the general population of the US and on the health of Veterans and Service Members in particular. It is a leading cause of death in the US and globally. [5,6] Global prevalence of moderate to severe COPD has been estimated to be as high as 10% of the population. [7]

In 2011, over 12 million adults in the US lived with diagnosed COPD. [8-10] In addition, COPD is thought to be frequently underdiagnosed. Therefore, the number of Americans with COPD may be even larger. Based on a recent survey, it was estimated that as many as 24 million Americans have evidence of impaired lung function, nearly twice the number that have received an actual diagnosis. [8]

Since 1964, mortality rates due to COPD have climbed. Recently, there has been a shift in the population affected by COPD, and the mortality rate in women has surpassed that of men. [11] The condition does not affect all ethnicities equally; non-Hispanic white males were affected more than other ethnic groups.

[8] Due to the chronic and progressive nature of the condition and the long duration of the exposure to tobacco smoke necessary, the prevalence of COPD increases with age.

The condition also has important health care resource implications. The US spent approximately $49.9 billion on COPD, predominantly on direct health care expenditures. [12] In adults over the age of 25 in 2010, there were an estimated 699,000 hospitalizations for which COPD was the first diagnosis. However, there was a decline in the overall age-adjusted prevalence of those who have had COPD diagnoses, perhaps related to the overall population decrease in smoking. [10]

Veterans are at higher risk of COPD than those in the general US population. [13] Within the VA population, patients with COPD have significantly higher all-cause and respiratory-related health care utilization than patients without COPD. [14] Because some of their activities may pose a risk of environmental and occupational exposure, patients in the military are under particular scrutiny from their health care providers to look for COPD. Additionally, the physical activity associated with military life may uncover symptoms of COPD earlier among people in the armed forces. Patients in the military or veterans may therefore show signs of COPD earlier in their lives than their civilian counterparts. [15]

Progress in COPD

Despite the high number of people in the US that have been diagnosed with COPD, the age-adjusted prevalence has actually declined since 1999, possibly due to overall population decrease in smoking rates. [10] Furthermore, there has been an increase in the understanding of the disease and effective management methods. COPD is now recognized as a significant public health problem, and a greater amount of research is being conducted on the underlying mechanisms and effectiveness of various treatment methods. [16] Pharmacologic therapy is improving with better understanding of the disease process and novel drugs. Furthermore, non-pharmacologic therapy such as pulmonary rehabilitation is becoming increasingly recognized as an effective therapy. [16] While these treatment methods may not all be appropriate for all patients, they allow providers to intervene early with numerous treatment options in order to help benefit patients. The increasing amount of COPD research leading to further understanding of the disease and effective management strategies allows patients and providers alike to be optimistic that they can manage COPD effectively to provide patients with an improved quality of life (QoL).

About this Clinical Practice Guideline (CPG)

The Department of Veterans Affairs (VA) and the Department of Defense (DoD) Clinical Practice Guideline (CPG) on the Management of Chronic Obstructive Pulmonary Disease is intended to assist primary care providers in patient care. It is an update of the 2007 CPG. The system-wide goal of evidence-based CPGs is to improve patients' health and well-being. The overall expected outcomes of successful implementation of this guideline are to:

1. Formulate an efficient and effective assessment of the patient's condition;
2. Optimize the use of therapy to reduce symptoms and enhance functionality;
3. Minimize preventable complications and morbidity; and
4. Emphasize the use of personalized, proactive, patient-driven care.

This guideline represents a significant step toward achieving these goals for patients in the VA and the DoD. However, as with other CPGs, remaining challenges involve developing effective strategies for guideline implementation and evaluating the effect of guideline adherence on clinical outcomes.

Scope of this CPG

This CPG is designed to assist primary care providers in treating and managing patients with COPD. It addresses the following elements.

Population

The patient population of interest is adults (men and women) who are eligible for care in the VA or the DoD health care delivery systems. It includes Veterans and deployed and non-deployed active duty Service Members.

The population includes adults with a diagnosis or a suspicion of COPD. Patients with bronchiectasis, asthma, cystic fibrosis, or other chronic lung diseases but without COPD are not considered in this CPG.

Interventions and Management Methods

Interventions covered in this CPG include inhaled and systemic pharmacologic treatments as well as non-pharmacologic treatments used in acute and maintenance management of COPD.

Pharmacologic interventions considered include various drugs, such as long-acting beta 2-agonists (LABAs), short-acting beta 2-agonists (SABAs), short-acting antimuscarinic agents (SAMAs), long-acting antimuscarinic agents (LAMAs), inhaled corticosteroids (ICS), phosphodiesterase-4-inhibitors (PDE4), chronic macrolides, theophylline, and N-acetylcysteine (NAC). These agents are considered either alone or in combination as part of a stepped approach to managing the symptoms of COPD. This CPG also considers the use of corticosteroids or antibiotics to treat COPD exacerbations.

Non-pharmacologic interventions considered include pulmonary rehabilitation and interventions that comprise an overall disease management program for patients with COPD. This CPG also considers the use of oxygen therapy and the use of non-invasive ventilation (NIV).

Additionally, this CPG considers the use of spirometry, symptom severity, risk of exacerbations, and comorbidities to diagnose, classify, and manage COPD. It also considers diagnostic tests that may be more effective in distinguishing COPD exacerbations from other causes of dyspnea, such as cardiovascular disease. Finally, this CPG considers the question of risk and benefit of using beta-blockers in patients with COPD who have a cardiovascular indication for this treatment.

Methods

The methodology used in developing the 2014 CPG follows the *Guideline for Guidelines*, [17] an internal document of the VA/DoD Evidence-Based Practice Working Group (EBPWG). This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA and the DoD, known as the Work Group, and ultimately, the submission of an updated COPD CPG to the EBPWG.

The Champions and Work Group for this CPG were charged with updating the 2007 evidence-based clinical practice recommendations and publishing a guideline document to be used by providers within the VA/DoD health care system. Specifically, the Champions for this guideline were responsible for identifying the key questions (KQs) of greatest clinical relevance, importance, and interest for the management of patients with COPD. In addition, the Champions assisted in:

1. Conducting the evidence review, including providing direction on inclusion and exclusion criteria;
2. Assessing the level and quality of the evidence;
3. Identifying appropriate disciplines to be included as part of the Work Group;

4. Directing and coordinating the Work Group; and
5. Participating throughout the guideline development and review processes.

The Lewin Team (Team), including DutyFirst Consulting, ECRI Institute, and Sigma Health Consulting, LLC, was contracted by the VA and the DoD to support the development of this CPG and conduct the evidence review. The Team held the first conference call in September 2013, with participation from the contracting officer's representatives (COR), leaders from the VA Office of Quality, Safety and Value and the DoD Office of Evidence Based Practice, and the Champions. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing specific research questions on which to base a systematic review on the diagnosis and management of COPD. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the management of COPD from which the Work Group members were recruited. The specialties and clinical areas of interest included: family practice, internal medicine, nurse case management, nursing, pharmacy, pulmonology, social work, primary care, physical therapy, nutritional service, and dietetics.

The VA Office of Quality, Safety and Value, in collaboration with the Office of Evidence Based Practice, US Army Medical Command, the lead agency for the DoD, identified four clinical leaders, Drs. Marta Render, Kathryn Rice, and Amir Sharafkhaneh from VA and Dr. John Sherner from DoD, as Champions for the 2014 CPG.

The guideline development process for the 2014 CPG consisted of the following steps:

1. Formulating evidence questions (KQs);
2. Conducting the systematic review;
3. Convening a three and one-half day face-to-face meeting with the CPG Champions and Work Group members; and
4. Drafting and submitting a final CPG on the management of COPD to the VA/DoD EBPWG.

The KQs were developed specifically to address the current state of COPD treatment and management and significant scientific developments since the 2007 guideline. The questions selected were of high priority for the VA and the DoD key populations. Each question focused on a specific population, intervention, comparison, and outcome.

These KQs guided a systematic evidence review, which identified the body of evidence relevant to each KQ. The overall quality of the body of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology, which takes multiple factors (overall study quality, consistency of evidence, directness of evidence, and precision of evidence) into consideration to rate the overall quality of the evidence as "High," "Moderate," "Low," and "Very Low." [18]

At a three and one-half day face-to-face meeting, the CPG Champions and Work Group members, with support from the Team, drew on the body of evidence to develop recommendations. During this process, they took into account the GRADE rating for the strength of the evidence, as well as a number of other factors (balance of desirable and undesirable outcomes, values and preferences, and other considerations), to rate the strength of the recommendation as "Strong For," "Weak For," "Strong Against," or "Weak Against." They also reconciled the new recommendations with the 2007 CPG recommendations. The details of this specific process are further explained in the following section. Following, the face-to-face meeting, the Champions and Work Group members drafted the CPG document. They submitted a final CPG document in December 2014.

A more detailed description of these tasks can be found in Appendix A.

Reconciling 2007 CPG Recommendations

Evidence-based CPGs should be current, which typically requires revisions based on new evidence or as scheduled subject to time-based expirations. For example, the US Preventive Services Task Force (USPSTF) has a process for refining or otherwise updating its recommendations pertaining to preventive services. [19] Further, the inclusion criteria for the National Guideline Clearinghouse specify that a guideline must have been developed, reviewed, or revised with the past five years.

The COPD Guideline Work Group focused largely on developing new and updated recommendations based on the evidence review conducted for the priority areas addressed by the KQs. In addition to those new and updated recommendations, the Guideline Work Group considered the current applicability of other recommendations that were included in the previous CPG on management of COPD, published in 2007, subject to evolving practice in today's environment. Subject to Guideline Work Group consensus, recommendations that were no longer relevant to the current practice environment, or were otherwise out of scope for this CPG, were not carried forward to this CPG. Recommendations that were considered to be relevant to the current practice environment and still in scope for this CPG, and that required no substantive (i.e., entailing clinically meaningful) rewording, were carried forward in this CPG. The wording was, however, modified slightly to be best utilized in today's clinical environment and to uphold the GRADE recommendation format. (For more information on GRADE methodology, please refer to Grading Recommendations in Appendix A). For modified recommendations, the Guideline Work Group referred to the available evidence as summarized in the body of the 2007 CPG, though not to the evidence review that was conducted for the 2007 CPG. The modified recommendations carried forward from the 2007 CPG were not based on an updated systematic review. These "modified" recommendations are noted in the Recommendations.

The Guideline Work Group recognized the need to accommodate the transition in evidence rating systems from the 2007 CPG to the current CPG. In order to report the strength of all recommendations using a consistent format (i.e., the GRADE system), the Guideline Work Group converted the USPSTF strengths of the recommendation accompanying the carryover recommendations from the 2007 guideline to the GRADE system. As such, the Guideline Work Group considered the strength of the evidence cited for each recommendation in the 2007 CPG as well as harms and benefits, values and preferences, and other implications, where applicable. In some instances, evidence published since the 2007 CPG was considered along with the evidence base used for that CPG. Appendix B notes where such newer literature was considered when converting the strength of the recommendation from the USPSTF to GRADE system.

The Guideline Work Group recognizes that, while there are practical reasons for incorporating findings from a previous systematic review or previous recommendations [20] or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive systematic review and therefore may introduce bias.

Conflict of Interest

At the start of this guideline development process and at other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential conflict of interest in the past two years, including verbal affirmations of no conflict of interest at regular meetings. The project team was also subject to random web-based surveillance (e.g., ProPublica). If there was a positive (yes) conflict of interest response (actual or potential), then action was taken by the co-chairs and evidence-based practice program office, based on level and extent of involvement to mitigate the conflict of

interest. Actions ranged from restricting participation and/or voting on sections related to a conflict, to removal from the Work Group. Recusal was determined by the individual, co-chairs, and evidence-based practice office. No member of the final project team had any conflict of interest.

Patient-Centered Care

Guideline recommendations are patient-centered. Regardless of setting or availability of professional expertise, any patient in the health care system should be provided with the interventions that are recommended in this guideline and found to be appropriate to the patient's specific condition.

Treatment and care should take into account a patient's needs and preferences. Good communication between healthcare professionals and the patient is essential. It should be supported by evidence-based information tailored to the patient's needs. The information that patients are given about treatment and care should be culturally appropriate and available to people who do not speak or read English or who have limited literacy skills. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities.

Care of Veterans and Service Members in transition between facilities, services, or from the DoD health care system to the VA health care system should have a transition plan and be managed according to best practice guidance. Healthcare teams should work jointly to provide assessment and services to patients within this transitioning population. Management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

Implementation

The COPD CPG and algorithms are designed to be adapted by individual facilities in consideration of local needs and resources. The algorithm serves as a guide that providers can use to advise their patients on best interventions and timing of care in order to optimize quality of care and clinical outcomes.

Although this CPG represents medical practice on the date of its publication, the practice is evolving. This evolution requires continuous updating based on published research. New technology and additional research may improve patient care in the future. The CPG can assist in identifying priority areas for research and optimal allocation of resources. Future studies examining the results of CPG implementation may lead to the development of new practice-based evidence.

Limitations

It is important to note that the Work Group did not formally update all aspects of the 2007 CPG. The KQs chosen for this CPG are those of highest priority that would be supported by a comprehensive evidence review. For instance, though vitally important, an evidence synthesis was not performed for the effects of various methods of smoking cessation. This is because the authors/editors felt that the methods used for smoking cessation and their effect on COPD in general are well-established and addressed elsewhere.[1] New research in this area would not likely substantially change recommendations regarding patient outcomes.

[1] See the VA/DoD Clinical Practice Guideline for the Management of Tobacco Use. Available at: http://www.healthquality.va.gov/guidelines/cd/mtu/index.asp.

Additionally, the systematic evidence review conducted for this CPG examined literature that was published up to February 2014. The Work Group recognizes that several new studies have been published since that time. Consequently, the group reviewed and incorporated new evidence in developing and refining the recommendations. During the face-to-face meeting the group also identified additional clinical areas important to this CPG that were not covered in the original systematic review. As a result, subsequent searches were conducted to identify relevant literature addressing these areas and the methodological and overall quality of all newly identified studies were evaluated.

Guideline Working Group

Guideline Working Group*	
VA	**DOD**
Marta Render, MD (Co-Chair)*	**LTC John Sherner, MD, FCCP (Co-Chair)***
Kathryn Rice, MD (Co-Chair)*	Teresa Anekwe, PharmD, BCPS*
Amir Sharafkhaneh, MD, PhD, DABSM (Co-Chair)*	CDR Jeffrey Feinberg, MD, MPH, FAAFP*
Jennifer Ellis, RN	James Sall, PhD, FNP-BC*
Anna Fritz, MS, RD	MAJ Jason Sapp, MD, FACP*
Cynthia Hintz, MSW, LICSW	CDR Robert M. Selvester, MD
Deborah Khachikian, PharmD	LTC Sonya Shaw, FNP-BC
Catherine Staropoli, MD, FACP*	Maj Melissa Tennant, DPT
	LCDR Jennifer Wallinger, MPH, RD
The Office of Quality, Safety and Value	**Office of Evidence Based Practice, US Army Medical Command**
M. Eric Rodgers, PhD, FNP, BC	Ernest Degenhardt, RN, MSN, ANP/FNP, BC
Rene M. Sutton, BS, HCA	James Sall, PhD, FNP-BC
The Lewin Group	**Sigma Health Consulting, LLC**
Cliff Goodman, PhD	Frances Murphy, MD, MPH
Erika Beam, MS	**ECRI Institute**
Nicolas Stettler, MD, MSCE	Stacey Uhl, MS
Hillary Kleiner, MPH	Kristen D'Anci, PhD
Christine Jones, MS, MPH	Oluwaseun Akinyede, MPH
	Rebecca Rishar, BS
	Amy Tsou, MD
	Duty First Consulting
	Kathryn Laws, BA
	Anita Ramanathan, BA

*Indicates members of the core editing panel
Additional contributor contact information is available in Appendix C.

Algorithms

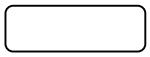
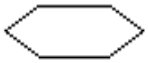
This CPG includes algorithms designed to best facilitate clinical decision-making for the management of COPD.

Algorithm Format

The format of the algorithm was chosen based on the understanding that it allows for informed diagnostic and therapeutic decision-making and has the potential to change patterns of resource use. The provider follows a pathway of critical information needed during the clinical process and decision points encountered during the provision of care. The algorithms include:

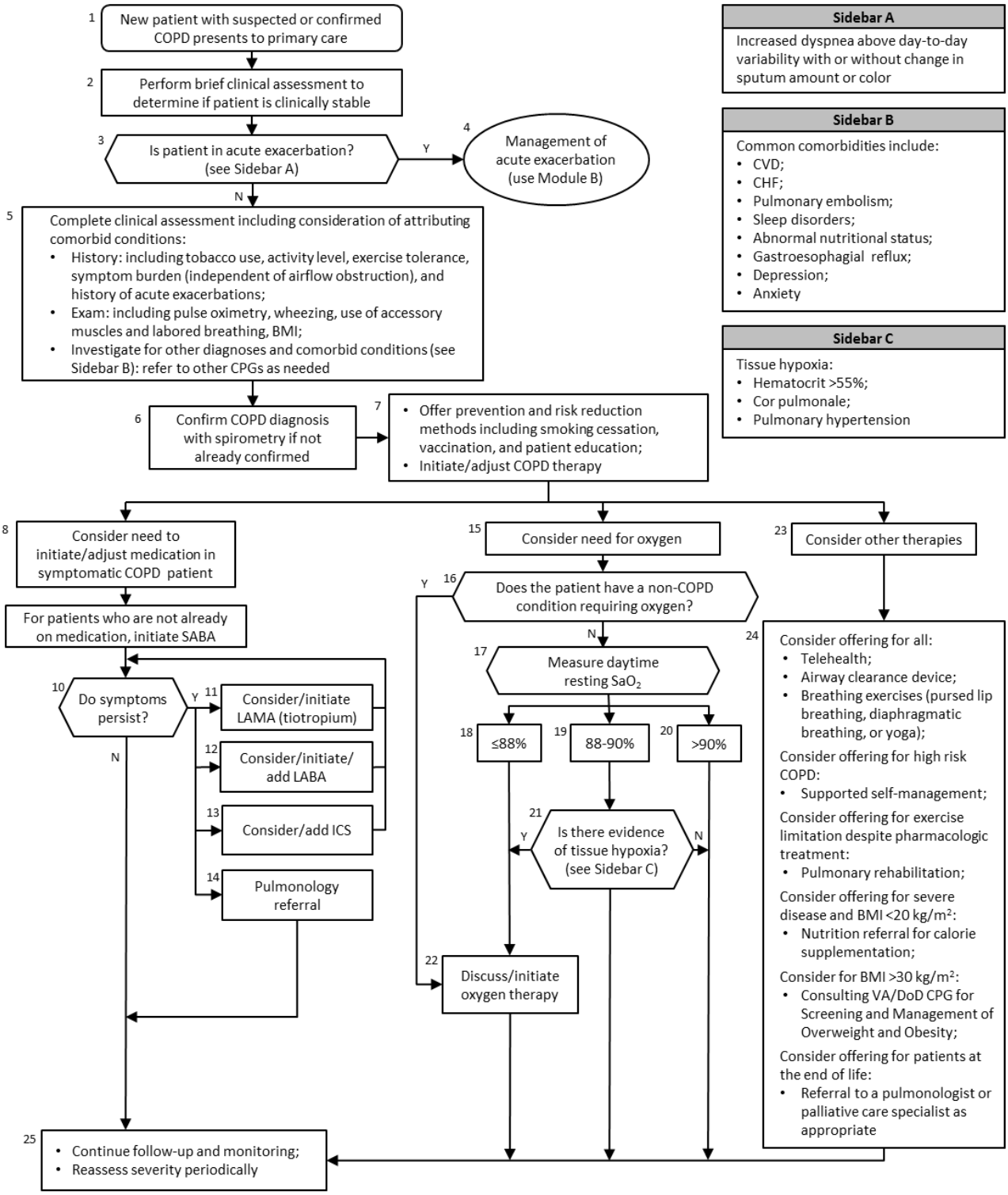
- Ordered sequences of steps of care;
- Recommended observations;
- Decisions to be considered; and
- Actions to be taken.

A clinical algorithm diagrams guideline recommendations and content into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, and arrows connect the numbered boxes indicating the order in which the steps should be followed. [21]

	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No.
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within the guideline.

This CPG is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and as patterns evolve. This CPG is based on information available at the date of publication. It is intended to provide a general guide to best practices. The guideline can assist care providers. However, its content should be considered a recommendation and should be used within the context of a provider's clinical judgment in the care of an individual patient.

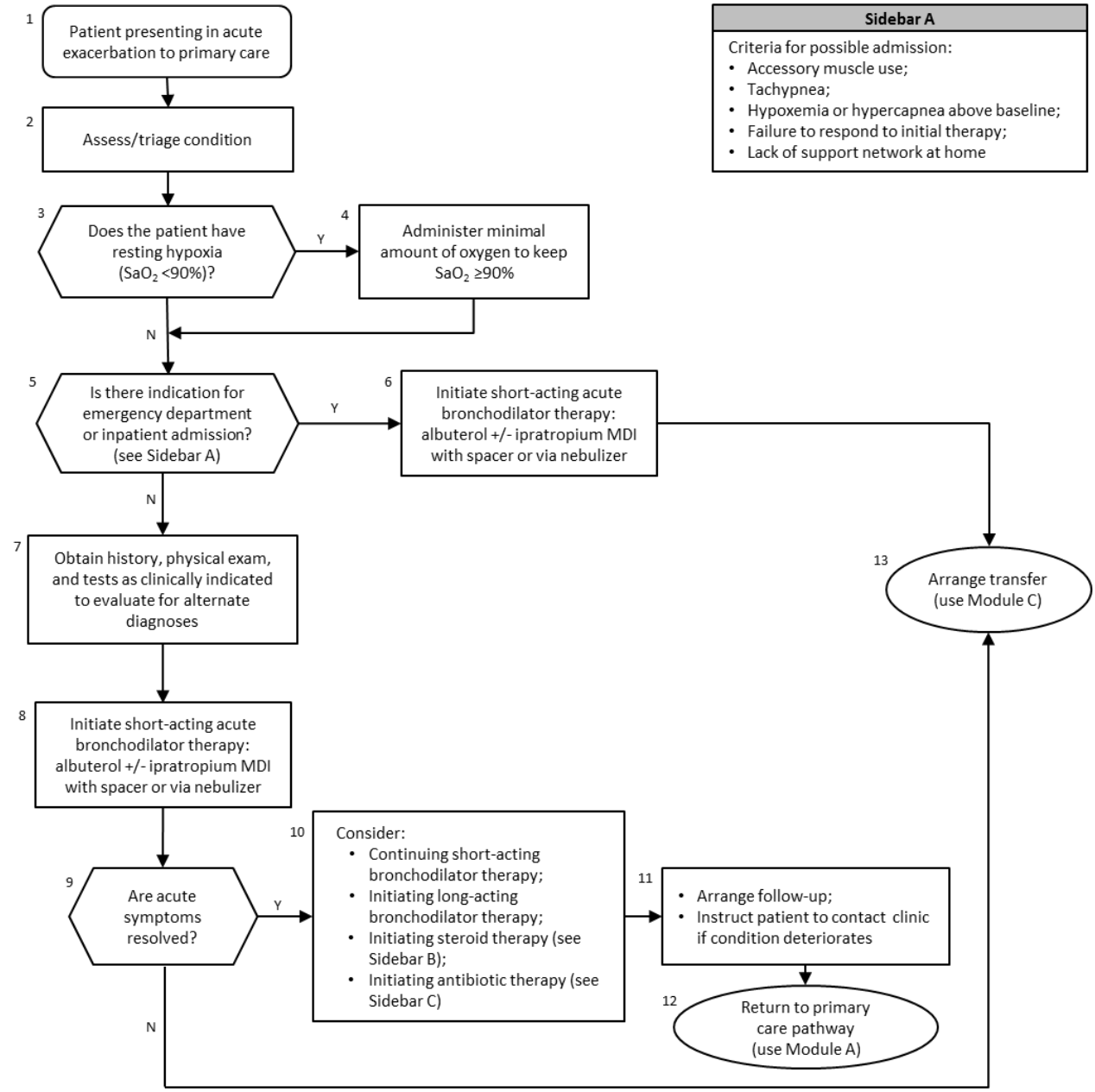
Algorithm A: Management of COPD in Primary Care



Abbreviations

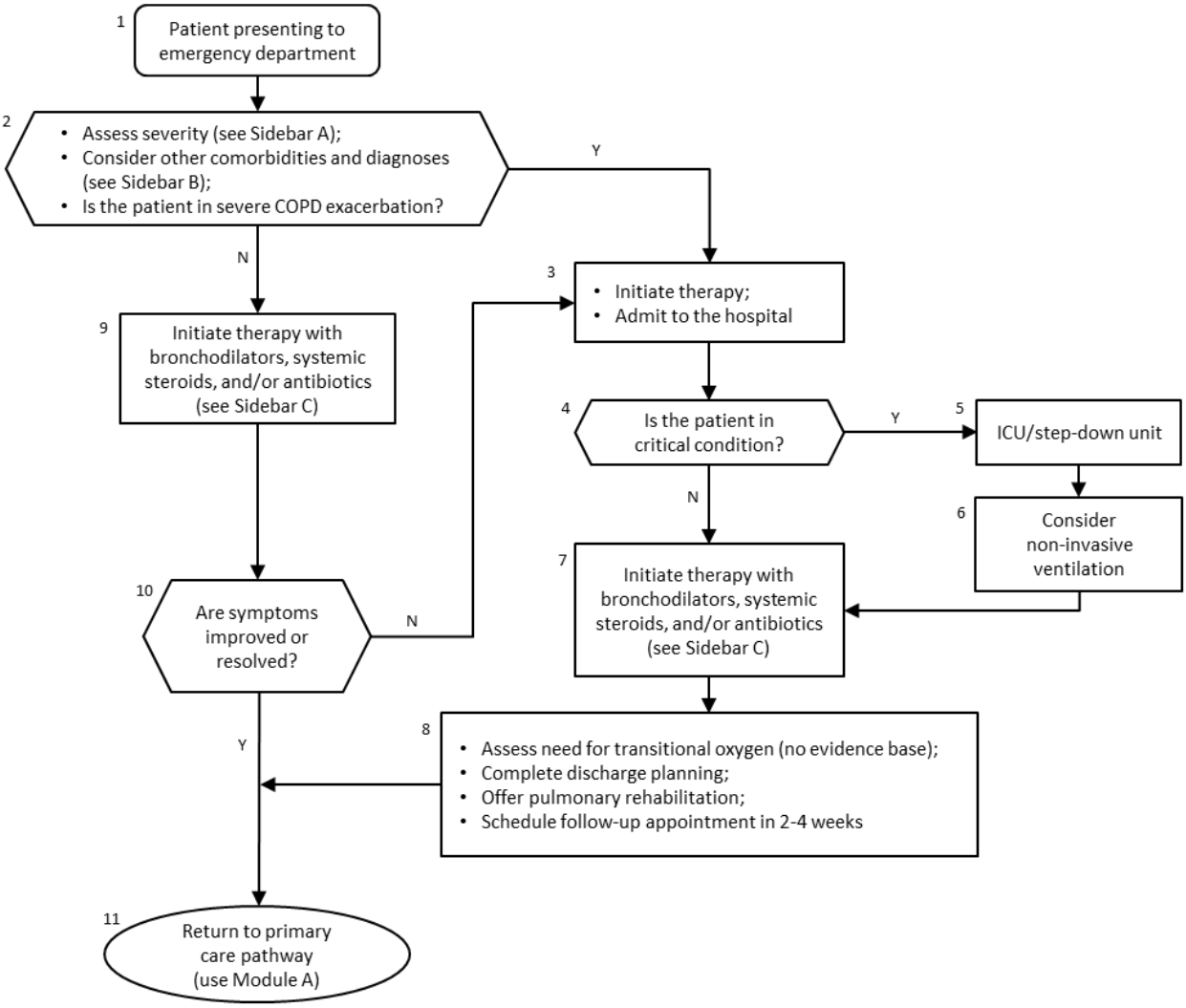
BMI: body mass index; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CPG: clinical practice guideline; CVD: cardiovascular disease; ICS: inhaled corticosteroid; kg: kilogram; LABA: long-acting beta 2-agonist; LAMA: long-acting antimuscarinic agent; m: meter; SABA: short-acting beta 2-agonist; SaO_2: peripheral capillary oxygen saturation; VA/DoD: Department of Veterans Affairs/Department of Defense

Algorithm B: Management of Acute Exacerbations of COPD



Abbreviations
COPD: chronic obstructive pulmonary disease; MDI: metered-dose inhaler; mg: milligram; SaO_2: peripheral capillary oxygen saturation

Algorithm C: Management of COPD in the Hospital or Emergency Department



Sidebar A

Indicators of severity include:
- Accessory muscle use;
- Tachypnea;
- Hypoxemia or hypercapnea above baseline;
- Failure to respond to initial therapy;
- Lack of support network at home;
- Other acute comorbid conditions presenting while patient is in acute exacerbation

Sidebar B

- Oximetry +/- ABG/VBG;
- Chemistry;
- BNP;
- EKG;
- CXR;
- D-Dimer;
- Troponin

Sidebar C

- Albuterol +/- ipratropium MDI with spacer or via nebulizer;
- Prednisone 40 mg or IV equivalent;
- Antibiotic choices:
  - Doxycycline;
  - Trimethoprim/sulfamethoxazole (TMP-SMX);
  - Second generation cephalosporin;
  - Amoxicillin;
  - Amoxicillin/clavulanate;
  - Azithromycin;
  - Reserve broader spectrum antibiotics for severe or specific risk (see text)

Abbreviations

ABG/VBG: arteriole or venous blood gas; BNP: B-type natriuretic peptide; COPD: chronic obstructive pulmonary disease; CXR: chest X-ray; EKG: electrocardiogram; ICU: intensive care unit; IV: intravenous; LTOT: long-term oxygen therapy; MDI: metered-dose inhaler; mg: milligram

Recommendations

Recommendations	Strength of Recommendation
Diagnosis and Assessment of COPD	
1. We recommend 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 For
2. We have no recommendations regarding utilization of existing clinical classification systems at this time.	Not Applicable
3. 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.	Weak For
4. We recommend offering prevention and risk reduction efforts including smoking cessation and vaccination. *Modified from the 2007 CPG without an updated systematic review of the evidence.**	Strong For
5. We recommend investigating additional comorbid diagnoses particularly in patients who experience frequent exacerbations (two or more/year, defined as prescription of corticosteroids, prescription of antibiotics, hospitalization, or ED visit) using simple tests and decision rules (cardiac ischemia [troponin, electrocardiogram], congestive heart failure [B-type natriuretic peptide (BNP), pro-BNP], pulmonary embolism [D-dimer plus clinical decision rule], and gastroesophageal reflux).	Strong For
6. We suggest that patients with COPD and signs or symptoms of a sleep disorder have a diagnostic sleep evaluation. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Weak For
7. We suggest that patients presenting with early onset COPD or a family history of early onset COPD be tested for alpha-1 antitrypsin (AAT) deficiency. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Weak For
8. We recommend that patients with AAT deficiency be referred to a pulmonologist for management of treatment. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Strong For

Recommendations	Strength of
Management of Patients with COPD in the Outpatient Setting	
Pharmacologic Therapy	
9. We recommend prescribing inhaled short-acting beta 2-agonists (SABAs) to patients with confirmed COPD for rescue therapy as needed. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Strong For
10. We suggest using spacers for patients who have difficulty actuating and coordinating drug delivery with metered-dose inhalers (MDIs). *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Weak For
11. We recommend offering long-acting bronchodilators to patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough).	Strong For
12. We suggest offering the inhaled long-acting antimuscarinic agent (LAMA) tiotropium as first-line maintenance therapy in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough).	Weak For
13. We recommend inhaled tiotropium 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 For
14. For clinically stable patients with a confirmed diagnosis of COPD and who have not had exacerbations on short-acting antimuscarinic agents (SAMAs), we suggest continuing with this treatment, rather than switching to long-acting bronchodilators. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Weak For
15. For patients treated with a SAMA who are started on a LAMA to improve patient outcomes, we suggest discontinuing the SAMA. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Weak For
16. We recommend against offering an inhaled corticosteroid (ICS) in symptomatic patients with confirmed, stable COPD as a first-line monotherapy.	Strong Against
17. We recommend against the use of inhaled long-acting beta 2-agonists (LABAs) without an ICS in patients with COPD who may have concomitant asthma.	Strong Against

Recommendations	Strength of
18. In patients with confirmed, stable COPD who are on inhaled LAMAs (tiotropium) or inhaled LABAs alone and have persistent dyspnea on monotherapy, we recommend combination therapy with both classes of drugs.	Strong For
19. In patients with confirmed, stable COPD who are on combination therapy with LAMAs (tiotropium) and LABAs and have persistent dyspnea or COPD exacerbations, we suggest adding ICS as a third medication.	Weak For
20. We suggest against offering roflumilast in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist.	Weak Against
21. We suggest against offering chronic macrolides in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist.	Weak Against
22. We suggest against offering theophylline in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist.	Weak Against
23. 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 who continue to have respiratory symptoms (e.g., dyspnea, cough).	Not Applicable
24. We suggest not withholding cardio-selective beta-blockers in patients with confirmed COPD who have a cardiovascular indication for beta-blockers.	Weak For
25. We suggest using non-pharmacologic therapy as first-line therapy and using caution in prescribing hypnotic drugs for chronic insomnia in primary care for patients with COPD, especially for those with hypercapnea or severe COPD. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Weak For
26. For patients with COPD and anxiety, we suggest consultation with a psychiatrist and/or a pulmonologist to choose a course of anxiety treatment that reduces, as much as possible, the risk of using sedatives/anxiolytics in this population. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Weak For
Oxygen Therapy	
27. We recommend providing long-term oxygen therapy (LTOT) to patients with chronic stable resting severe hypoxemia (partial pressure of oxygen in arterial blood [PaO_2] <55 mm Hg and/or peripheral capillary oxygen saturation [SaO_2] ≤88%) or chronic stable resting moderate hypoxemia (PaO_2 of 56-59 mm Hg or SaO_2 >88% and ≤90%) with signs of tissue hypoxia (hematocrit >55%, pulmonary hypertension, or cor pulmonale). *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Strong For

Recommendations	Strength of
28. We recommend that patients discharged home from hospitalization with acute transitional oxygen therapy are evaluated for the need for LTOT within 30-90 days after discharge. LTOT should not be discontinued if patients continue to meet the above criteria. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Strong For
29. We suggest against routinely offering ambulatory LTOT for patients with chronic stable *isolated* exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen.	Weak Against
30. For patients with COPD and hypoxemia and/or borderline hypoxemia (SaO_2 <90%) who are planning to travel by plane, we suggest a brief consultation or an e-consult with a pulmonologist. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Weak For
31. When other causes of nocturnal hypoxemia have been excluded, we suggest against routinely offering LTOT for the treatment of outpatients with stable, confirmed COPD and *isolated* nocturnal hypoxemia.	Weak Against
Stable Hypercapnea	
32. In the absence of other contributors (e.g., sleep apnea), we suggest referral for a pulmonary consultation in patients with stable, confirmed COPD and hypercapnea.	Weak For
Supported Self-Management	
33. We suggest supported self-management for selected high risk patients with COPD.	Weak For
34. We suggest against using action plans *alone* in the absence of supported self-management.	Weak Against
Telehealth	
35. We suggest using telehealth for ongoing monitoring and support of the care of patients with confirmed COPD.	Weak For
Pulmonary Rehabilitation	
36. We recommend 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 For
Breathing Exercise	
37. We suggest offering breathing exercise (e.g., pursed lip breathing, diaphragmatic breathing, or yoga) to patients with dyspnea that limits physical activity.	Weak For

Recommendations	Strength of Recommendation
Nutrition Referral	
38. We suggest referral to a dietitian for medical nutritional therapy recommendations (such as oral calorie supplementation) to support patients with severe COPD who are malnourished (body mass index [BMI] <20 kg/m^2).	Weak For
Lung Volume Reduction Surgery and Lung Transplant	
39. We recommend that any patient considered for surgery for COPD (lung volume reduction surgery [LVRS] and lung transplant) be first referred to a pulmonologist for evaluation. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Strong For
Management of Patients in Acute Exacerbation of COPD	
40. We recommend antibiotic use for patients with COPD exacerbations who have increased dyspnea and increased sputum purulence (change in sputum color) or volume.	Strong For
41. We suggest basing choice of antibiotic on local resistance patterns and patient characteristics. a. First-line antibiotic choice may include doxycycline, trimethoprim/sulfamethoxazole (TMP-SMX), second-generation cephalosporin, amoxicillin, amoxicillin/clavulanate, and azithromycin. b. Despite the paucity of evidence regarding the choice of antibiotics, we suggest reserving broader spectrum antibiotics (e.g., quinolones) for patients with specific indications such as: i. Critically ill patients in the intensive care unit (ICU); ii. Patients with recent history of resistance, treatment failure, or antibiotic use; and iii. Patients with risk factors for health care associated infections.	Weak For
42. For outpatients with acute COPD exacerbation who are treated with antibiotics, we recommend a five-day course of the chosen antibiotic.	Strong For
43. There is insufficient evidence to recommend for or against procalcitonin-guided antibiotic use for patients with acute COPD exacerbations.	Not Applicable
44. For acute COPD exacerbations, we recommend a course of systemic corticosteroids (oral preferred) of 30-40 mg prednisone equivalent daily for 5-7 days.	Strong For
Management of Patients with COPD in the Hospital or Emergency Department	
45. We suggest use of airway clearance techniques utilizing positive expiratory pressure (PEP) devices for patients with COPD exacerbations and difficulty expectorating sputum.	Weak For

Recommendations	Strength of
46. We recommend the early use of non-invasive ventilation (NIV) in patients with acute COPD exacerbations to reduce intubation, mortality, and length of hospital stay.	Strong For
47. We recommend the use of NIV to support weaning from invasive mechanical ventilation and earlier extubation of intubated patients with COPD.	Strong For

*For additional information please refer to Reconciling 2007 CPG Recommendations

Diagnosis and Assessment of COPD

The diagnosis of COPD can be challenging, as can be the evaluation of its severity and its impact on patients' daily life. There is no single diagnostic test that can positively identify COPD; therefore, its diagnosis requires a combination of patient history, especially past history of smoking and detailed history of symptoms, physical exam, and diagnostic tests. COPD should be suspected in patients with a history of smoking, or other environmental/ occupational exposures, and symptoms compatible with COPD, such as dyspnea, cough, and a chronic, progressively worsening course. Once COPD is suspected, confirmation requires spirometry, as discussed in the recommendation below.

Because the treatment of COPD is aimed at improving symptoms and slowing progression, assessing and monitoring the severity of symptoms and their impact on the patient's life is important to direct treatment. Additionally, manifestations of COPD are non-specific and may mask other severe and treatable conditions that present with similar signs and symptoms, such as asthma, heart failure, or pulmonary embolism. Therefore, careful monitoring and evaluation of new or worsening symptoms is critical both in the primary care and in the acute care settings, at initial diagnosis, during acute exacerbations, and as part of long-term management. Since, in the US, most patients with COPD are current or former smokers, other complications of smoking, such as coronary artery disease, are not infrequent among these patients. Recommendations to facilitate the diagnosis of COPD, its assessment, and monitoring of severity over time are presented in this section.

Recommendation

1. We recommend 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 For)

Discussion

The hallmark of COPD is airway obstruction, as indicated by spirometry measurement of FEV1/FVC <70%. This level of airway obstruction is not completely reversible in a typical patient that is symptomatic with dyspnea, cough, exercise limitation, and a history of exposure (e.g., to tobacco, significant air pollution, or secondhand smoke). Clinical diagnosis based on history and physical alone lacks sensitivity and specificity. It is associated with a delay in diagnosis of COPD in some patients, as well as over diagnosis and treatment in others. [22-26] Earlier diagnosis is associated with an earlier opportunity for risk factor modification. Earlier use of appropriate pharmacotherapy has been shown to slow the decline of lung function as measured by FEV1. Historically, administration of a bronchodilator was needed to confirm that airway obstruction could not be completely reversed. Many clinics that are capable of preforming spirometry lack the resources to do post-bronchodilator measurements. Because of this, the post-bronchodilator requirement can form a significant barrier to care. Eliminating the post-bronchodilator requirement is more convenient, but it does potentially misdiagnosis the few patients who actually have asthma rather than COPD. [27-29]

Some suggest that a ratio of FEV1/FVC <70% is acceptable confirmation of the presence of COPD in older patients without a prior history of asthma. Clinicians must use caution when applying this criterion to the most elderly patients because FEV1/FVC <70% can be a normal part of aging. Relying on history of exposure, history of asthma, and symptoms, as well as the lower limit of normal (LLN) of FEV1/FVC, to confirm the diagnosis may be more beneficial in this specific population. [30]

Furthermore, absence of acute reversibility after treatment with a bronchodilator may not predict response to long-term pharmacotherapy. [31-33] Therefore, reversibility testing should not be used to gauge potential for benefits of treatment.

We do not recommend spirometry for screening for COPD in an asymptomatic population because it has not been shown to be beneficial. There is also a lack of evidence to form a specific recommendation on a time period for follow-up after spirometry. We also do not recommend routinely repeating spirometry in patients with confirmed COPD once the diagnosis has been made with initial use of spirometry. This has not been shown to contribute to management or classification.

Recommendation

2. We have no recommendations regarding utilization of existing clinical classification systems at this time. (Strength of recommendation not applicable)

Discussion

The American Thoracic Society (ATS) classifies patients with COPD based on degree of airflow obstruction into mild (FEV1 percent predicted [pp] >80%), moderate (FEV1 pp 50-80%), severe (FEV1 pp 30-50%), and very severe (FEV1 pp <30%). While mortality, exacerbations, and symptoms correlate with severity of airway obstruction, this classification does not provide useful guidance for either treatment or evaluation. For example, in one study of exacerbations, 30% of patients in the moderate COPD group experienced exacerbations. [34] While this rate was less than that in the severe group (47%), the moderate group represented the largest number of patients experiencing exacerbations since it contained the largest number of patients. [34]

Other classification systems such as BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) and GOLD (Global Initiative for Chronic Obstructive Pulmonary Disease) combine measures of airway obstruction, symptoms, and/or exacerbation risk. [35,36] However, none of them provide sufficiently valid categories to be useful alone to direct decision-making regarding treatment or prognostication. For example, Han et al. (2013) examined the relationship between symptom measure and results of the classification system. The authors used the GOLD ABCD classification where the "highest" or "worst" group is determined by mapping exacerbation risk or airflow limitation (which classifies patients into one of four GOLD groups) against symptom burden using either the COPD Assessment Test (CAT) or the modified Medical Research Council (mMRC) dyspnea scale. [37] They found a discrepancy across groups dependent on which of the measures was employed. This suggests that the clinical utility of the GOLD classification system remains limited.

While we do not recommend any clinical classification system, there may be some benefit to quantifying and monitoring symptoms over time. Symptom burden in COPD patients is only loosely correlated with the degree of airway obstruction, frequency of exacerbations, or QoL; therefore these metrics are not optimal to monitor response to treatment. [38] However, two short questionnaires, mMRC and CAT, used in research, can also be clinically useful in the assessment of symptom burden in COPD. The mMRC is a brief, validated, publicly available tool that asks patients to self-classify their symptoms into one of five groups. It may not be sufficiently calibrated to detect changes in dyspnea in response to treatment and/or exacerbations, but the score does change over time as lung function declines. [39] The CAT determines health status using ten questions. It can be self-administered and has been shown to be sensitive to changes in response to treatment and exacerbation. [40] Presence of comorbid diseases is also associated with higher (worse) CAT scores in patients with COPD. [41] Tracking symptoms systematically using these tools can facilitate:

- Early identification, investigation, and treatment of patients with comorbid conditions that may otherwise be difficult to detect in the context of COPD, such as congestive heart failure, cardiac ischemia, or gastroesphageal reflux; and
- Identification of patients who may benefit from exercise conditioning in a pulmonary rehabilitation setting.

Recommendation

3. 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.

(Weak For)

Discussion

Exacerbations are defined by prescription of antibiotics, prescription of corticosteroids, a COPD-related hospitalization, or a COPD-related ED visit. [42] Patients with frequent exacerbations are present across all GOLD Stages, and prior history of exacerbation is the best predictor of a future exacerbation regardless of FEV1. [34] Patients in the frequent exacerbation group also experience poorer QoL, more rapid lung loss, and increased rates of CVD, gastroesophageal reflux, depression, osteoporosis, cognitive impairment, hospital admission, and mortality. [34,43,44]

Recommendation

4. We recommend offering prevention and risk reduction efforts including smoking cessation and vaccination. (Strong For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

Discussion

Smoking cessation should be the cornerstone of COPD treatment. Tobacco smoke is an irritant that results in rapid progression of the disease. Removing tobacco smoke as a respiratory irritant can preserve lung function and slow progression of the disease more than any medical treatment available. Individuals with COPD who stopped smoking were found to have improved FEV1 in the following year and a decreased rate of decline in FEV1. [45] For details regarding tobacco cessation please refer to the VA/DoD Clinical Practice Guideline for Management of Tobacco Use.[2]

Patients with COPD can be particularly adversely affected by illnesses such as influenza and pneumonia. [46-48] Influenza may cause increased morbidity and mortality in the population with COPD. [49] Large observational studies of COPD, elderly, and high-risk patients have shown improved exacerbation outcomes associated with receiving influenza vaccinations. [50] This conclusion suggests that patients with COPD can benefit from routine influenza vaccinations. Vaccinations against pneumonia also may be beneficial. There is a limited amount of research available on pneumococcal vaccination in patients with COPD specifically; however, based on systematic review of randomized controlled trials (RCTs) in the general adult population, pneumococcal vaccination may be beneficial for protecting against invasive pneumococcal disease. [51,52]

[2] See the VA/DoD Clinical Practice Guideline for Management of Tobacco Use. Available at: http://www.healthquality.va.gov/guidelines/cd/mtu/index.asp.

Recommendation

5. We recommend investigating additional comorbid diagnoses particularly in patients who experience frequent exacerbations (two or more/year, defined as prescription of corticosteroids, prescription of antibiotics, hospitalization, or ED visit) using simple tests and decision rules (cardiac ischemia [troponin, electrocardiogram], congestive heart failure [B-type natriuretic peptide (BNP), pro-BNP], pulmonary embolism [D-dimer plus clinical decision rule], and gastroesophageal reflux). (Strong For)

Discussion

Differentiation of a COPD exacerbation from congestive heart failure (CHF), cardiac ischemia, infection, pulmonary embolus, and/or gastroesophageal reflux (GER) was challenging but has recently become easier. [53] CVD is a common comorbid condition in patients with COPD and the most common cause of death. Measurement of circulating BNP helps differentiate dyspnea from pulmonary or CHF origin. Two studies have confirmed that pro-BNP and BNP have good sensitivity (92%) and specificity (94%) in separating dyspnea from pulmonary or heart failure decompensation origin in the ED. [54,55]

Observational studies describe increased mortality (odds ratio 1.33) and reduced likelihood of appropriate medication treatment (such as use of beta-blockers) or interventional procedures in patients with COPD presenting with acute myocardial infarction. [56,57] One observational study of 242 patients found 10% of patients admitted with COPD exacerbation actually met standard criteria for myocardial infarction (chest pain combined with elevated troponin and/or electrocardiogram changes). [58] Therefore, it is important to exclude a myocardial infarction in patients with COPD who present with symptoms and signs suggestive of an exacerbation.

A systematic review and meta-analysis found that 25% of patients with "COPD exacerbations" actually have pulmonary emboli. [59,60] Use of age-adjusted D-dimer in conjunction with a clinical decision rule can exclude pulmonary embolus in a significant proportion of patients. Another study examining the diagnosis of pulmonary embolism in COPD suggested improved specificity with a higher cut-point of D-dimer to rule out a diagnosis of pulmonary embolism in patients with COPD and exacerbation. However, the analysis was not controlled for age, which could confound these findings. [61] Pulmonary embolus can, however, be safely excluded using a clinical decision rule (Well's, Geneva, etc.) in conjunction with D-dimer measurement. [62]

Symptoms of GER have been independently associated with a history of COPD exacerbation. The diagnosis of GER is usually based on typical symptoms of heartburn and regurgitation.

These studies highlight the challenges in differentiating COPD exacerbation from other treatable conditions based on clinical presentation alone. Therefore, careful investigation of comorbid conditions is challenging but critical for optimal care of patients with COPD, especially during what appears to be a simple COPD exacerbation.

Recommendation

6. We suggest that patients with COPD and signs or symptoms of a sleep disorder have a diagnostic sleep evaluation. (Weak For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

Discussion

Disturbed sleep is more frequently seen in patients with COPD than in the general population. Specifically, insomnia, nightmares, and daytime sleepiness are prevalent in patients with COPD. [63,64]

Patients with COPD may also have a longer latency to sleep onset, more frequent disruption and stage changes, and decreased sleep efficiency than in the general population. [63-65] Sleep disorders also seem to increase as patients with COPD age. [63] Patients with signs or symptoms of a sleep disorder should be referred for a diagnostic sleep evaluation, which may include diagnostic tests and diagnostic interviews.

Recommendations

7. We suggest that patients presenting with early onset COPD or a family history of early onset COPD be tested for alpha-1 antitrypsin (AAT) deficiency. (Weak For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

8. We recommend that patients with AAT deficiency be referred to a pulmonologist for management of treatment. (Strong For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

Discussion

Those with early onset COPD (i.e., age of onset of 45 years or less [66]) or a family history of early onset COPD should be tested for AAT deficiency. The prevalence of AAT deficiency in the US is about one in 5,000. This condition is significantly underdiagnosed with as many as 90% of cases going undetected. [67,68] AAT deficiency by itself does not induce lung disease; however, patients with AAT deficiency and exposure to tobacco and other irritants can develop more severe lung disease than non-deficient patients. [67] Patients with AAT deficiency are prone to more rapid progression of COPD given the same exposures as the general population.

The prevalence of severe AAT deficiency among patients with COPD is 1-2%. [66,69] Screening for AAT deficiency in selected patients has the potential to limit occupational exposure as well as enhance tobacco cessation efforts. Although evidence on the relationship between awareness of AAT deficiency and smoking cessation is limited, information about genetic predisposition to lung cancer has been shown to increase quit attempts. [66] There is evidence that adolescents aware of AAT deficiency status are less likely to start smoking than their peers. [70] Also, although therapy for replacing AAT has led to conflicting findings regarding FEV1 decline, there have been positive findings regarding lung density as determined by computed tomography (CT). [71] The ATS recommends screening all symptomatic adult patients with COPD and asymptomatic adult patients with a history of smoking or occupational exposure; the ATS also recommends discussing screening with asymptomatic adult patients and those who develop COPD during adolescence. [66] However, augmentation or replacement therapy has not been shown to improve exacerbation rates. [67,71,72] A Cochrane review of 140 patients showed no benefit of augmentation therapy in exacerbations or FEV1. [73] Therefore, patients with severe AAT deficiency should be referred to a specialist for evaluation and management, as appropriate.

Management of Patients with COPD in the Outpatient Setting

Clinicians should consider various approaches, as appropriate, to manage patients with COPD in the outpatient setting. Recommendations related to each approach can be found in the following sections.

Pharmacologic Therapy

While there is no curative treatment for COPD, patient outcomes such as symptom burden and disease progression can improve with appropriate treatment including pharmacologic therapy. Inhaled

medications are the main approach to pharmacologic treatment in COPD. However, inhaled treatment for acute symptoms and for maintenance in COPD differs from that of asthma, in which inhaled steroids are a first-line treatment. The section below will present recommendations on pharmacologic treatment of COPD and concern that may arise for use of non-COPD medications among patients with COPD. Additional information including about the referenced medications can be found in Appendix D.

Recommendation

9. We recommend prescribing inhaled short-acting beta 2-agonists (SABAs) to patients with confirmed COPD for rescue therapy as needed. (Strong For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

Discussion

The confidence in the evidence is high regarding the use of inhaled SABAs as rescue therapy in COPD patients. Beta 2-agonists promote smooth muscle relaxation by stimulating cyclic adenosine monophosphate in airway smooth muscle. The onset of the bronchodilatory effects is short with inhaled SABA, within 1-5 minutes, and can last 3-6 hours. Treatment with SABA is associated with improvements in FEV1 and respiratory symptoms as well as reductions in exacerbations in stable COPD (during the recovery period after acute exacerbation) compared with placebo. [74,75] A systematic review of 13 trials showed that regular use of inhaled SABA in COPD resulted in improvements in post-bronchodilator lung function and decreases in dyspnea. [76]

Recommendation

10. We suggest using spacers for patients who have difficulty actuating and coordinating drug delivery with metered-dose inhalers (MDIs). (Weak For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

Discussion

If a patient with COPD is using an MDI, a qualified clinician should carefully observe and evaluate the patient's inhalation technique and ability to use the MDI as recommended. Correct technique is essential for optimal MDI use, and incorrect technique is common. Patients may benefit from the use of a spacer device, particularly if they exhibit poor technique after instruction.

The confidence in the available evidence is high. However, it is a weak recommendation because most of the available evidence comparing spacers to MDIs is in patients with asthma, including pediatric populations, and not COPD. Benefits of offering this therapeutic modality likely outweigh the potential harms.

Medication delivery via MDI can result in excessive deposition in the back of the throat and tongue, leading to poor delivery to the lungs. In some cases, only 10% of medication delivered reaches the lungs. [77] Other potential pitfalls with using MDIs that may result in decreased medication delivery to the lungs include poor patient coordination of actuation and inhalation along with inadequate breath-hold. [78] Spacer devices tend to retain large particles emitted from the MDI allowing a higher proportion of small, respirable particles to be inhaled, and may increase the bioavailability of the medication. [79,80] Most of the studies using spacers were done in either healthy patients or those with asthma. Little evidence exists regarding relative performance of different spacer devices. [81]

Recommendation

11. We recommend offering long-acting bronchodilators to patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). (Strong For)

Discussion

We strongly recommend offering long-acting bronchodilators to patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough), even in those patients without a post-bronchodilator response on spirometry. The confidence in the available evidence is high, and the benefits of offering therapy likely outweigh the harms of not offering therapy and the adverse effects of the medications.

In patients with confirmed, stable COPD who continue to have respiratory symptoms, both LAMAs and LABAs are beneficial in the chronic management of this condition, in addition to the use of as-needed short-acting bronchodilators. LAMAs (specifically tiotropium) improve FEV1 and QoL. Additionally, LAMAs reduce the rate of COPD exacerbations and exacerbations requiring hospitalization. [82] LABAs (specifically formoterol and salmeterol) also improve FEV1 and QoL. However, rates of COPD exacerbations, mortality, and non-fatal serious adverse events do not vary between patients using LABAs and those using placebo. [83] Indacaterol, a once daily LABA, was also demonstrated to improve FEV1 compared to placebo. [84] There is no difference among different types of LABAs for the outcome of COPD exacerbations. [85]

Recommendation

12. We suggest offering the inhaled long-acting antimuscarinic agent (LAMA) tiotropium as first-line maintenance therapy in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). (Weak For)

Discussion

Both LABAs and LAMAs, such as tiotropium, are important in the management of patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). We recommend tiotropium (a LAMA) as first-line maintenance therapy (in addition to SABA for rescue therapy) because this medication is more effective than LABAs as a group in preventing COPD exacerbations and COPD-related hospitalizations with fewer serious adverse events. LAMAs (specifically tiotropium) have been shown to improve FEV1 and QoL and to prevent moderate to severe exacerbations in patients with confirmed, stable COPD who continue to have respiratory symptoms, despite the use of as-needed short-acting bronchodilators. [82] Compared to LABAs as a group, tiotropium reduces the frequency of COPD exacerbations.

However, this is a weak recommendation because there is no difference in all-cause hospitalization rates, mortality, symptom improvement, and FEV1 between tiotropium and LABAs. [85] The confidence in the available evidence is moderate, and the benefits-harm balance may slightly favor tiotropium over LABAs as first-line therapy. Further harm-benefit or cost-benefit analysis research is needed to compare these two medication classes.

Recommendation

13. We recommend inhaled tiotropium 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 For)

Discussion

Although similar to the previous recommendation, the strength of evidence for using inhaled tiotropium as a first-line therapy in this specific population is stronger, and therefore the strength of this recommendation is stronger than that of the previous recommendation. Tiotropium reduces the frequency of COPD exacerbations and disease-related hospitalizations compared to LABAs as a group. We strongly recommend tiotropium as first-line maintenance therapy for patients with very severe COPD (post bronchodilator FEV1 <50%) or a history of frequent COPD exacerbations, as this medication is more effective than LABAs in preventing COPD exacerbations and COPD-related hospitalizations with fewer serious adverse events in this population. [85] The confidence in the available evidence is moderate, and the benefits of offering therapy with tiotropium may likely outweigh the harms of offering LABAs as first-line therapy in these subgroups of patients. Appendix D lists the contraindications, therapeutic considerations, and common adverse effects of tiotropium (Table D-2).

Recommendation

14. For clinically stable patients with a confirmed diagnosis of COPD and who have not had exacerbations on short-acting antimuscarinic agents (SAMAs), we suggest continuing with this treatment, rather than switching to long-acting bronchodilators. (Weak For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

Discussion

Despite the fact that long-acting bronchodilators are associated with greater clinical benefits than short-acting formulations, there is a body of evidence demonstrating the benefits of SAMAs as maintenance treatment for COPD patients. Ipratropium, a SAMA, reduces vagal tone, decreases airway resistance, and subsequently improves pulmonary function. In clinical trials, ipratropium demonstrated improvements in FEV1 and respiratory symptoms compared to placebo. [86-88] Ipratropium has also been shown to improve health-related QoL when compared to placebo. [86,87,89,90] In one study, ipratropium had similar beneficial effects on lung function measurements and respiratory symptoms as formoterol. [88] In another, ipratropium reduced dyspnea related to activities of daily living to a similar degree as salmeterol compared to placebo. [87] Though long-acting agents are preferred, SAMA may be a reasonable alternative particularly in patients who are already clinically stable on SAMA maintenance therapy.

Recommendation

15. For patients treated with a SAMA who are started on a LAMA to improve patient outcomes, we suggest discontinuing the SAMA. (Weak For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

Discussion

A review of the available published literature of RCTs of a LAMA compared to placebo and ipratropium provides evidence for significant and substantial improvement in FEV1, exacerbations, respiratory symptoms, and COPD-related QoL. [91] There is a substantial trend to a reduction in hospitalizations compared to placebo and ipratropium. [92] More recent RCTs support these conclusions. [93] There is a significant substantial improvement in FEV1 and cycle ergometer exercise capacity with tiotropium compared to placebo in one study. [94]

Recommendation

16. We recommend against offering an inhaled corticosteroid (ICS) in symptomatic patients with confirmed, stable COPD as a first-line monotherapy. (Strong Against)

Discussion

ICS are widely prescribed for COPD. Controversy still exists regarding which patients with COPD will benefit, as well as selection of the optimal agent and dosage. Moderate quality evidence suggests that ICS may improve FEV1, may reduce the risk of exacerbation, and may improve symptoms and QoL in patients with severe COPD. [95-97]

COPD is a progressive inflammatory disease of the airways and lungs. Thus, an ICS is often prescribed for management of stable COPD. Further, an ICS is prescribed more often when a practitioner is not able to rule out asthma as a differential diagnosis or as an additional diagnosis to COPD. ICS is not approved as monotherapy for management of stable COPD by the US Food and Drug Administration (FDA). However, large randomized double-blind controlled trials of combination ICS and LABA tested the effects of ICS alone in patients with COPD. In these trials, ICS, when compared to placebo, improved lung function, QoL, breathlessness score, and COPD exacerbation rate. [98] However, ICS also caused more adverse events compared to placebo, including oropharyngeal candidiasis, hoarseness, bruising, and pneumonia. [98] Furthermore, in a network meta-analysis, the effects of ICS alone on lung function and QoL was inferior compared to LABA. [99] Considering the increased risk of pneumonia and the availability of effective inhaled medication with less side effects, we recommend against offering ICS as first-line monotherapy in symptomatic patients with confirmed, stable COPD.

Recommendation

17. We recommend against the use of inhaled long-acting beta 2-agonists (LABAs) without an ICS in patients with COPD who may have concomitant asthma. (Strong Against)

Discussion

Asthma and COPD both are obstructive diseases of airways. The clinical presentation differs between asthma and COPD in the majority of cases. However, in some cases, differentiating asthma from COPD may prove to be difficult. Clinical features that may be used to help differentiate between COPD and asthma can be found in Table 1, below. LABA as monotherapy has been proven to be safe for COPD in several randomized clinical trials; the same is not true for patients with asthma. In fact, all products containing LABA have a black box warning about use of LABA monotherapy and increased risk of death in patients with asthma. A Cochrane meta-analysis examining the use of LABAs showed increased mortality in those who were asthmatic and who were on LABA monotherapy. [100] In a large RCT comparing the effects of salmeterol and placebo in patients with asthma, there were small, statistically significant increases in respiratory-related and asthma-related deaths, as well as in combined asthma-related deaths or life-threatening experiences, in the group receiving salmeterol. [101] Thus, we recommend against the use of LABA alone in patients who may have concomitant asthma, as harms outweigh benefits.

Table 1. Clinical Features That May Be Helpful In Differentiating COPD and Asthma

Clinical Features That May Be Helpful in Differentiating COPD and Asthma	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Onset before age 35	Rare	Often
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Night time waking with breathlessness and or wheeze	Uncommon	Common
Commonly associated with atopic symptoms and seasonal allergies	Uncommon	Common
Significant diurnal or day-to-day variability of symptoms	Uncommon	Common
Favorable response to inhaled glucocorticoids	Inconsistent	Consistent

Recommendation

18. In patients with confirmed, stable COPD who are on inhaled LAMAs (tiotropium) or inhaled LABAs alone and have persistent dyspnea on monotherapy, we recommend combination therapy with both classes of drugs. (Strong For)

Discussion

When monotherapy is insufficient to control symptoms, it is recommended to assess patient adherence to therapy and inhaler technique prior to initiating additional drug therapy to determine if these factors are contributing to/responsible for inadequate control. Once this reason has been eliminated, the different mechanisms and sites of action of LABA and LAMA provide the rationale for combination therapy when a single agent does not provide adequate control.

Combination bronchodilators

Compared to tiotropium alone, the combination of tiotropium and LABA resulted in greater improvement in FEV1, QoL, and dyspnea in a systematic review of the literature. However, there was no significant difference in rate of exacerbations. Overall adverse events were not increased with combination therapy versus tiotropium alone. [102]

The combination of tiotropium and LABA compared to LABA alone showed no significant difference in exacerbations, FEV1, or QoL in a systematic review of the literature. However, these results should be interpreted with caution, as the quality of the evidence was rated very low due to various study limitations. [103]

Many of the newer agents were not included in these meta-analyses. A review of the individual trials for the approved dose of combined umeclidinium bromide and vilanterol (UMEC/VI) showed greater improvement in FEV1 versus LAMA or LABA alone. There was no significant difference in QoL, dyspnea, or exacerbations. [104,105]

Combination ICS and LABA compared to long-acting bronchodilator

The combination of ICS and LABA compared to LABA alone reduced the risk of exacerbation and resulted in greater improvement in FEV1 and QoL. However, patients receiving combination ICS and LABA had a higher rate of pneumonia than patients receiving LABA alone. [106]

Compared to LAMA alone, combination ICS and LABA resulted in greater improvement in FEV1 and QoL. There was no significant difference in exacerbations or dyspnea. Patients receiving combination ICS and LABA had a greater risk for pneumonia and severe adverse events compared to LAMA alone. [102]

Combination ICS and LABA compared to combination LABA and LAMA

The data are very limited comparing combination LAMA and LABA and combination ICS and LABA. Indirect comparison of combination LAMA and LABA versus combination ICS and LABA in a meta-analysis suggests there is no significant difference in risk of exacerbation. [107] One six-week trial directly comparing treatments found greater lung function improvement with combination tiotropium and formoterol compared to combination salmeterol and fluticasone. [108] Long-term studies directly comparing dual bronchodilator versus combination ICS and long-acting bronchodilators are needed.

Combination ICS and LABA and regimens containing tiotropium reduce the risk of exacerbations and improve dyspnea. However, ICS-containing regimens have been shown to increase the risk of pneumonia. Therefore, we recommend dual bronchodilator therapy over combination ICS and LABA as the next step after failure of bronchodilator monotherapy for patients with persistent dyspnea. When choosing between combination LAMA and LABA or combination ICS and LABA, patient-specific factors (co-existing diseases, ability to adhere to treatment, ability to use inhaler devices, contraindications to therapy, etc.) and costs versus benefits should also be considered.

Recommendation

19. In patients with confirmed, stable COPD who are on combination therapy with LAMAs (tiotropium) and LABAs and have persistent dyspnea or COPD exacerbations, we suggest adding ICS as a third medication. (Weak For)

Discussion

Goals of therapy in patients with COPD include improvement of symptoms and reduction in COPD exacerbations and hospitalizations. Data on the effect of triple therapy on these outcomes are scarce. One meta-analysis compared triple therapy to tiotropium monotherapy or combination ICS and LABA. [109] The quality of the data was low, partially due to the limited number of studies included. QoL, lung function, and symptoms (daytime and nighttime) improved significantly in patients receiving triple therapy compared to those receiving tiotropium monotherapy. In contrast, there was no difference between the two groups in mortality, hospitalization, and pneumonia. Although pneumonia was not different between triple therapy and tiotropium monotherapy in this report, several other clinical trials and meta-analyses showed increased risk of pneumonia with use of ICS. Thus, the lack of difference in pneumonia prevalence between triple therapy and tiotropium monotherapy most likely is due to an underpowered study that could not detect the difference. Serious adverse events were not different between triple therapy and tiotropium monotherapy. Further, data are lacking on combination LAMA and LABA compared to triple therapy. Thus, we suggest, rather than recommend, triple therapy.

Recommendation

20. We suggest against offering roflumilast in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. (Weak Against)

Discussion

Roflumilast, a PDE4, is sometimes used as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Pooled study results show a modest effect of roflumilast on FEV1 relative to placebo. [110] Studies that evaluated health-related QoL and dyspnea found no significant difference between roflumilast and placebo. Fewer patients receiving roflumilast had at least one COPD exacerbation compared to placebo. The rate and number of exacerbations per patient year was reduced. However, the improvements were driven primarily by results of participants with moderate exacerbations. The rate of severe exacerbations did not differ between groups.

In general, adverse events were more common in patients receiving roflumilast compared to placebo. Gastrointestinal events such as diarrhea, nausea, vomiting, dyspepsia, and abdominal pain were observed more frequently in patients treated with roflumilast than placebo. There was also a higher risk of psychiatric adverse events in patients receiving roflumilast 500 mcg compared to placebo. Adverse events reported include insomnia or sleep disorders, anxiety, and depression. Suicidal ideation and behavior, including completed suicide, were reported in clinical trials. Patients with psychological disorders were generally excluded in the clinical trials. Therefore, it is unknown what risk roflumilast poses in populations such as those served by the VA/DoD, where the risk for psychiatric disorders may be more common. [111-113] A pooled analysis of clinical trials ranging from 12-52 weeks found no increased risk for major cardiovascular adverse events or for all-cause mortality with roflumilast relative to placebo. [110,114]

There is a recently completed 52-week RCT (results pending) that will evaluate exacerbation rate, pulmonary function, and safety of roflumilast versus placebo as add-on therapy to a fixed-dose combination LABA/ICS. Trials comparing ICS to roflumilast as add-on therapy to bronchodilators are needed to better define the place of roflumilast in therapy.

Because of the modest benefits of roflumilast and the potential risks, consultation with, or referral to, a pulmonologist is recommended prior to prescribing roflumilast.

Recommendation

21. We suggest against offering chronic macrolides in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. (Weak Against)

Discussion

We suggest against offering chronic macrolide therapy in patients with confirmed, stable COPD in a primary care setting. The confidence in the available evidence is moderate, but the harms of offering therapy appear to slightly outweigh the benefits. While the pooled evidence suggests an improvement in acute exacerbations and a reduction in hospitalizations, the benefit is limited to erythromycin and azithromycin, and treatment duration of six months or longer. Chronic macrolide therapy was associated with no difference in mortality and an increased risk of adverse medication effects. While there may be a role in select patients, the decision to start a patient with confirmed, stable COPD on chronic macrolide therapy should only be made in conjunction with a pulmonologist.

More specifically, two systemic reviews of the same six RCTs compared chronic macrolide therapy to placebo, riboflavin, or usual care. Combined analysis of all macrolides ranging in duration from 3-12 months demonstrated a statistically significant reduction in acute COPD exacerbations. Patients using macrolides were less likely to experience one or more acute COPD exacerbations. Patients on macrolides for six months or longer derived the most benefit in regard to reduction in acute exacerbations. However, a subgroup analysis by specific type of macrolide indicated that only the use of erythromycin may be associated with reduction in acute COPD exacerbation rates. Mortality did not differ between patients using macrolides and controls. Patients using macrolides were less likely to require hospitalization. Combined analysis of all macrolides ranging in duration from 3-12 months demonstrated a statistically significant increase in drug-related nonfatal adverse events with the highest risk in those on macrolides longer than six months. Subgroup analysis by macrolide type indicated no significant difference between each drug type and controls in the frequency of nonfatal adverse events. [115,116]

Recommendation

22. We suggest against offering theophylline in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist. (Weak Against)

Discussion

Theophylline, as an addition to inhaled bronchodilators, does not improve outcomes compared to LABA alone and can pose some risks. Two large systematic reviews provided a moderate level of evidence on the subject. Theophylline alone has been more effective than placebo in increasing FEV1 and FVC. [117] Theophylline in combination with LABA has been slightly more effective than placebo in increasing FEV1 and improving dyspnea, but this comparison did not allow assessment of the effect of theophylline independent of LABA. [118] In a different analysis, there was no difference between the use of theophylline in combination with LABA in improving outcomes compared to LABA alone. [119] It should be noted, however, that the most recent evidence, published in 2007, does not consider the effects of theophylline in combination with modern long-term bronchodilators.

Theophylline also has associated harms. Because it is metabolized through the cytochrome P450 pathway, there may be significant associated food and medication interactions. Patients receiving theophylline had significantly greater risk of experiencing nausea compared to patients receiving placebo. [117] It is also associated with adverse reactions including insomnia, anxiety, nausea, vomiting, tremor, arrhythmias, delirium, seizures, and death. Thus, we do not recommend theophylline as monotherapy. Further, we suggest against offering theophylline as an added therapy in symptomatic, confirmed COPD patients without prior consultation with a pulmonologist.

Recommendation

23. 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 who continue to have respiratory symptoms (e.g., dyspnea, cough). (Strength of recommendation not applicable)

Discussion

The confidence in the available evidence is weak, but the benefits of offering therapy likely outweigh the harms, as there are no apparent major adverse effects in using NAC. NAC did not show improvement in dyspnea compared to placebo. However there is weak evidence that NAC may favorably affect the risk of exacerbations in patients with COPD who are not on ICS. The oral form of NAC in the US is not a FDA-approved drug, but rather a dietary supplement. As such, FDA doesn't oversee the manufacturing

quality or safety of oral NAC. Therefore, NAC supplements may not be standardized across and within brands and are not tested for safety, making their recommendation as part of evidence-based treatment difficult to support. For example, it is unclear if the NAC supplement forms currently available in the US are similar to the form used in randomized clinical trials, including a recent study from China, making the generalizability of these findings to the US population questionable. Furthermore, the sulfur smell may affect acceptability and compliance. Further research is required on the efficacy and effectiveness of NAC. [120-122]

Recommendation

24. We suggest not withholding cardio-selective beta-blockers in patients with confirmed COPD who have a cardiovascular indication for beta-blockers. (Weak For)

Discussion

There is weak evidence that the benefits of cardio-selective beta-blockers outweigh the harms in patients with COPD and a cardiovascular indication for this treatment. Although many clinicians consider COPD as a contraindication to beta-blockers, cardio-selective beta-blockers are safe in patients with stable COPD when there is a cardiovascular indication. Strong medical indications for the use of beta-blockers do exist in some patients, as reflected by existing guidelines (e.g., heart failure, post myocardial infarction). Observational studies have not shown an increase in mortality in patients with COPD. Due to the limited data on the subject, beta-blockers should be used with caution, and patients should be monitored for an increase in COPD symptoms. Further research is needed and should include patients with mild to moderate COPD. [123,124]

Recommendation

25. We suggest using non-pharmacologic therapy as first-line therapy and using caution in prescribing hypnotic drugs for chronic insomnia in primary care for patients with COPD, especially for those with hypercapnea or severe COPD. (Weak For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

26. For patients with COPD and anxiety, we suggest consultation with a psychiatrist and/or a pulmonologist to choose a course of anxiety treatment that reduces, as much as possible, the risk of using sedatives/anxiolytics in this population. (Weak For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

Discussion

Patients with COPD often experience depression and anxiety, especially patients with hypoxemia or severe dyspnea, which can lead to insomnia. [125] Various tools can be used to evaluate for depression and anxiety, although not all of these have been validated for the population with chronic disease. [32] Multiple types of non-pharmacologic therapy, such as cognitive-behavioral programs and pulmonary rehabilitation programs that include psychotherapy, as well as pharmacologic therapy, such as nortriptyline, buspirone, and sertraline, have been shown to reduce anxiety and, in some cases, depression. [126] However, sedatives/anxiolytics, such as non-selective benzodiazepines, may be associated with adverse effects in COPD patients. [127] Therefore, we recommend consultation with a psychiatrist and/or a pulmonologist before deciding on an appropriate course of treatment.

Oxygen Therapy

As COPD progresses, patients may become chronically hypoxic, with associated pulmonary hypertension, cor pulmonale, erythrocytosis, right heart failure, and reduced life expectancy. Some patients with less severe COPD may have hypoxemia limited to periods of exertion or sleep.

Recommendation

27. We recommend providing long-term oxygen therapy (LTOT) to patients with chronic stable resting severe hypoxemia (partial pressure of oxygen in arterial blood [PaO_2] <55 mm Hg and/or peripheral capillary oxygen saturation [SaO_2] ≤88%) or chronic stable resting moderate hypoxemia (PaO_2 of 56-59 mm Hg or SaO_2 >88% and ≤90%) with signs of tissue hypoxia (hematocrit >55%, pulmonary hypertension, or cor pulmonale). (Strong For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

Discussion

There is strong evidence that LTOT in these clinical situations reduces mortality. [128-130] Chronic stable hypoxemia is defined as two measurements at least six weeks apart and at least six weeks from any acute illness resulting in hypoxemia.

There is insufficient evidence that LTOT reduces mortality in COPD patients with more mild to moderate hypoxemia (66 mm Hg <PaO_2 ≤74 mm Hg) in the absence of signs of tissue hypoxia. [130]

There is insufficient evidence that LTOT for chronically hypoxic COPD patients improves dyspnea, QoL, hospitalization rates, or readmission rates. [130]

If transitional home oxygen is provided after an acute respiratory illness, the need for LTOT should be re-evaluated in 30-90 days. RCTs that found a survival benefit with LTOT did not measure oxygen levels or re-evaluate the need for LTOT after initial qualification. [128,129] Up to 50% of these patients will not qualify for continued LTOT (see Recommendation 29). [131] In contrast, patients with chronic stable hypoxemia who have met the criteria for LTOT prior to hospitalization do not require reassessment. [132] Discontinuing LTOT in these patients can result in subsequent worsening of hypoxemia. [132,133] Furthermore, the safety of discontinuing LTOT under these circumstances is unknown.

Recommendation

28. We recommend that patients discharged home from hospitalization with acute transitional oxygen therapy are evaluated for the need for LTOT within 30-90 days after discharge. LTOT should not be discontinued if patients continue to meet the above criteria. (Strong For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

Discussion

Patients who are hypoxemic at discharge from the hospital for an acute respiratory illness may be provided supplemental oxygen as they continue to recover. A substantial portion of these patients will not be hypoxemic after 30-90 days. Patients should be re-evaluated at that time and oxygen should be discontinued in those who longer meet the criteria for LTOT, as there no proven evidence of reduction in mortality in such patients. [132]

Exercise Hypoxemia

Recommendation

29. We suggest against routinely offering ambulatory LTOT for patients with chronic stable *isolated* exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen. (Weak Against)

Discussion

Based on a recent review of four relatively long-term RCTs (2-12 weeks) of home oxygen supplementation, there is insufficient evidence to recommend ambulatory LTOT for COPD patients with isolated exertional hypoxemia. [134] The mean improvement in dyspnea scores in these RCTs (Chronic Respiratory Questionnaire: 0.28; 95% confidence interval [CI] 0.10-0.45) did not meet the accepted minimal clinically significant improvement of 0.50. Only one of the studies reported a statistically significant improvement in exercise capacity (12 steps), but this did not meet the accepted minimal clinically significant improvement of 20-30 meters. [135] Another study found that 41% of the patients who had a positive response to exertional oxygen supplementation declined treatment with ambulatory LTOT when it was offered. [136]

This recommendation, based on the recent review of the highest quality RCTs of ambulatory oxygen in the home, differs from the previous recommendation in the 2007 CPG. The 2007 CPG recommends oxygen therapy during exercise for those with exertional hypoxia (SaO_2 <88%). However, the 2007 CPG recommendation cites observational studies, studies of supplemental oxygen with formal exercise training, and acute data obtained in laboratory settings. [137-141] There is insufficient evidence to suggest that these results correlate with clinically important benefits in the ambulatory community setting.

If LTOT is nonetheless offered to COPD patients with isolated exertional hypoxemia, a careful shared decision-making process should be applied to address the benefits and burdens of treatment. Patients who receive ambulatory LTOT for isolated exercise hypoxemia should also be subsequently evaluated for individual response to treatment.

Air Travel

Recommendation

30. For patients with COPD and hypoxemia and/or borderline hypoxemia (SaO_2 <90%) who are planning to travel by plane, we suggest a brief consultation or an e-consult with a pulmonologist. (Weak For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

Discussion

Commercial airplanes are pressurized to cabin altitudes of up to 8000 feet, which may result in hypoxemia in patients with COPD. While testing in a high altitude chamber is the gold standard for predicting hypoxemia, this test is not widely available, and predictive equations based on FEV1, SaO_2, and other variables [142-144] are generally unreliable. Adverse clinical outcomes of commercial air travel in COPD patients are relatively uncommon, and these outcomes have not been correlated with predicted hypoxemia. [145] Given the lack of consensus regarding the evidence for predicting the safety of air travel for patients with COPD, these decisions are primarily based on clinical judgment.

Nocturnal Hypoxemia

Recommendation

31. When other causes of nocturnal hypoxemia have been excluded, we suggest against routinely offering LTOT for the treatment of outpatients with stable, confirmed COPD and *isolated* nocturnal hypoxemia. (Weak Against)

Discussion

Two relatively small RCTs assessing the use of LTOT for treatment of isolated nocturnal hypoxemia found no effect on mortality, likely due to the small number of events. [146,147]

Stable Hypercapnea

The benefits of acute treatment with NIV for patients hospitalized with acute COPD exacerbation are well-established (see Management of Patients in Acute Exacerbation of COPD). The clinically relevant benefits of chronic NIV for COPD patients in the home setting are less well established.

Recommendation

32. In the absence of other contributors (e.g., sleep apnea), we suggest referral for a pulmonary consultation in patients with stable, confirmed COPD and hypercapnea. (Weak For)

Discussion

Patients with stable, confirmed COPD and hypercapnea should be referred to a pulmonologist for evaluation. NIV should not be routinely offered for the treatment of chronic, stable COPD to outpatients in the primary care setting in the absence of some other diagnosis that makes it advisable or without consultation with a specialist. A meta-analysis of seven small studies (247 patients) of NIV in patients with stable, severe COPD and chronic hypercapnia found no difference in health-related QoL, sleep efficiency, dyspnea, gas exchange, decline in lung function, or exercise tolerance. [148] Two RCTs of home NIV (each in about 200 patients) have recently been published, and their results characterize the confusion surrounding this issue. One RCT of home NIV after hospitalization for acute respiratory failure and prolonged hypercapnia support found no effect on re-hospitalizations or admission or time to death. [149] However, another recent RCT found that home NIV improved survival at one year in stable hypercapnic (partial pressure of carbon dioxide in arterial blood [$PaCO_2$] >50) patients with COPD without a history of exacerbation. [150] Patients in this second study were initially electively hospitalized for five days to optimize care and adjust NIV settings with the goal of decreasing their $PaCO_2$ by 20% along with a trend toward increased 6 minute walk. Patients were subsequently electively re-hospitalized every three months for several days. Until these results are reproduced with a more pragmatic intervention, it is unclear how generalizable they are.

Supported Self-Management

Supported self-management is a comprehensive strategy for patients with chronic conditions such as diabetes, CHF, and COPD that is aimed at reducing hospitalizations and improving overall health status. Supported self-management for patients with COPD generally includes disease-specific patient education, self-management strategies, smoking cessation, encouraging regular physical activity, optimization of COPD maintenance medication, patient-specific written COPD exacerbation action plans with refillable antibiotics and systemic corticosteroids, and ongoing follow-up with a disease manager. Supported self-management for patients with COPD shares many elements with pulmonary rehabilitation, but pulmonary rehabilitation focuses on formal exercise training.

Recommendation

33. We suggest supported self-management for selected high risk patients with COPD. (Weak For)

Discussion

A recent meta-analysis of 23 RCTs found that supported self-management for selected high risk (history of hospitalization or ED visits for COPD, or risk factors for these events) patients with COPD decreases respiratory-related hospitalizations and improves respiratory-related QoL and dyspnea, but has no effect on mortality or exercise capacity. [151] The meta-analysis included the largest RCT to date, which was performed in the Upper Midwest Veterans Affairs health care system. [152] Two other relatively large recent RCTs were not included in the meta-analysis. These studies found supported self-management had no effect on re-hospitalization rates. [153,154] One of these studies, a Veterans Affairs Co-operative trial, found an increase in mortality in the self-management group, an outcome that remains unexplained despite extensive analysis. [153,154] Two meta-analyses that included the Veterans Affairs Co-operative trial found no excess mortality with supported self-management. [155,156]

Recommendation

34. We suggest against using action plans *alone* in the absence of supported self-management. (Weak Against)

Discussion

Action plans with refillable antibiotics are a key component of supported self-management. A meta-analysis of five studies assessing the effectiveness of action plans in the absence of supported self-management found that action plans alone increased the use of antibiotics and systemic corticosteroids, but had no effect on all-cause hospitalization. [157] A subsequent RCT found that action plans alone decreased the impact of exacerbations on health status, but had no effect on COPD-related hospitalization. [158]

Telehealth

Telehealth care for patients with COPD is designed to provide ongoing communication, education, more frequent monitoring, and care collaboration. Additional potential advantages of telehealth include patient convenience and more efficient health resource utilization. Telehealth care for patients with COPD includes nurse case management, telephone contacts or videoconferences, and internet sites, and may or may not include physiological tele-monitoring.

Recommendation

35. We suggest using telehealth for ongoing monitoring and support of the care of patients with confirmed COPD. (Weak For)

Discussion

There is moderate evidence that telehealth care for patients with COPD decreases hospitalizations and ED visits based on systematic review of ten RCTs of heterogeneous interventions. [159] There is insufficient evidence that telehealth care for patients with COPD affects mortality, QoL, patient satisfaction, or health care costs.

Pulmonary Rehabilitation

The American Thoracic Society (ATS) and the European Respiratory Society (ERS) defines Pulmonary Rehabilitation as a “comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and

behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors." [160]

Recommendation

36. We recommend 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 For)

Discussion

A systematic review including eight RCTs of pulmonary rehabilitation for patients with stable COPD found that pulmonary rehabilitation improved exercise capacity, dyspnea, and QoL. [130] A systematic review of nine RCTs (432 patients) of pulmonary rehabilitation for patients who had recently been hospitalized for COPD found that pulmonary rehabilitation decreased hospital readmissions and mortality, and improved exercise capacity and health-related QoL. [161]

Although pulmonary rehabilitation programs have traditionally been provided in a clinical setting, a systematic review of 18 RCTs (733 patients) found that home-based programs improved QoL, exercise capacity, and dyspnea, although with no effect on hospitalizations or mortality. [162] A more recent, relatively large (389 patients) RCT of home rehabilitation shortly after a recent hospitalization for COPD found no effect on hospitalizations, mortality, exercise performance, or health-related QoL. [163]

Breathing Exercise

Dyspnea is a prominent symptom in patients with COPD, resulting in limitation in physical functioning and reduced QoL. Apart from formal pulmonary rehabilitation programs, breathing training techniques and breathing exercises are aimed at improving physical function and reducing dyspnea.

Recommendation

37. We suggest offering breathing exercise (e.g., pursed lip breathing, diaphragmatic breathing, or yoga) to patients with dyspnea that limits physical activity. (Weak For)

Discussion

A systematic review found that pursed lip breathing, diaphragmatic breathing, and yoga improved exercise capacity in the clinical setting, but had no consistent effects on dyspnea or health-related QoL. [164]

Nutrition Referral

Underweight and severely malnourished (BMI <20 kg/m^2) states in patients with COPD are associated with reduced exercise performance, peripheral muscle strength, and lung function.

Recommendation

38. We suggest referral to a dietitian for medical nutritional therapy recommendations (such as oral calorie supplementation) to support patients with severe COPD who are malnourished (body mass index [BMI] <20 kg/m^2). (Weak For)

Discussion

A systematic review of 12 RCTs, found that nutritional supplementation for malnourished COPD patients improves exercise performance, as measured by clinical tests. [165] Nutritional supplementation improves peripheral (hand grip) muscle strength, but has indeterminate effects on pulmonary function tests.

There is, however, insufficient evidence to show that nutritional supplementation for malnourished patients with COPD affects other, more clinically relevant outcomes, such as QoL, dyspnea, hospitalizations, or mortality.

Obese or morbidly obese individuals (BMI >30 kg/m^2) should take action to achieve a healthy weight. For details regarding strategies for screening and management in the overweight or obese population, please refer to the VA/DoD Clinical Practice Guideline for Screening and Management of Overweight and Obesity.[3]

Lung Volume Reduction Surgery and Lung Transplantation

Some patients with severe COPD may benefit from surgery, such as lung volume reduction surgery (LVRS) or lung transplantation.

Recommendation

39. We recommend that any patient considered for surgery for COPD (lung volume reduction surgery [LVRS] and lung transplant) be first referred to a pulmonologist for evaluation. (Strong For)

Modified from the 2007 CPG without an updated systematic review of the evidence.

Discussion

LVRS and lung transplantation have efficacy in the treatment of specific patients with advanced COPD. [166-172] In fact, there is a tremendous amount of overlap in the selection criteria for both procedures. As a result, patients should be referred to pulmonary medicine for evaluation by a specialist to ensure that they receive the optimal surgical procedure for their individual condition.

Patients with very severe COPD who also meet the following criteria may benefit from LVRS and may be considered for referral:

- High-resolution CT confirming predominant upper lobe bilateral emphysema;
- Total lung capacity before rehabilitation and after treatment with bronchodilators is greater than 100 percent predicted (pp) and residual volume is greater than 150 pp;
- Post-bronchodilator FEV1 is less than 45 pp but > 20 pp; diffusing capacity of the lungs for carbon monoxide [DLCO]> 20% pp;
- $PaCO_2$ less than 60 mm Hg, and PaO_2 greater than 45 mm Hg;
- Patient has a low baseline exercise capacity and has completed a pulmonary rehabilitation program.

In many cases, terminal COPD is difficult to manage. For terminal COPD care and palliation, patients should be referred to a pulmonologist or palliative care specialist as appropriate.

Management of Patients in Acute Exacerbation of COPD

The slow progression of COPD is punctuated by periodic acute deteriorations. Prevention and management of these acute exacerbations is a focus of optimizing care of patients with COPD. An acute exacerbation is typically defined as an increase in symptoms above baseline which necessitates a change

[3] See the VA/DoD Clinical Practice Guideline for Screening and Management of Overweight and Obesity. Available at: http://www.healthquality.va.gov/guidelines/CD/obesity/.

in management. Cardinal symptoms are generally considered to be an increase in dyspnea or cough, or an increase in sputum volume or sputum purulence. COPD exacerbations are associated with increased costs, an increase in rate of decline in FEV1, and decreased QoL and activity levels for patients. Recurrent exacerbations are common; the greatest predictor of a future exacerbation is having had a prior exacerbation. Recommendations to inform the management of patients in acute exacerbation of COPD are presented in this section.

Recommendation

40. We recommend antibiotic use for patients with COPD exacerbations who have increased dyspnea and increased sputum purulence (change in sputum color) or volume. (Strong For)

Discussion

Both viral and bacterial infections can trigger acute COPD exacerbations, defined as an increase in dyspnea above baseline or an increase in sputum production or purulence. However, because exacerbations can also be triggered by non-infectious causes and because antibiotics are ineffective in viral infections, the role of antibiotics in treatment of exacerbations has been controversial. There is evidence that bronchial bacterial load plays a role in exacerbations. Relapse rates after treatment for COPD exacerbation are unacceptably high. [173-176] Reliable identification of patients who will benefit from antibiotic treatment would be ideal to optimize outcomes and limit bacterial resistance.

Traditionally, antibiotic use is recommended for patients with signs of bacterial infection, defined as having two of three cardinal features: increased dyspnea, increased sputum volume, and increased sputum purulence. [177] Recent data from a study conducted in primary care suggests that sputum purulence may be the best predictor of antibiotic response and can guide antibiotic use. [178,179] One small pilot study assessed the effects of withholding antibiotics from inpatients with and without purulent sputum. The study demonstrated that antibiotics could be safely withheld from patients without purulent sputum without a difference in outcomes. [180,181]

A recent large systematic review of 16 randomized trials comparing antibiotics (from various classes) to placebo showed a significant reduction in treatment failure and relapse rates. These benefits were strongest in inpatients and intensive care unit (ICU) patients. [182] This study also demonstrated a mortality benefit in the subgroup of ICU patients. Antibiotic use is, however, associated with an increased rate of diarrhea. In summary, moderate quality evidence suggests a significant benefit for antibiotics in moderate to severe exacerbations of COPD, such as those with purulent sputum or requiring hospitalization. [182] Further research into identification of which patients can be safely treated without antibiotics is warranted.

Recommendation

41. We suggest basing choice of antibiotic on local resistance patterns and patient characteristics.
    a. First-line antibiotic choice may include doxycycline, trimethoprim/sulfamethoxazole (TMP-SMX), second-generation cephalosporin, amoxicillin, amoxicillin/clavulanate, and azithromycin.
    b. Despite the paucity of evidence regarding the choice of antibiotics, we suggest reserving broader spectrum antibiotics (e.g., quinolones) for patients with specific indications such as:
        i. Critically ill patients in the intensive care unit (ICU);
        ii. Patients with recent history of resistance, treatment failure, or antibiotic use; and
        iii. Patients with risk factors for health care associated infections.

(Weak For)

Discussion

The confidence in the evidence is low to moderate based on the lack of head-to-head studies adequately designed to show superiority of one antibiotic over another. The evidence, in general, shows comparable clinical cure rates with no clinically relevant difference in adverse events among antibiotics within the same class [179,183-187] or different classes. [188-191]

In a systematic review of 19 trials, short-term effectiveness of quinolones, macrolides, and amoxicillin/clavulanate were similar, although quinolones were associated with lower rates of recurrent exacerbations. Amoxicillin/clavulanate was associated with more adverse events. [192]

In order to conserve the activity of this class of antibiotics, and reduce the development of resistant strains, fluoroquinolones should be reserved for the subset of patients with confirmed acute bacterial exacerbations of COPD who are at a higher risk of treatment failure. A non-inferiority study of moderate quality conducted in this patient population demonstrated increased rates of bacterial eradication with a quinolone antibiotic compared to amoxicillin/clavulanate. [193] This suggests that in this subset of patients, a quinolone may result in better bacterial eradication than amoxicillin/clavulanate.

When choosing an antibiotic, providers should consider the antibiotic spectrum and local resistance profiles of pathogenic microorganisms to commonly used antibiotics. [194] The suggested first-line choices listed in the recommendation are based largely on expert opinion. Providers should consider the spectrum of activity of the agent, reserving broader spectrum antibiotics for more severely ill patients as defined above. [194] Details on antibiotic choices and recommended doses can be found in Table 2.

Further research is needed to determine which patients would benefit from specific antibiotics or antibiotic classes.

Table 2. Antibiotic Choices and Recommended Doses for Acute Exacerbations of COPD [173,195]

Antibiotic	Recommended Oral Dose
doxycycline	100 mg PO every 12 hrs
trimethoprim/sulfamethoxazole (TMP-SMX)	1 DS tab PO every 12 hrs
Second generation cephalosporins: cefuroxime cefprozil	 250-500 mg PO every 12 hrs 500 mg PO every 12 hrs
amoxicillin	500-875 mg PO twice daily
amoxicillin/clavulanate	875 mg PO every 12 hrs
azithromycin	500 mg PO day 1, then 250 mg daily x 4 days
Fluoroquinolones:* levofloxacin moxifloxacin	 500 mg PO daily 400 mg PO daily

*Reserve use for patients with severe disease or specific risk
Abbreviations: DS: double strength; hrs: hours; mg: milligram; PO: orally

Recommendation

42. For outpatients with acute COPD exacerbation who are treated with antibiotics, we recommend a five-day course of the chosen antibiotic. (Strong For)

Discussion

The confidence in the current evidence is high given the number of patients studied and the consistent effect observed across trials. The benefits of short-term antibiotic therapy outweighs harms given the potential for enhanced patient compliance, fewer antibiotic related complications, lower cost burden, and decreased antibiotic resistance rates.

Current evidence demonstrates that short-term antibiotic therapy, defined as no longer than a five-day course, is preferable to longer duration therapy for patients with acute bacterial COPD exacerbations. A large systematic review found that clinical cure rates, at both early and late follow-up, and bacteriological cure rates observed with short-course antibiotic therapy were comparable with those achieved with conventional antibiotic treatment courses. [196]

A meta-analysis of outpatients with chronic bronchitis found that short-course treatment (five-day) proved as effective as longer duration treatment (7-10 days) in terms of treatment success and was associated with fewer adverse events. [197]

These findings, and our recommendation, support good antibiotic stewardship principles aimed at minimizing the risk for resistance. Most of the patients in the above studies were outpatients, although some inpatients were included. Further research is needed to identify subgroups of patients prone to relapse or who would require longer courses of antibiotics.

Recommendation

43. There is insufficient evidence to recommend for or against procalcitonin-guided antibiotic use for patients with acute COPD exacerbations. (Strength of the recommendation not applicable)

Discussion

Use of procalcitonin, a protein secreted in response to bacterial infection, has gained interest as a way to potentially guide antibiotic therapy in several conditions, including COPD exacerbations. One

systematic review extracted data on patients with COPD from studies that used procalcitonin-based algorithms to determine antibiotic use for respiratory conditions. In this study, an algorithm-based approach reduced antibiotic use without negatively affecting clinical end points such as mortality, re-exacerbation, or readmission. [198] Another randomized trial compared usual care to procalcitonin guidance for initiation of antibiotics in patients admitted to the ED for COPD exacerbations. Only 40% of the procalcitonin group received antibiotics, compared to 72% of the usual care group. Despite this, similar outcomes were noted in both groups, including six-month exacerbation rate, readmission rate, and time to next exacerbation, suggesting low procalcitonin levels identified patients who did not benefit from antibiotics. [199] In contrast to these data, a review of prospectively collected data suggested that some patients with low procalcitonin levels still benefited from antibiotics. [200]

Enthusiasm for the use of procalcitonin to potentially reduce antibiotic exposure and development of resistance must be tempered by the paucity of outcome data in patients with COPD and the risk of withholding treatment from patients who may benefit. Furthermore, the test is costly and not widely available. Many of the algorithms described require testing at multiple intervals throughout a patient's course, increasing the burden of care. For these reasons, we believe there is insufficient evidence at this time to recommend procalcitonin-guided antibiotic use. There is a growing body of research on procalcitonin and other biomarkers such as C-reactive protein. Further research is likely to affect recommendations in this area.

Recommendation

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

Discussion

There is consistent evidence to support the use of doses of prednisone at 30-40 mg in the treatment of COPD exacerbation. [201,202] A large systematic review compared use of higher dose steroid (80 mg prednisone equivalent daily and higher) to lower dose steroids (30-80 mg prednisone equivalent doses). [201] It found no statistically significant differences in treatment failure or rate of improvement of FEV1 when using the lower doses. In addition, patients taking lower doses of prednisone were less likely to experience hyperglycemia. [201,203] Given the lack of treatment benefit and increase in adverse effects, routine use of doses of corticosteroids in excess of 80 mg prednisone daily is not recommended.

There is also moderate quality evidence from a large RCT and a systematic review demonstrating that shorter duration of corticosteroids (seven days or less) is as efficacious as a longer duration of 14 days with respect to treatment failure, time to next exacerbation, all-cause mortality, change in FEV1, and length of stay. [202,204]

Side effects of systemic steroids should be closely monitored, especially in patients with diabetes mellitus, psychiatric comorbid conditions, and insomnia. There is no evidence exploring tapering steroids versus not tapering corticosteroids specific to COPD exacerbations.

Management of Patients with COPD in the Hospital or Emergency Department

Patients with COPD frequently present at EDs with symptoms of worsening dyspnea or other acute changes in their usual state of health. They are also frequently hospitalized for COPD exacerbations or other conditions, especially conditions associated with a history of smoking or aging. As discussed in the

previous sections, the initial diagnosis of COPD, the diagnosis of COPD exacerbations, the assessment of the severity of COPD, the differential diagnosis from other causes for the observed symptoms, and the diagnosis of other conditions that can co-occur with COPD can be challenging in this population, including in the emergency care and hospital settings. This section addresses the management of patients with confirmed COPD who present at EDs or who are hospitalized for COPD exacerbation or other reasons.

Recommendation

45. We suggest use of airway clearance techniques utilizing positive expiratory pressure (PEP) devices for patients with COPD exacerbations and difficulty expectorating sputum. (Weak For)

Discussion

Patients with COPD may be troubled by excess sputum production or by a perceived inability to clear their airways by coughing up secretions. Commonly used airway clearance techniques for mobilizing and clearing respiratory secretions deliver PEP by mask, mouthpiece or oscillation. Other techniques include postural drainage, percussion and vibration, breathing exercises, and high-frequency external chest wall oscillation.

A low-quality systematic review found a small but significant benefit with the use of airway clearance techniques that utilized PEP devices. This study showed a decreased need for assisted ventilation, decrease duration of ventilation assistance, and decreased hospital length of stay compared to usual care. No adverse effects were noted. [205]

In patients hospitalized for acute exacerbations of COPD, there is moderate evidence that airway clearance techniques reduce the need for invasive or non-invasive ventilatory assistance, days of ventilatory assistance, and length of hospital stay. [205]

In patients with stable COPD, there is weak or insufficient evidence that airway clearance techniques reduce the frequency of acute exacerbations of COPD, respiratory-related hospitalizations, or respiratory-related QoL. [205]

There is insufficient evidence that the use of PEP-based airway clearance techniques is more effective than the use of non-PEP-based airway clearance techniques. [205]

Use of the PEP device requires patient effort and cooperation, as well as respiratory therapists' assistance and instruction. Therefore, although of potential benefit, decisions to prescribe this therapy should take into account the preferences of the patient and the impact upon respiratory therapy resources.

Recommendation

46. We recommend the early use of non-invasive ventilation (NIV) in patients with acute COPD exacerbations to reduce intubation, mortality, and length of hospital stay. (Strong For)

Discussion

NIV is defined as the delivery of ventilatory support via the patient's upper airway using a mask or similar device. A large systematic review of 11 RCTs including patients with COPD found the combination of NIV and usual care superior to usual care alone. NIV versus usual care reduced the need for intubation in patients with mild (pH >7.35), moderate (pH 7.30-7.35), severe (pH 7.25-7.30), and very severe (pH <7.25) respiratory failure. NIV versus usual care reduced hospital mortality in patients with moderate and severe respiratory failure (relative risk (RR) 0.50 and 0.45 respectively). The mortality

difference was not significant for mild or very severe disease. NIV compared to usual care reduced hospital length of stay in patients with mild, severe, and very severe respiratory failure. [206,207]

These findings are particularly important since the combination of NIV and usual care compared to usual care alone is also associated with an overall reduction in complications (pneumonia, gastrointestinal bleeding, or sepsis). Moreover, early application of NIV is essential since NIV started after failure of usual medical care does not carry these benefits (reduction in mortality, intubation, or length of stay). [208,209]

Most patients with COPD exacerbations and respiratory failure will tolerate NIV. Common side effects from NIV include skin abrasions, gastric insufflation, and eye irritation. Patient factors that may preclude utilization of NIV include claustrophobia or facial trauma. About 30% of patients fail treatment with NIV requiring intubation and mechanical ventilation. [210] Risk factors for treatment failure include poor neurologic score (Glasgow coma score <11), tachypnea (respiratory rate >35), acidosis (pH <7.29), agitation, excessive secretions, and failure to improve during the first two hours of NIV (no change in pH, tachypnea, or hypercapnea). [211] Though the cause is uncertain, epidemiologic studies have reported increasing mortality in the small proportion of patients who require transition to intubation and mechanical ventilation, suggesting careful monitoring for early signs of failure may be important. [212]

It is preferred that NIV for acute respiratory failure be performed in an ICU. However a step down unit with highly skilled nursing staff and respiratory therapists who are able to closely monitor these patients may also be a consideration if an ICU bed is not available. This type of setting is particularly important in the first two hours, when failure of the modality is most likely to become evident. Starting this intervention sooner rather than later may prevent intubation and mechanical ventilation. [211]

Recommendation

47. We recommend the use of NIV to support weaning from invasive mechanical ventilation and earlier extubation of intubated patients with COPD. (Strong For)

Discussion

A systematic review included 16 trials involving nearly 1,000 subjects predominately with COPD. [207,213] Inclusion criteria included those who failed a spontaneous breathing trial and/or met established weaning criteria. This systematic review found that NIV following early extubation compared with usual weaning approaches (pressure support, synchronized intermittent mandatory ventilation) reduced mortality (RR 0.36 CI 0.25-0.56), weaning failure, ventilator associated pneumonia, and length of stay in the ICU as well as in the hospital. It also reduced total duration of mechanical ventilation, rate of tracheostomy, and reintubation. Similarly, in a systematic review of two RCTs with a total of 80 patients with COPD (ages 58-69), the use of NIV after failure of a trial of T-piece weaning showed significant improvement in mortality and decreased incidence of nosocomial ventilator associated pneumonia. There was no significant difference in the length of ICU stay or the duration of mechanical ventilation.

Future Research

The availability of high quality research on effects of varying interventions on COPD patients is limited in some areas. This results in enduring questions on which therapies are appropriate in which situations. During the course of reviewing the literature and developing the recommendations for this guideline, we identified a need for additional research to close the knowledge gap in the management and

treatment of patients with COPD. The need for clinical trials and comparative effectiveness research was identified in the following key areas.

Comparative effectiveness of various spacers in MDIs

For patients who have difficulty actuating and coordinating drug delivery with MDIs, we suggest using spacers. However, little evidence exists on the comparative effectiveness of various spacers in adults with COPD, although larger sized spacers seem to be more effective than smaller sized spacers.

LAMA (tiotropium) versus LABA as first-line therapy

We suggest using a LAMA, specifically tiotropium, as first-line pharmacotherapy for COPD. This is a weak recommendation because there is no evidence for differences in all-cause hospitalization rates, mortality, symptom improvement, and FEV1 between tiotropium and LABAs. However, the benefits-harm balance may slightly favor tiotropium over LABAs as first-line therapy. More research is needed in order to compare the benefits and harms of LAMAs, specifically tiotropium, and LABAs as first-line therapy.

Dual bronchodilators compared to combination ICS and long-acting bronchodilators

We recommended use of combination pharmacotherapy for patients who are on LABAs or LAMAs alone and have persistent dyspnea on monotherapy. There is evidence that combination therapy with tiotropium and LABA is more effective than monotherapy with tiotropium and combination therapy with ICS and LABA is more effective than monotherapy with LABA or LAMA. However, the difference in effects of different types of combination therapy is unclear. Data on combination LAMA and LABA compared to combination ICS and LABA are limited. Long-term studies directly comparing dual bronchodilator versus combination ICS and long-acting bronchodilators are needed.

Combination LAMA and LABA compared to triple therapy

Further, additional research is needed comparing the effectiveness of combination LAMA and LABA to triple therapy (LAMA+LABA+ICS). The weak recommendation for triple therapy for patients who are on combination therapy with LABA and LAMA and experience persistent dyspnea or COPD exacerbations is supported by evidence that triple therapy is more effective than tiotropium monotherapy or combination ICS and LABA in improving some outcomes such as QoL. The data are weak, and thus more research should be completed in this area.

Combined therapy with roflumilast compared to combination LABA and ICS

We recommended against using roflumilast in patients with COPD in primary care without consultation with a pulmonologist due to potential risks which outweighed modest benefits. The evidence for this recommendation centered on a systematic review of trials comparing roflumilast to placebo. However, roflumilast may have a different effect when added to combination LABA and ICS. Further research in this area is needed to determine if roflumilast can improve patient outcomes as part of a combined therapy.

Long-term oxygen therapy in patients with isolated exercise hypoxemia

There was insufficient evidence to recommend LTOT for patients with isolated exercise hypoxemia based on outcomes observed in a systematic review including 4 trials (331 patients). Additional adequately powered research is necessary to investigate the long-term effects of LTOT in the population with isolated exercise hypoxemia.

Air travel for patients with COPD

Additional research should be conducted to study patients with varying severity of COPD and interventions during and after air travel in order to assess their effects.

Long-term oxygen therapy in patients with isolated nocturnal hypoxemia

We suggest against the use of LTOT for the treatment of outpatients with stable, confirmed COPD and isolated nocturnal hypoxemia. Further research is needed to provide evidence of benefit in this area.

Home NIV in patients with stable COPD

Home NIV may be an appropriate target for future research. Balancing very limited utility associated with home NIV with modest harms (e.g., upper airway irritation, highly variable patient acceptability, and significant resource implications) suggests that routine application of this therapy is currently inadvisable. However, more research on hard endpoints should be conducted to allow stronger recommendations.

Supported self-management

While supported self-management has shown to be effective in selected high-risk patients with COPD in improving specific outcomes, the role of supported self-management in caring for patients with COPD and varying characteristics and disease severities has not been well-researched. Furthermore, there is concern that one of the studies showed an increase in mortality, but the other did not. Supported-self management is also not well-defined or uniform across studies. The various components of supported self-management should be analyzed individually in order to determine which components are most effective.

Telehealth

Telehealth has been found to be effective in patients with COPD in reducing ED visits and hospitalization. However, telehealth interventions vary between studies. Similarly to supported self-management, additional research should be conducted to isolate the portions of telehealth that are most effective at achieving improvement in patient outcomes.

Breathing exercise

Breathing exercise should be further investigated, with particular emphasis on its long-term effects. Additional understanding of the effectiveness of various breathing exercises could also be gained through comparative effectiveness research.

Nutrition referral

Further research on the effects of nutritional interventions in patients with COPD could inform their effects on relevant clinical outcomes, such as morbidity, mortality dyspnea, and QoL. By isolating nutrition modification as an intervention, additional insight into its effects can be gained.

Antibiotics in specific subgroups of COPD patients

Antibiotics were recommended for use in patients with COPD exacerbations with increased dyspnea and increased sputum purulence or volume. It is not clear, however, which patients can be treated safely without antibiotics. Therefore, research is needed to provide analysis of specific subgroups of patients.

Use of procalcitonin-guided antibiotics in patients with COPD exacerbations

Ongoing research may affect the evidence base for treatment of COPD. For instance, there is ongoing research on procalcitonin and other biomarkers such as C-reactive protein. This research may affect the recommendation that there is insufficient evidence to recommend for or against the use of procalcitonin-guided antibiotic use for patients with acute COPD exacerbations.

NIV to support weaning

There is a need for additional RCTs including patients with varying severity of COPD to assess the effects of using NIV as a substitute for conventional weaning strategies.

Appendix A: Evidence Review Methodology

Formulating Evidence Questions

The CPG Champions were tasked with identifying key evidence questions to guide the systematic review of the literature on COPD. These questions, which were developed in consultation with the Lewin Group's evidence review team, ECRI Institute, addressed clinical topics of the highest priority for the VA and the DoD populations. The KQs follow the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). [214] Table A-1 provides a brief overview of the PICOTS typology.

Table A-1. PICOTS [214]

P	Patients, Population or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-morbidities, and other patient characteristics or demographics.
I	Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
C	Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
O	Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as QoL, complications, mortality, morbidity, etc.
(T)	Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
(S)	Setting, of applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. The following population, interventions, and outcomes were considered. Table A-2 contains the final set of KQs used to guide the systematic review for this CPG.

Population

The population considered in this review includes adults who have a diagnosis of COPD that includes chronic bronchitis, emphysema, and chronic airflow limitation/obstruction. Patients with bronchiectasis, asthma, or other chronic lung diseases, such as cystic fibrosis, but not COPD are not considered in this guideline.

Interventions

The interventions covered in this systematic review included both pharmacologic and non-pharmacologic treatments used in the management of COPD.

Pharmacologic interventions considered in this review include various drugs, such as LABAs, SABAs, SAMAs, LAMAs, ICS, PDE4, chronic macrolides, theophylline, and NAC. These agents were considered either alone or, in the case of inhaled bronchodilators and ICS, in combination in approximation of a stepped approach to managing the symptoms of COPD. This review also considered the use of short-term corticosteroids or short-term courses of antibiotics to treat COPD exacerbations.

Non-pharmacologic interventions include pulmonary rehabilitation and interventions that comprised an overall disease management program for patients with COPD, such as self-management education and action planning for the management of COPD exacerbations and other symptoms. In this review, pulmonary rehabilitation includes physical rehabilitation and exercise, psychological assessment and support, nutrition and dietary assessment and support, and oxygen assessment and support. This review also considered the use of NIV for acute COPD exacerbations and use of oxygen therapy for patients with COPD who have hypoxemia during exercise or nocturnal hypoxemia.

Additionally, this review considered the use of spirometry, symptom severity, risk of exacerbations, and comorbidities to diagnose, classify, and manage COPD. It also considered diagnostics tests that may be more effective in distinguishing COPD exacerbations from other causes of acute symptoms, such as CVD. Finally, this review considers the use of beta-blockers in patients with COPD who have clinical indications for beta-blocker treatment.

Outcomes

Outcomes considered included QoL, morbidity, dyspnea, functional capacity, exacerbation rate and/or severity, mortality, harms, health care utilization (only for the KQs assessing pulmonary rehabilitation or chronic disease management), and diagnostic test accuracy (only for the KQ assessing tests used to distinguish between COPD exacerbation and other causes of acute symptoms).

Table A-2. Key Questions Used in the Systematic Review and Evidence Base Results

Key question		Evidence Base
Diagnostic Questions		
KQ1	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?	2 systematic reviews, 1 RCT, 3 case series, and 1 cohort trial
KQ8	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?	4 prospective cohort trials
Non-invasive Ventilation Questions		
KQ6	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?	2 systematic reviews and 1 RCT
Stepped Therapy Questions		
KQ5	In patients with COPD, what is the evidence that stepped therapy with the following drug classes, or combinations, improves outcomes?	25 systematic reviews

Key question		Evidence Base
	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 What is the evidence that certain subpopulations (e.g. COPD patients over 65 years) have increased benefits or risks from stepped therapy?	
Beta-Blocker Treatment Question		
KQ9	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?	2 systematic reviews, 1 RCT, and 2 cohort studies
Acute Exacerbation Questions		
KQ4	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? Can procalcitonin testing be used to determine when antibiotics should be initiated and the duration of therapy?	3 systematic reviews and 13 RCTs
KQ7	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?	2 systematic reviews and 1 RCT
Non-pharmacologic Therapy Questions		
KQ2	a. In patients with COPD, who have hypoxemia during exercise or nocturnal hypoxemia, does administration of oxygen compared to no O2 affect morbidity, mortality, dyspnea and quality of life (QoL)? b. In patients with stable, chronic COPD, what is the impact of nocturnal ventilation support treatments on patient outcomes?	4 systematic reviews
KQ3	In patients with severe COPD on optimized pharmacologic therapy, does a pulmonary rehabilitation program or chronic	15 systematic reviews and 12 RCTs

Key question	Evidence Base
disease management lead to better outcomes and decreased health care utilization than routine care without rehabilitation? Pulmonary rehabilitation includes: • physical rehabilitation • psychological assessment and support • nutrition and dietary assessment and support • O2 assessment and support What does the evidence show are the most effective interventions, or combination of interventions?	

Conducting the Systematic Review

The methods of the systematic review are described below. In part, these methods followed the guidelines for conducting a systematic review set forth by AHRQ in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. [215] Additionally, the methods followed the guidance set forth by the VA/DoD in the *Guideline for Guidelines* document. [17]

For all KQs, the following external and internal databases were searched: MEDLINE, PreMEDLINE, EMBASE, (via the OVID SP platform using the one-search and de-duplication features), the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. Searches were designed to identify unique reviews, trials, and technology assessments. Searches of the World Wide Web were also performed to capture relevant grey literature that had not been indexed to the databases listed previously. The searches covered the time period of January 1, 2005 to February 2014. The search strategy was based on a combination of Medical Subject Headings (MeSH) terminology and text key words, and can be found in Table A-3. The syntaxes used to search each of the previously listed databases can be found in Tables A-4 and A-5.

Table A-3. Topic-Specific Search Terms

Concept	Controlled Vocabulary	Keywords
COPD	**MeSH** exp emphysema/ exp pulmonary atelectasis/ exp pulmonary disease, chronic obstructive/ **EMBASE** exp atelectasis/ exp chronic obstructive lung disease/	atelectas* chronic airflow limitation* chronic airflow obstruction* chronic bronchitis chronic obstructive lung disease* chronic obstructive pulmonary disease* chronic obstructive respiratory disease* chronic obstructive airway disease* chronic obstructive airways disease* chronic pulmonary disfunction chronic pulmonary dysfunction chronic respiratory disease* chronic respiratory insufficien* COAD COPD

Concept	Controlled Vocabulary	Keywords
		emphysema* pulmonary emphysema*
Spirometry	**MeSH** exp spirometry/ exp respiratory function tests/ exp total lung capacity/ **EMBASE** exp lung function test/ exp lung volume/	spirometry
Exacerbations	**MeSH** disease progression/ **EMBASE** disease exacerbation/	acute exacerbate* progress*
Comorbidities	**MeSH** comorbidity/	comorbid*
Outcomes for KQ1	**MeSH** clinical protocols/ exp diagnosis/ **EMBASE** clinical classification/ treatment planning/	assess* classif* di.fs. diagno* outcome* plan* treatment
Exercise/Nocturnal Hypoxemia	**MeSH** anoxia/ exp exercise/ **EMBASE** exercise hypoxemia/ exp hypoxemia/ nocturnal hypoxemia/	activit* anoxemi* anoxi* exercise* exertion hypoxemi* hypoxi* night* nocturnal oxygen deficienc* physical sleep* walk*
Oxygen Intervention	**MeSH** oxygen/ oxygen inhalation therapy/ **EMBASE** exp oxygen therapy/	oxygen
Nocturnal		night* nocturnal sleep*

Concept	Controlled Vocabulary	Keywords
Ventilation	**MeSH** **exp respiration, artificial/** **EMBASE** **exp artificial ventilation/**	autoPAP bi-level positive airway pressure BiPAP continuous positive airway pressure CPAP intermittent positive pressure breathing intermittent positive pressure ventilation inverse ratio ventilation IPPV nocturnal mask pressure support noninvasive positive pressure ventilation NIPPV PAV positive end expiratory pressure ventilat*
Pulmonary Rehabilitation	**EMBASE** **pulmonary rehabilitation/**	chronic disease management pulmonary rehabilitation self-health self-manage*
Physical Rehabilitation	**MeSH** **exp exercise therapy/** **EMBASE** **physiotherapy/**	exercise therapy physical rehabilitation physical therapy
Psychological Assessment & Support	**MeSH** **exp psychotherapy/**	assess* manage* psycho* support therapy
Nutrition and Dietary Assessment & Support	**MeSH** **exp diet therapy/**	assess* diet* manage* nutrition support therapy
O2 Assessment & Support	**MeSH** **exp oxygen inhalation therapy/** **EMBASE** **exp oxygen therapy/**	assess* manage* O2 oxygen support therapy
Outcomes for KQ3	**MeSH**	dyspnea

Concept	Controlled Vocabulary	Keywords
	exp dyspnea/ **morbidity/** **mortality/** **exp quality of life/** **treatment outcome/**	morbidity mortality outcome* quality of life QoL
Antibiotics	**MeSH** **exp anti-bacterial agents/** **EMBASE** **exp antiinfective agent/**	antibacterial anti-bacterial anti-infective antibiotic* antiinfective bacteriocid*
Long-acting & Short-acting beta agonists	**MeSH** **exp adrenergic beta-agonists/** **EMBASE** **exp beta adrenergic receptor stimulating agent/**	beta agonist* LABA long-acting long acting longacting SABA short-acting shortacting
Long-acting & Short-acting Anticholinergics	**MeSH** **exp cholinergic antagonists/** **EMBASE** **exp cholinergic receptor blocking agent/**	anticholinergic* long-acting long acting longacting short-acting shortacting
Inhaled Corticosteroids	**MeSH** **exp Adrenal Cortex Hormones/** **EMBASE** **exp corticosteroid/**	corticosteroid* inhal*
Phosphodiesterase 4 Inhibitors	**MeSH** **phosphodiesterase 4 inhibitors/** **EMBASE** **phosphodiesterase IV inhibitor/**	PDE-4 PDE4 phosphodiesterase 4 inhibitor*
Azithromycin	**MeSH** **azithromycin/**	azithromycin
Theophylline	**MeSH** **exp Theophylline/**	theofylline theophylline
Leukotriene antagonists	**MeSH** **leukotriene antagonists/** **EMBASE** **exp leukotriene receptor blocking agent/**	antagonist* block* inhibit* leukotriene

Concept	Controlled Vocabulary	Keywords
Steroids	**MeSH** **exp adrenal cortex hormones/** **exp steroids/** **EMBASE** **exp glucocorticoid/** **exp steroid/**	corticosteroid* glucocorticoid* steroid*
Dosage & Duration	**MeSH** **EMBASE** **exp drug dose/** **treatment duration/**	ad.fs. dosage* dose* duration* taper*
Diagnosis	**MeSH** **diagnosis, differential/** **EMBASE** **differential diagnosis/**	diagnos* differential diagnosis distinguish*
Beta-Blockers	**MeSH** **exp adrenergic beta-antagonists/** **EMBASE** **exp beta adrenergic receptor blocking agent/**	antagonist* beta block*

Table A-4. OVID Conventions

Syntax	Meaning
* (within or following a term)	truncation character (wildcard)
* (preceding a term)	denotes major category focus/major MeSH
.ab.	limit to abstract
ADJ*n*	search terms within a specified number (*n*) of words from each other in any order
exp/	"explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
.de.	limit controlled vocabulary heading
.fs.	floating subheading
.hw.	limit to heading word
.mp.	combined search fields (default if no fields are specified)
.pt.	publication type
.ti.	limit to title
.tw.	limit to title and abstract fields

Table A-5. Search Strategies Conducted using EMBASE/MEDLINE/PsycINFO OVID Syntax

	Concepts	Search Statement
1	COPD	exp Chronic obstructive lung disease/ or exp pulmonary disease, chronic obstructive/ or exp emphysema/ or exp Pulmonary Atelectasis/ or exp atelectasis/ or (chronic obstructive pulmonary disease$ or COPD or chronic obstructive respiratory disease$ or chronic obstructive lung disease$ or chronic obstructive airway disease$ or chronic obstructive airways disease$ or COAD or chronic airflow obstruction$ or chronic airflow limitation$ or chronic respiratory disease$ or chronic pulmonary disfunction or chronic pulmonary dysfunction or chronic respiratory insufficien$ or chronic bronchitis or pulmonary emphysema$ or emphysema$ or atelectas$).ti,ab.
2	Spirometry	(spirometry or (bronchodilator$ adj2 respon$)).ti,ab. or exp spirometry/ or exp respiratory function tests/ or exp total lung capacity/ or exp lung function test/ or exp lung volume/
3	Disease severity	((symptom$ OR disease) AND severity).ti,ab.
4	Exacerbations	exacerbat$.ti,ab. OR Disease Progression/ OR disease exacerbation/
5	Comorbidities	comorbid$.ti,ab. OR Comorbidity/
6	KQ 1 Outcomes	(outcome$ OR classif$ OR assess$ OR (treatment ADJ2 plan$) OR diagnos$).ti,ab. OR di.fs. OR Clinical Protocols/ OR treatment planning/ OR clinical classification/ OR exp diagnosis/
7	KQ 1 Combine	1 and (2 or 3 or 4 or 5) and 6
8	Exercise OR Nocturnal Hypoxemia	(((exercise$ or physical or activit$ or walk$ or exertion or nocturnal or sleep$ or night$).ti,ab. or exp exercise/) and ((Anoxi$ or Anoxemi$ or Hypoxi$ or Hypoxemi$ or Oxygen Deficienc$).ti,ab. or Anoxia/ or exp hypoxemia/)) or exercise hypoxemia/ or nocturnal hypoxemia/
9	Oxygen Intervention	oxygen.ti,ab. or Oxygen Inhalation Therapy/ or Oxygen/ or exp Oxygen Therapy/
10	KQ 2a Combine	1 and 8 and 9
11	Nocturnal	(nocturnal or sleep$ or night$).ti,ab.

	Concepts	Search Statement
12	Ventilation	(AutoPAP or Bi-level positive airway pressure or BiPAP or Continuous positive airway pressure or CPAP or Intermittent positive pressure breathing or Intermittent positive pressure ventilation or Inverse ratio ventilation or IPPV or Nocturnal mask pressure support or Noninvasive positive pressure ventilation or NIPPV or PAV or Positive end expiratory pressure or ventilat$).ti,ab. or exp artificial ventilation/ OR exp Respiration, Artificial/
13	KQ2b Combine	1 and 11 and 12
14	Pulmonary Rehabilitation	(pulmonary rehabilitation or chronic disease management or self-health or self-manage$).ti,ab. or pulmonary rehabilitation/
15	Physical Rehabilitation	(physical rehabilitation or exercise therapy or physical therapy).ti,ab. or exp Exercise Therapy/ or physiotherapy/
16	Psychological Assessment & Support	(psycho$ and (assess$ or support or therapy or manage$)).mp. or exp Psychotherapy/
17	Nutrition and Dietary Assessment & Support	((nutrition or diet$) and (assess$ or support or therapy or manage$)).ti,ab. or exp diet therapy/
18	O2 Assessment & Support	((oxygen or O2) and (assess$ or support or therapy or manage$)).ti,ab. or exp oxygen therapy/ or exp Oxygen Inhalation Therapy/
19	KQ3 Intervention Combine	14 or 15 or 16 or 17 or 18
20	KQ3 Outcomes	(morbidity or mortality or quality of life or QoL or dyspnea or outcome$).ti,ab. or Morbidity/ or Mortality/ or exp Quality of Life/ or Treatment Outcome/ or exp Dyspnea/
21	KQ3 Combine	1 and 19 and 20
22	Antibiotics	(antibiotic$ OR Anti-Bacterial OR antibacterial OR bacteriocid$ OR antiinfective OR anti-infective).ti,ab. OR exp Anti-Bacterial Agents/ OR exp antiinfective agent/
23	Exacerbations	(exacerbate$ OR progress$ OR acute).ti,ab. OR Disease Progression/ OR disease exacerbation/
24	KQ4 Combine	1 and 22 and 23
25	Long-acting & Short-acting beta agonists	((longacting or long acting or long-acting or shortacting or short-acting).ti,ab. ADJ2 (beta

	Concepts	Search Statement
		agonist*.ti,ab. or exp Adrenergic beta-Agonists/ or exp beta adrenergic receptor stimulating agent/)) or (LABA or SABA).ti,ab.
26	Long-acting & Short-acting Anticholinergics	(longacting or long acting or long-acting or shortacting or short-acting).ti,ab. ADJ2 (anticholinergic*.ti,ab. or exp Cholinergic Antagonists/ or exp cholinergic receptor blocking agent/)
27	Inhaled Corticosteroids	(inhal$ ADJ5 corticosteroid*).ti,ab. OR exp Adrenal Cortex Hormones/ OR exp corticosteroid/
28	Phosphodiesterase 4 Inhibitors	(phosphodiesterase 4 inhibitor* OR “PDE4” OR “PDE-4”).ti,ab. OR Phosphodiesterase 4 Inhibitors/ OR phosphodiesterase IV inhibitor/
29	Azithromycin	azithromycin.ti,ab. OR azithromycin/
30	Theophylline	(Theophylline or Theofylline).ti,ab. or exp Theophylline/
31	Leukotriene antagonists	(Leukotriene ADJ5 (Antagonist$ or block$ or inhibit$)).ti,ab. or Leukotriene Antagonists/ or exp leukotriene receptor blocking agent/
32	Combine	25 or 26 or 27 or 28 or 29 or 30
33	Outcomes	(outcome$ OR morbidity OR mortality OR exacerbate$ OR dyspnea).ti,ab. OR Treatment Outcome/ OR Morbidity/ OR Mortality/ OR Disease Progression/ OR disease exacerbation/ OR exp dyspnea/
34	KQ5 Combine	1 and 32 and 33
35	Exacerbations	(acute or exacerbat$).ti,ab. or Disease Progression/ OR disease exacerbation/
36	Ventilation	(AutoPAP or Bi-level positive airway pressure or BiPAP or Continuous positive airway pressure or CPAP or Intermittent positive pressure breathing or Intermittent positive pressure ventilation or Inverse ratio ventilation or IPPV or Nocturnal mask pressure support or Noninvasive positive pressure ventilation or NIPPV or PAV or Positive end expiratory pressure or noninvasive ventilat$ or non-invasive ventilat$ or pressure support ventilat$ OR volume ventilation OR Negative-pressure ventilat$ OR proportional-assist ventilat$ OR PAV).ti,ab. or exp artificial ventilation/ OR exp Respiration, Artificial/
37	KQ6 Combine	1 and 35 and 36

	Concepts	Search Statement
38	Steroids	(Corticosteroid$ or glucocorticoid$ or steroid$).ti,ab. or exp glucocorticoid/ or exp adrenal cortex hormones/ or exp steroids/ or exp steroid/
39	Dosage & Duration	(dose$ or dosage$ or duration$ or taper$).ti,ab. or ad.fs. or treatment duration/ or exp drug dose/
40	KQ7 Combine	1 and 38 and 39
41	Diagnosis	(distinguish$ or differential diagnosis or diagnos$).ti,ab. or differential diagnosis/ or Diagnosis, Differential/
42	KQ8 Combine	1 and 35 and 41
43	Beta Blockers	(beta ADJ3 (block$ OR antagonist$)).ti,ab. OR exp Adrenergic beta-Antagonists/ OR exp beta adrenergic receptor blocking agent/
44	KQ9 Combine	1 and 43
45	All KQ Results Combine	7 or 10 or 13 or 21 or 24 or 34 or 37 or 40 or 42 or 44
46	Eliminate Certain Publication Types	45 not (book/ or edited book/ or case report/ or case reports/ or comment/ or conference abstract/ or conference paper/ or conference review/ or editorial/ or letter/ or news/ or note/ or proceeding/ or (book or edited book or case report or case reports or comment or conference or editorial or letter or news or note or proceeding).pt.)
47	Systematic Reviews	46 and (Systematic review/ or meta analysis/ or metaanalysis/ or pooled.mp. or meta-analysis.pt. or "systematic review".mp. or search$.ab.)
48	Trials	46 and (Randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or placebo$.mp. or random$.ti. or crossover$.mp. or cross over.mp. or ((singl$ or doubl$ or tripl$ or trebl$) and (blind$ or mask$ or sham$)).mp. or latin square.mp. or ISRTCN.mp. or ACTRN$.mp. or (NCT$ not NCT).mp.)
49	Reviews & Studies Combine	47 or 48
50	English	limit 49 to english language
51	Human	limit 50 to human
52	Publish Date	limit 51 to yr="2005 - 2014"

	Concepts	Search Statement
53	Humans	limit 52 to humans
54	Remove Duplicates	remove duplicates from 53

Extensive literature searches identified 2,717 citations potentially addressing the KQs of interest to this evidence review. In each stage of the evidence review process, studies were included or excluded based on a set of criteria (Table A-6). Of the original 2,717 identified studies, 1,110 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, or not a full-length article). Overall, 1,607 abstracts were reviewed with 836 of those being excluded for the following reasons: not a systematic review or clinical study, did not address a KQ of interest to this review, did not enroll population of interest, or published prior to January 2005. A total of 771 full-length articles were reviewed. Of those, 317 were excluded at a first pass review for the following: not addressing a KQ of interest, not enrolling the population of interest, not meeting inclusion criteria for clinical study or systematic review, or being a duplicate. A total of 454 full-length articles were thought to address one or more KQs and were further reviewed. Of these, 360 were ultimately excluded. Reasons for their exclusion are presented in Figure A-1, below. Overall, our original searches identified 94 studies that addressed one or more of the KQs and were considered as evidence in this review. Table A-2, above, indicates the number of studies that addressed each of the questions. Subsequent searches were conducted to identify new studies or studies covering clinical areas not covered in the original systematic review. These searches identified additional studies that were incorporated as evidence in the final CPG.

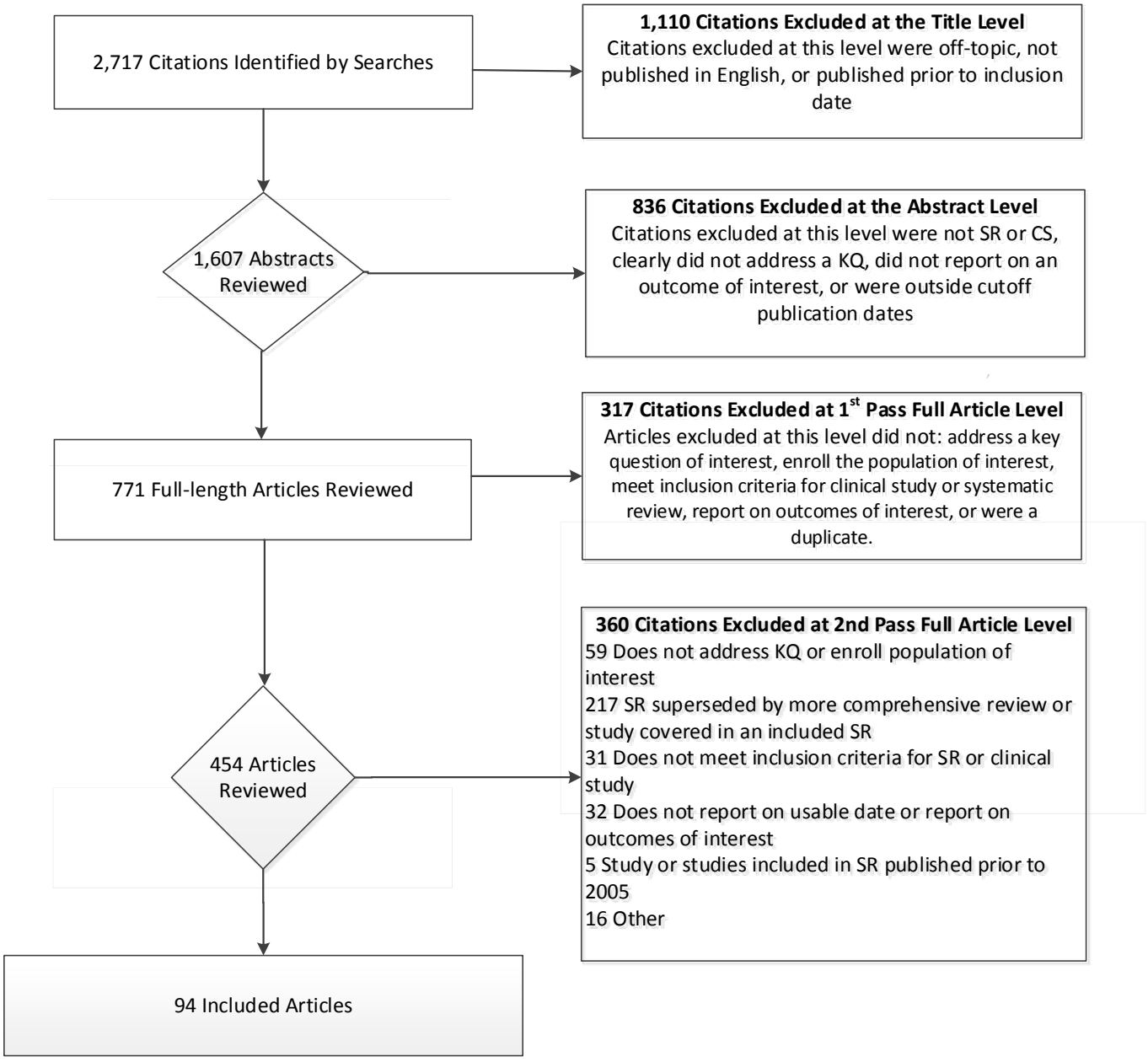
Table A-6. Criteria for Study Inclusion and Exclusion

General Criteria
• Clinical studies or systematic reviews published on or after January 1, 2005 to February 2014. If multiple systematic reviews addressed a KQ, we selected the most recent and/or comprehensive review. Systematic reviews will be supplemented with clinical studies published subsequent to the systematic review. • Studies must be published in English. • Publication must be a full clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that were not full-length, clinical studies were not accepted as evidence. • Study must have enrolled a patient population in which at least 85 percent of patients had COPD, with identifiable data for the population of interest (i.e., patients with COPD should be identifiable in the dataset). • Only studies assessing the efficacy of drugs that have received FDA approval for marketing in the US were included in this review.
Screening, Treatment and Management Studies
• For KQ 1, studies focusing on COPD biomarkers were not included as evidence addressing this KQ. Further, studies addressing this KQ must have reported on patient outcomes or on other outcomes of interest to the question, which include improvement in diagnoses or clinical classification, treatment planning, and clinician adherence to treatment protocols. • For KQ 1, 8, 9, non-RCTs, case-controlled trials, and other observational studies were accepted as evidence. Case studies or narrative reviews were not accepted as evidence for these KQs. • For KQs 2, 3, 4a, 4b, 5 a-j, 6, and 7, study must have been a systematic review of RCTs or an RCT.

Observational studies were not considered as evidence for these questions.

- Study must have enrolled at least 20 patients (10 per study group)
- Study must have reported on an outcome of interest
- For KQ 4; short-term antibiotic use was defined as 21 days or less.

Figure A-1. Review Flow Diagram



As per the VA/DoD *Guideline for Guidelines* document, risk-of-bias (or study quality) of individual studies and previous systematic reviews was assessed using the USPSTF method. [17] Each study was assigned a rating of "Good," "Fair," or "Poor" based on sets of criteria that vary depending on study design. Detailed lists of criteria and definitions of "Good," "Fair," or "Poor" ratings for different study designs

appear in Appendix VII of the USPSTF procedure manual at http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual---appendix-vii.

A narrative approach to synthesizing the evidence for all the KQs was used. As indicated in the VA/DoD *Guideline for Guidelines* document, the first-line of evidence was previous systematic reviews. [17] For questions in which a previous review was available, individual studies that met this review's inclusion criteria were used to supplement or update the previous review. For questions for which no previous review was available, we summarized the overall findings for the outcomes of interest of the studies that addressed a KQ.

The overall quality of the body of evidence supporting the findings for the outcomes of interest in this report was assessed using the GRADE system. [18] The GRADE system primarily involves consideration of the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. Given time and resources, other factors such as publication bias may also be considered. The GRADE system rates the overall quality of the evidence as "High," "Moderate," "Low," and "Very Low." For more information on the GRADE system go to the GRADE working group website at the following link: http://www.gradeworkinggroup.org/.

Convening the Face-to-Face Meeting

In consultation with the COR, the Champions, and the Work Group, the Lewin Team convened a three and one-half day face-to-face meeting of the CPG Champions and Work Group members on April 28-May 1, 2014. These experts were gathered to develop and draft clinical recommendations based on the evidence review for an update to the 2007 CPG. Lewin presented detailed information on the process used to grade the evidence. ECRI presented findings from the evidence review for each of the KQs. The presentations helped prepare the Champions and Work Group for their work in reviewing and synthesizing the evidence and forming new recommendations.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review and were asked to retain, revise, or reject each recommendation from the 2007 CPG. In addition, members developed new clinical practice recommendations, not presented in the 2007 CPG, based on the 2013 evidence review. At this meeting, Work Group members were assigned to one of four smaller subgroups depending on their area of clinical expertise.

Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation: [18]

- Balance of desirable and undesirable outcomes;
- Confidence in the quality of the evidence;
- Values and preferences;
- Other implications, as appropriate, e.g.,:
    - Resource Use;
    - Equity;
    - Acceptability;
    - Feasibility;
    - Subgroup considerations.

The following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved QoL, decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse event, impaired QoL, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that the majority of clinicians will offer patients therapeutic or preventive measures as long as the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The evidence review used for the development of recommendations for the management of COPD, conducted by ECRI, assessed the confidence in the quality of the evidence base and assigned a rate of "High," "Moderate," "Low," or "Very Low."

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

Values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term "values" has the closest connotation to these processes. For others, the connotation of "preferences" best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having "similar values", "some variation", or "large variation" in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient's values and preferences?
- Are the assumed or identified relative values similar across the target population?

Other implications consider the practicality of the recommendation, including resources use, equity, acceptability, feasibility and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example statin use in the frail elderly and others with multiple comorbidities may not be effective and depending on the societal benchmark

for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility and subgroup considerations require similar judgments around the practicality of the recommendation.

The framework in Table A-7, below, was used by the Work Group to guide discussions on each domain.

Table A-7: Evidence to Recommendation Framework

Decision Domain	Judgment
Balance of desirable and undesirable outcomes	
Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? Are the desirable anticipated effects large? Are the undesirable anticipated effects small? Are the desirable effects large relative to undesirable effects?	Benefits outweigh harms/burden Benefits slightly outweigh harms/burden Benefits and harms/burden are balanced Harms/burden slightly outweigh benefits Harms/burden outweigh benefits
Confidence in the quality of the evidence	
Is there high or moderate quality evidence that answers this question? What is the overall certainty of this evidence?	High Moderate Low Very low
Values and preferences	
Are you confident about the typical values and preferences and are they similar across the target population? What are the patient's values and preferences? Are the assumed or identified relative values similar across the target population?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations):	
Are the resources worth the expected net benefit from the recommendation? What are the costs per resource unit? Is this intervention generally available? Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Is there lots of variability in resource requirements across settings?	Various considerations

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains. [18] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low. [216] In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above);
- Relative strength (Strong or Weak);
- Direction (For or Against).

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "We recommend offering this option …");
- Weak For (or "We suggest offering this option …");
- Weak Against (or "We suggest not offering this option …");
- Strong Against (or "We recommend against offering this option …").

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

Drafting and Submitting the Final CPG

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments for the update of specific sections of the 2007 COPD CPG that would form portions of the narrative text for the 2014 COPD CPG. During this time, the Champions also revised the 2007 COPD algorithms and identified the content for the guideline summary and pocket card, as part of the provider toolkits that will be developed by the Office of Evidence-Based Practice, HQ MEDCOM following the publication of the 2014 COPD CPG. The algorithms are included as part of this COPD CPG to provide a clear description of the flow of patient care. The final 2014 COPD CPG was submitted to the EBPWG in December 2014.

Appendix B: Evidence Table

The Evidence Table below links each recommendation in the 2014 COPD CPG (column 1) to the following:

- The USPSTF grade for the corresponding recommendation(s) in the 2007 COPD CPG (column 2);
- The evidence identified in the 2014 systematic review for new recommendations or the evidence in addition to the 2007 COPD CPG evidence base for the recommendations that were carried forward (column 3); and
- The GRADE strength of the recommendation (column 4).

Table B-1. Evidence Table

Recommendation	USPSTF Grade[4,5]	Evidence[6]	GRADE Strength of Recommendation[7]
Diagnosis and Assessment of COPD			
1. We recommend 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).	--	[27]	Strong For
2. We have no recommendations regarding utilization of existing clinical classification systems at this time.	--	[37]	Not Applicable

[4] The 2007 VA/DoD COPD CPG used the USPSTF evidence grading system (http://www.uspreventiveservicestaskforce.org).

[5] In some instances, multiple recommendations from the 2007 VA/DoD COPD CPG were combined to form one recommendation which was carried forward. These instances are noted through the use of multiple grades for each 2007 VA/DoD COPD CPG recommendation. Where necessary, the specific portion of the recommendation to which each grade relates is noted.

[6] For new recommendations, developed by the 2014 guideline Work Group, the literature cited corresponds directly to the 2014 evidence review. This can include articles that were captured as part of an included study (e.g., an RCT that was included in a systematic review). For new recommendations which did not cite evidence identified through the systematic evidence review, "additional evidence" is listed. These are studies that support the recommendation, but which were not systematically identified through a literature review. For recommendations that have been carried over from the 2007 VA/DoD COPD CPG, slight modifications were made to the language in order to better reflect the current evidence and/or the change in grading system used for assigning the strength of each recommendation (USPSTF to GRADE). For these "modified" recommendations, the evidence column indicates "additional evidence," which can refer to relevant studies that support the recommendation, but which were not systematically identified through a literature review.

[7] Refer to the Grading Recommendations section for more information on how the strength of the recommendation was determined using GRADE methodology.

Recommendation	USPSTF Grade[4,5]	Evidence[6]	GRADE Strength of Recommendation[7]
3. 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.	--	**Additional evidence:** [34]	Weak For
4. We recommend offering prevention and risk reduction efforts including smoking cessation and vaccination. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	Smoking Cessation: A, A, C, A Vaccination: A, A, I	**Additional evidence:** [45] [47]	Strong For
5. We recommend investigating additional comorbid diagnoses particularly in patients who experience frequent exacerbations (two or more/year, defined as prescription of corticosteroids, prescription of antibiotics, hospitalization, or ED visit) using simple tests and decision rules (cardiac ischemia [troponin, electrocardiogram], congestive heart failure [B-type natriuretic peptide (BNP), pro-BNP], pulmonary embolism [D-dimer plus clinical decision rule], and gastroesophageal reflux).	--	[54] [55]	Strong For
6. We suggest that patients with COPD and signs or symptoms of a sleep disorder have a diagnostic sleep evaluation. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	I		Weak For
7. We suggest that patients presenting with early onset COPD or a family history of early onset COPD be tested for alpha-1 antitrypsin (AAT) deficiency. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	I	**Additional evidence:** [69]	Weak For

Recommendation	USPSTF Grade[4,5]	Evidence[6]	GRADE Strength of Recommendation[7]
8. We recommend that patients with AAT deficiency be referred to a pulmonologist for management of treatment. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	C	**Additional evidence:** [72] [73]	Strong For
Management of Patients with COPD in the Outpatient Setting			
Pharmacologic Therapy			
9. We recommend prescribing inhaled short-acting beta 2-agonists (SABAs) to patients with confirmed COPD for rescue therapy as needed. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	A		Strong For
10. We suggest using spacers for patients who have difficulty actuating and coordinating drug delivery with metered-dose inhalers (MDIs). *Modified from the 2007 CPG without an updated systematic review of the evidence.*	B	**Additional evidence:** [77] [78] [79] [81]	Weak For
11. We recommend offering long-acting bronchodilators to patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough).	--	[82] [83] [84] [85]	Strong For
12. We suggest offering the inhaled long-acting antimuscarinic agent (LAMA) tiotropium as first-line maintenance therapy in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough).	--	[82] [85]	Weak For

Recommendation	USPSTF Grade[4,5]	Evidence[6]	GRADE Strength of Recommendation[7]
13. We recommend inhaled tiotropium 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.	--	[85]	Strong For
14. For clinically stable patients with a confirmed diagnosis of COPD and who have not had exacerbations on short-acting antimuscarinic agents (SAMAs), we suggest continuing with this treatment, rather than switching to long-acting bronchodilators. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	B, B, I →		→ Weak For
15. For patients treated with a SAMA who are started on a LAMA to improve patient outcomes, we suggest discontinuing the SAMA. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	I →		→ Weak For
16. We recommend against offering an inhaled corticosteroid (ICS) in symptomatic patients with confirmed, stable COPD as a first-line monotherapy.	--	[95] [98]	Strong Against
17. We recommend against the use of inhaled long-acting beta 2-agonists (LABAs) without an ICS in patients with COPD who may have concomitant asthma.	--	**Additional evidence:** [100] [101]	Strong Against
18. In patients with confirmed, stable COPD who are on inhaled LAMAs (tiotropium) or inhaled LABAs alone and have persistent dyspnea on monotherapy, we recommend combination therapy with both classes of drugs.	--	[102] [103] [104] [106] [107]	Strong For
19. In patients with confirmed, stable COPD who are on combination therapy with LAMAs (tiotropium) and LABAs and have persistent dyspnea or COPD exacerbations, we suggest adding ICS as a third medication.	--	[109]	Weak For
20. We suggest against offering roflumilast in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist.	--	[110] [114]	Weak Against

Recommendation	USPSTF Grade[4,5]	Evidence[6]	GRADE Strength of Recommendation[7]
21. We suggest against offering chronic macrolides in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist.	--	[115] [116]	Weak Against
22. We suggest against offering theophylline in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist.	--	[117] [118]	Weak Against
23. 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 who continue to have respiratory symptoms (e.g., dyspnea, cough).	--	[120]	Not Applicable
24. We suggest not withholding cardio-selective beta-blockers in patients with confirmed COPD who have a cardiovascular indication for beta-blockers.	--	[123] [124]	Weak For
25. We suggest using non-pharmacologic therapy as first-line therapy and using caution in prescribing hypnotic drugs for chronic insomnia in primary care for patients with COPD, especially for those with hypercapnea or severe COPD. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	I →		Weak For

Recommendation	USPSTF Grade[4,5]	Evidence[6]	GRADE Strength of Recommendation[7]
26. For patients with COPD and anxiety, we suggest consultation with a psychiatrist and/or a pulmonologist to choose a course of anxiety treatment that reduces, as much as possible, the risk of using sedatives/anxiolytics in this population. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	D →		→ Weak For
Oxygen Therapy			
27. We recommend providing long-term oxygen therapy (LTOT) to patients with chronic stable resting severe hypoxemia (partial pressure of oxygen in arterial blood [PaO_2] <55 mm Hg and/or peripheral capillary oxygen saturation [SaO_2] ≤88%) or chronic stable resting moderate hypoxemia (PaO_2 of 56-59 mm Hg or SaO_2 >88% and ≤90%) with signs of tissue hypoxia (hematocrit >55%, pulmonary hypertension, or cor pulmonale). *Modified from the 2007 CPG without an updated systematic review of the evidence.*	A, A →	**Additional evidence:** [130] [131]	→ Strong For
28. We recommend that patients discharged home from hospitalization with acute transitional oxygen therapy are evaluated for the need for LTOT within 30-90 days after discharge. LTOT should not be discontinued if patients continue to meet the above criteria. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	B →		→ Strong For
29. We suggest against routinely offering ambulatory LTOT for patients with chronic stable *isolated* exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen.	--	[134]	Weak Against

Recommendation	USPSTF Grade[4,5]	Evidence[6]	GRADE Strength of Recommendation[7]
30. For patients with COPD and hypoxemia and/or borderline hypoxemia (SaO_2 <90%) who are planning to travel by plane, we suggest a brief consultation or an e-consult with a pulmonologist. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	C →		Weak For
31. When other causes of nocturnal hypoxemia have been excluded, we suggest against routinely offering LTOT for the treatment of outpatients with stable, confirmed COPD and *isolated* nocturnal hypoxemia.	--	**Additional evidence:** [146] [147]	Weak Against
Home Non-Invasive Ventilation			
32. In the absence of other contributors (e.g., sleep apnea), we suggest referral for a pulmonary consultation in patients with stable, confirmed COPD and hypercapnea.	--	[148] [149] [150]	Weak For
Supported Self-Management			
33. We suggest supported self-management for selected high risk patients with COPD.	--	[152] [153] [154]	Weak For
34. We suggest against using action plans *alone* in the absence of supported self-management.	--	[158]	Weak Against
Telehealth			
35. We suggest using telehealth for ongoing monitoring and support of the care of patients with confirmed COPD.	--	[159]	Weak For
Pulmonary Rehabilitation			
36. We recommend offering pulmonary rehabilitation to stable patients with exercise limitation despite pharmacologic treatment and to patients who have recently been hospitalized for an acute exacerbation.	--	[162]	Strong For

Recommendation	USPSTF Grade[4,5]	Evidence[6]	GRADE Strength of Recommendation[7]
Breathing Exercise			
37. We suggest offering breathing exercise (e.g., pursed lip breathing, diaphragmatic breathing, or yoga) to patients with dyspnea that limits physical activity.	--	[164]	Weak For
Nutrition Referral			
38. We suggest referral to a dietitian for medical nutritional therapy recommendations (such as oral calorie supplementation) to support patients with severe COPD who are malnourished (body mass index [BMI] <20 kg/m^2).	--	[165]	Weak For
Lung Volume Reduction Surgery and Lung Transplant			
39. We recommend that any patient considered for surgery for COPD (lung volume reduction surgery [LVRS] and lung transplant) be first referred to a pulmonologist for evaluation. *Modified from the 2007 CPG without an updated systematic review of the evidence.*	A →	→	Strong For
Management of Patients in Acute Exacerbation of COPD			
40. We recommend antibiotic use for patients with COPD exacerbations who have increased dyspnea and increased sputum purulence (change in sputum color) or volume.	--	[175] [178] [179] [182]	Strong For

Recommendation	USPSTF Grade[4,5]	Evidence[6]	GRADE Strength of Recommendation[7]
41. We suggest basing choice of antibiotic on local resistance patterns and patient characteristics. a. First-line antibiotic choice may include doxycycline, trimethoprim/sulfamethoxazole (TMP-SMX), second-generation cephalosporin, amoxicillin, amoxicillin/clavulanate, and azithromycin. b. Despite the paucity of evidence regarding the choice of antibiotics, we suggest reserving broader spectrum antibiotics (e.g., quinolones) for patients with specific indications such as: i. Critically ill patients in the intensive care unit (ICU); ii. Patients with recent history of resistance, treatment failure, or antibiotic use; and iii. Patients with risk factors for health care associated infections.	--	[179] [183] [184] [185] [186] [187] [188] [189] [190] [191] [192] [193]	Weak For
42. For outpatients with acute COPD exacerbation who are treated with antibiotics, we recommend a five-day course of the chosen antibiotic.	--	[196]	Strong For
43. There is insufficient evidence to recommend for or against procalcitonin-guided antibiotic use for patients with acute COPD exacerbations.	--	[198]	Not Applicable
44. For acute COPD exacerbations, we recommend a course of systemic corticosteroids (oral preferred) of 30-40 mg prednisone equivalent daily for 5-7 days.	--	[201] [202] [204]	Strong For
Management of Patients with COPD in the Hospital or Emergency Department			
45. We suggest use of airway clearance techniques utilizing positive expiratory pressure (PEP) devices for patients with COPD exacerbations and difficulty expectorating sputum.	--	[205]	Weak For
46. We recommend the early use of non-invasive ventilation (NIV) in patients with acute COPD exacerbations to reduce intubation, mortality, and length of hospital stay.	--	[206] [207]	Strong For
47. We recommend the use of NIV to support weaning from invasive mechanical ventilation and earlier extubation of intubated patients with COPD.	--	[207] [213]	Strong For

Appendix C: Participant List

Participants	
Teresa Anekwe, PharmD, BCPS Formulary Management Branch Pharmacy Operations Division Defense Health Agency San Antonio, TX	Ernest Degenhardt, RN, MSN, ANP/FNP, BC Chief, Office of Evidence-Based Practice Clinical Performance Assurance Directorate US Army Medical Command Ft. Sam Houston, TX
Jennifer Ellis, RN VA Eastern Kansas Health Care System Topeka, KS	CDR Jeffrey Feinberg, MD, MPH, FAAFP Family Medicine Naval Hospital Camp Pendleton Camp Pendleton, CA
Anna Fritz, MS, RD Aleda E Lutz VA Medical Center Saginaw, MI	Cynthia Hintz, MSW, LICSW Minneapolis VA Health Care System Minneapolis, MN
Deborah Khachikian, PharmD Pharmacy Benefits Management Service Hines, IL	Marta Render, MD (Co-Chair) Cincinnati VA Medical Center Cincinnati, OH
Kathryn Rice, MD (Co-Chair) Minneapolis VA Health Care System Minneapolis, MN	M. Eric Rodgers, PhD, FNP, BC Acting Director Evidence-Based CPG Program Office of Quality, Safety and Value Department of Veterans Affairs Glendale, CO
James Sall, PhD, FNP-BC Office of Evidence-Based Practice US Army Medical Command Joint Base San Antonio - Fort Sam Houston San Antonio, TX	MAJ Jason Sapp, MD, FACP Department of Medicine Madigan Army Medical Center Joint Base Lewis-McChord Tacoma, WA
CDR Robert M. Selvester, MD Joint Base San Antonio - Fort Sam Houston San Antonio, TX	Amir Sharafkhaneh, MD, PhD, DABSM (Co-Chair) Michael Debakey VA Medical Center Houston, TX

Participants	
LTC Sonya Shaw, FNP-BC Joint Base Langley-Eustis Newport News, VA	LTC John Sherner, MD, FCCP (Co-Chair) MC Program Director Walter Reed National Military Medical Center Bethesda, MD
Catherine Staropoli, MD, FACP VA Maryland Health System Baltimore, MD	Rene M. Sutton, BS, HCA Evidence-Based CPG Program Office of Quality, Safety and Value Department of Veterans Affairs Washington, DC
Maj Melissa Tennant, DPT Joint Base Elmendorf-Richardson Anchorage, AK	LCDR Jennifer Wallinger, MPH, RD MSC, USN Chief, Inpatient Nutrition Walter Reed National Military Medical Center

Appendix D: Pharmacotherapy

Refer to current product information for additional prescribing information.

Table D-1. Delivery, Strength, and Dosing of Pharmacologic Agents for COPD

Drug	Delivery	Strength	Dosing
SABAs			
albuterol*	MDI	90 mcg	1-2 inhalations every 4-6 hrs PRN
levalbuterol*	MDI	45 mcg	1-2 inhalations every 4-6 hrs PRN
SAMAs			
ipratropium*	MDI	21 mcg	2 inhalations every 6 hrs
Combination SAMA/SABA			
ipratropium/albuterol*	SMI	20/100 mcg	1 inhalation four times daily
LABAs			
formoterol*	DPI (capsule)	12 mcg	1 inhalation twice daily
salmeterol	DPI	50 mcg	1 inhalation twice daily
indacaterol	DPI (capsule)	75 mcg	1 inhalation once daily
olodaterol^	SMI	2.5 mcg	2 inhalations once daily
LAMAs			
tiotropium	DPI (capsule)/SMI	18 mcg/2.5 mcg	1 inhalation (DPI)/2 inhalations (SMI) once daily
aclidinium	DPI	400 mcg	1 inhalation twice daily
umeclidinium^	DPI	62.5 mcg	1 inhalation once daily
Combination LAMA/LABA			
umeclidiniun/vilanterol ^	DPI	62.5/25 mcg	1 inhalation once daily
Combination ICS/LABA			
budesonide/formoterol	MDI	160/4.5 mcg	2 inhalations twice daily
mometasone/formoterol	MDI	100/5; 200/5 mcg	Not approved for COPD
fluticasone/salmeterol	DPI	250/50 mcg	1 inhalation twice daily
fluticasone/vilanterol^	DPI	100/25 mcg	1 inhalation once daily

*Available as a solution for nebulizer use

^These newer agents may not have been included in meta-analyses and systematic reviews used to develop the VA/DoD COPD Clinical Practice Guideline.

Abbreviations: DPI: dry powder inhaler; hrs: hours; ICS: inhaled corticosteroid; LABA: long-acting beta 2-agonist; LAMA: long-acting anticholinergic; mcg: microgram; MDI: metered-dose inhaler; PRN: as needed; SABA: short-acting beta 2-agonist; SAMA: short-acting anticholinergic; SMI: soft mist inhaler; VA/DoD: Department of Veterans Affairs/Department of Defense

Table D-2. Information for Pharmacologic Agents for COPD, by Drug Class

Comments by Drug Class*
Beta 2-agonists
• LABAs increase the risk of asthma-related death; do not use as monotherapy in asthma • May cause palpitations, chest pain, rapid heart rate, increased blood pressure, tremor, nervousness • Decreases in potassium levels have occurred • SABAs are used for acute treatment of bronchospasm, LABAs used for chronic treatment of bronchospasm • Formoterol and indacaterol: capsules are for oral inhalation only; capsules should not be swallowed; administer using supplied inhalation device only
Antimuscarinic Agents
• Use with caution in patients with narrow angle glaucoma, prostatic hyperplasia, or bladder neck obstruction • Caution patient to getting product in eyes; temporary blurred vision may result • For relief of dry mouth, suggest use of saliva substitute, practice of good oral hygiene, rinsing of mouth after inhalation; instruct patient to take sips of water frequently, suck on ice chips or sugarless hard candy, or chew sugarless gum • Tiotropium: capsules are for oral inhalation only; capsules should not be swallowed; administer using supplied inhalation device only
Inhaled Glucocorticoids
• Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported • Advise patients to rinse mouth after inhalation to reduce risk of oral fungal infections (e.g., oropharyngeal candidiasis)

*Table not intended as a comprehensive list of all warnings, precautions, and risks.

Note: Each drug class has agents available in a dry powder formulation. Dry powder formulations contain lactose and small amounts of milk proteins; do not use in patients with severe hypersensitivity to milk proteins.

Abbreviations: LABA: long-acting beta 2-agonist; SABA: short-acting beta 2-agonist

Appendix E: Abbreviations and Acronyms

AAT	alpha-1 antitrypsin
ABG/VBG	arteriole or venous blood gas
AHRQ	Agency for Healthcare Research and Quality
ATS	American Thoracic Society
BIPAP	bi-level positive airway pressure
BMD	bone mineral density
BMI	body mass index
BNP	B-type natriuretic peptide
BODE	body mass index, airflow obstruction, dyspnea, and exercise capacity
CAT	COPD Assessment Test
CHF	congestive heart failure
CI	confidence interval
COAD	chronic obstructive airways disease
COPD	chronic obstructive pulmonary disease
COR	contracting officer's representative
CPAP	continuous positive airway pressure
CPG	clinical practice guideline
CT	computed tomography
CXR	chest X-ray
DLCO	diffusing capacity of the lungs for carbon monoxide
DoD	Department of Defense
DPI	dry powder inhaler
DS	double strength
EBPWG	Evidence-Based Practice Working Group
ED	emergency department
EKG	electrocardiogram
ERS	European Respiratory Society
FDA	U.S. Food and Drug Administration
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
GER	gastroesophageal reflux
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hg	mercury
ICS	inhaled corticosteroid
ICU	intensive care unit
IPPV	intermittent positive pressure ventilation
IV	intravenous
kg	kilogram
KQ	key question
LABA	long-acting beta 2-agonist
LAMA	long-acting antimuscarinic agent
LLN	lower limit of normal
LTOT	long-term oxygen therapy
LVRS	lung volume reduction surgery
MDI	metered-dose inhaler
m	meter
MeSH	Medical Subject Headings
mcg	microgram

mg	milligram
mm	millimeter
mMRC	modified Medical Research Council
NAC	N-acetylcysteine
NIV	non-invasive ventilation
O_2	oxygen
OSA	obstructive sleep apnea syndrome
PaO_2	partial pressure of oxygen in arterial blood
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PAV	proportional-assist ventilation
PDE4	phosphodiesterase-4-inhibitor
PICOTS	population, intervention, comparison, outcome, timing, and setting
PRN	as needed
PO	orally
pp	percent predicted
QoL	quality of life
RCT	randomized controlled trial
REM	rapid eye movement
RR	relative risk
SABA	short-acting beta 2-agonist
SAMA	short-acting antimuscarinic agent
SaO_2	peripheral capillary oxygen saturation
SMI	soft mist inhaler
TMP-SMX	trimethoprim/sulfamethoxazole
UMEC/VI	umeclidinium bromide and vilanterol
US	United States
USPSTF	US Preventive Services Task Force
VA	Department of Veterans Affairs

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