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

Department of Veterans Affairs
Department of Defense

Clinical Practice Guideline Summary

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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Summary

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]

While COPD is primarily a respiratory condition, it is associated with systemic inflammation and has been described as a condition with cardiovascular, muscular, and immunologic manifestations. [2,3] COPD results from an inflammatory process in the distal airways possibly linked to oxidative stress. [1] Large and small airways narrow in response to the inflammation, and additional pathophysiological changes occur. [1]

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 is also a risk factor for COPD complications, such as pneumonia. [4] Smoking is more common among military personnel than among civilians, especially in those who have been deployed. [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.

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] Veterans are at higher risk of COPD than those in the general US population. [7] Within the VA population, patients with COPD have significantly higher all-cause and respiratory-related healthcare utilization than patients without COPD. [8] Additionally, patients in the military or Veterans may show signs of COPD earlier in their lives than their civilian counterparts. [9]

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. [10] 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).

The Department of Veterans Affairs (VA) and 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
4. Emphasize the use of personalized, proactive, patient-driven care

This CPG addresses various diagnostic, treatment, and management strategies for patients with COPD. This CPG includes methods used to diagnose, classify, and manage COPD. It also includes inhaled and systemic pharmacologic treatments as well as non-pharmacologic treatments used in acute and maintenance management of COPD.

Grading Recommendations

This CPG uses the GRADE (Grading of Recommendations Assessment, Development and Evaluation) 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: [11]

- 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 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 in Table 1, which combines the four domains. [11]

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.

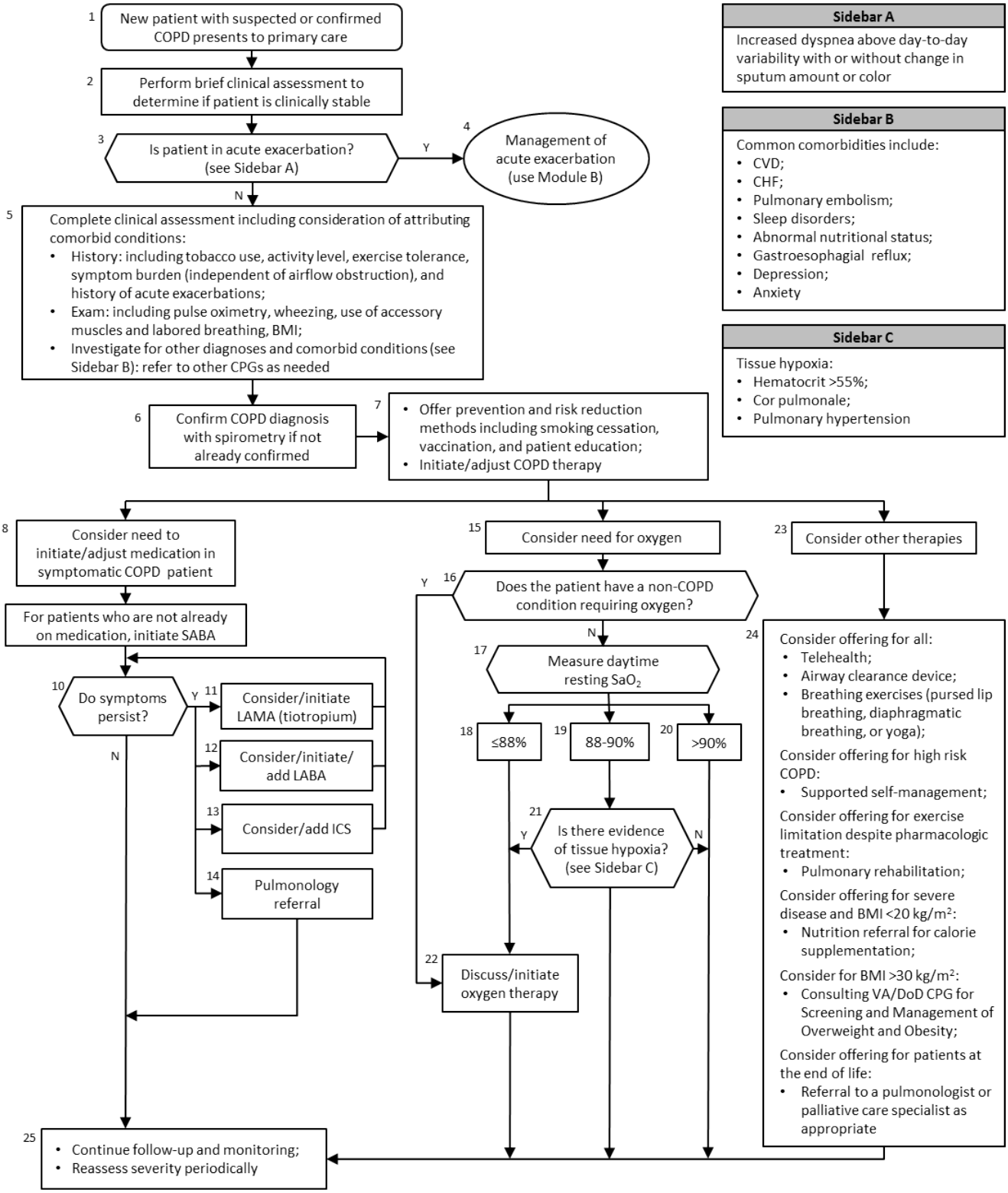
Using these elements, the grade of each recommendation is presented as part of a continuum:

- 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 …”)

Table 1. 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

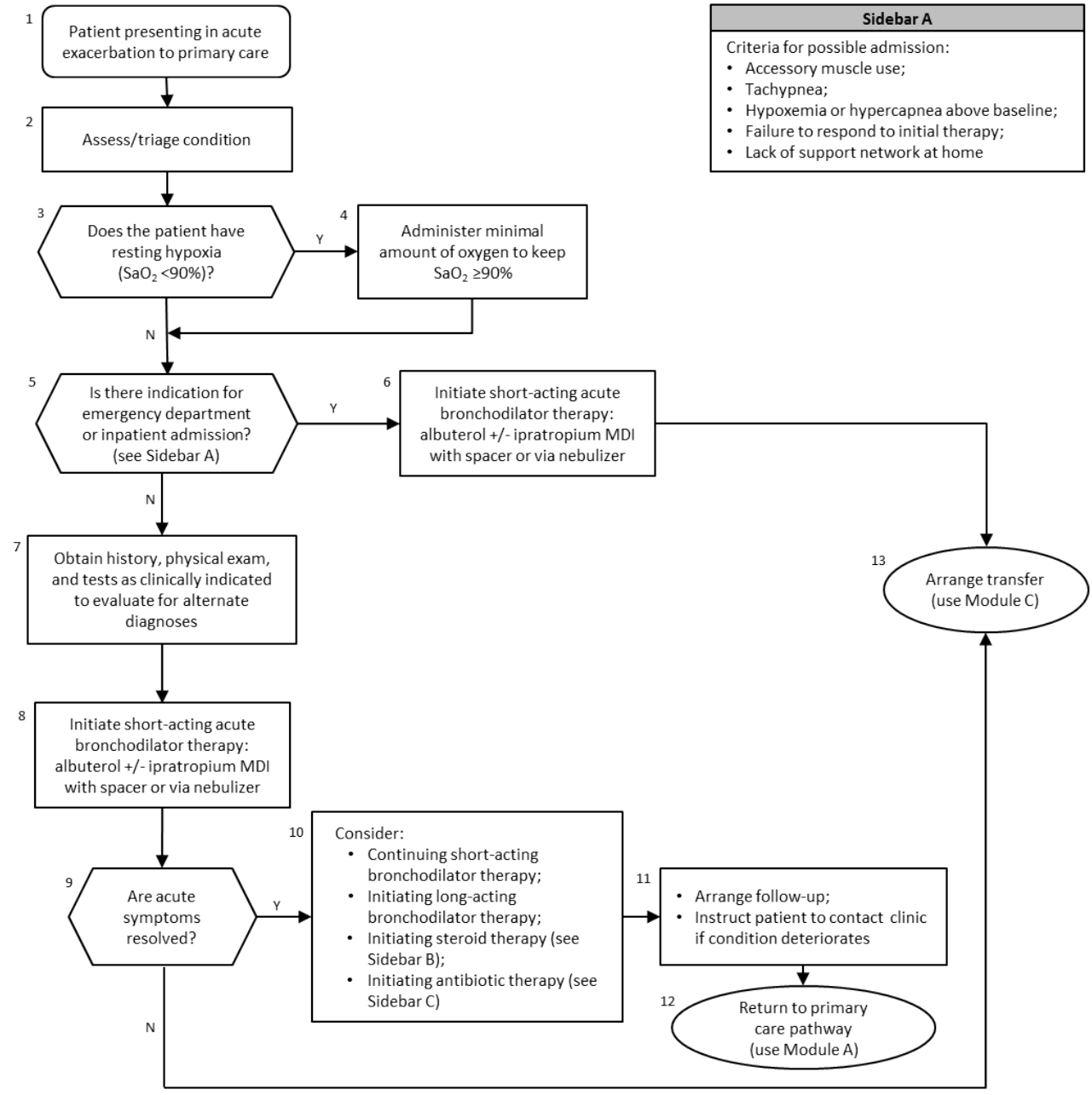
Algorithm A: Management of COPD in Primary Care



Abbreviations

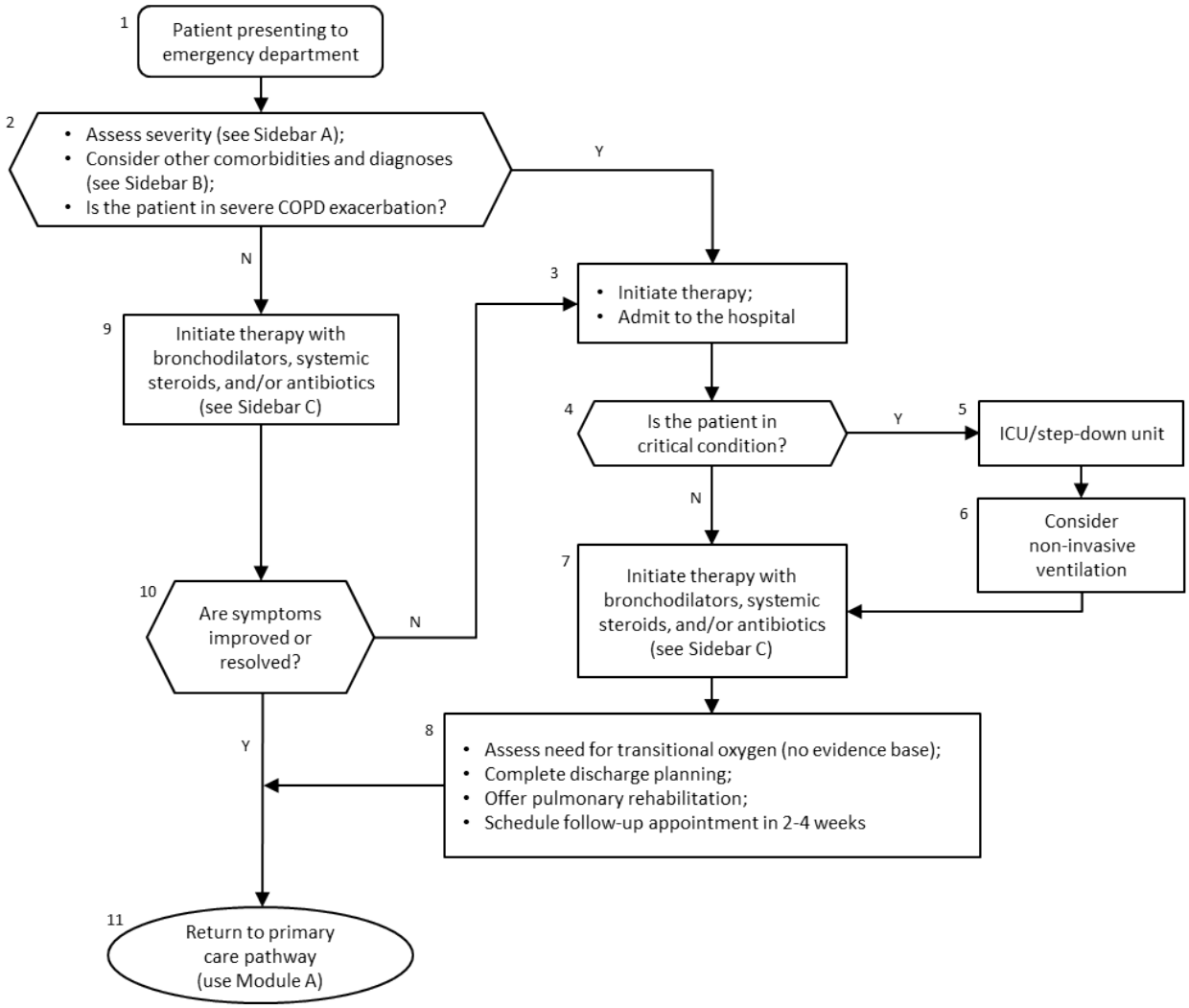
BMI: body mass index; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CPG: clinical practice guideline; CVD: cardiovascular disease; ICS: inhaled corticosteroid; kg: kilogram; LABA: long-acting beta 2-agonist; LAMA: long-acting antimuscarinic agent; m: meter; SABA: short-acting 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 Recommendation
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
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

Recommendations	Strength of 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
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 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. *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 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
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 the section Reconciling 2007 CPG Recommendations in the full CPG.

Additional Information on Pharmacologic Therapy

Table 2. 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 3. Antibiotic Choices and Recommended Doses for Acute Exacerbations of COPD [12,13]

Antibiotic	Recommended Oral Dose
doxycycline	100 mg PO every 12 hrs
trimethoprim/sulfamethoxazole	1 DS tab PO every 12 hrs
Second generation cephalosporins:	
cefuroxime	250-500 mg PO every 12 hrs
cefprozil	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	500 mg PO daily
moxifloxacin	400 mg PO daily

*Reserve use for patients with severe disease or specific risk

Abbreviations: DS: double strength; hrs: hours; mg: milligram; PO: orally

Table 4. 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, or 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

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