CHEST™
OFFICIAL PUBLICATION OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

ONLINE FIRST

Word Count: 6742

Executive Summary

Prevention of Acute Exacerbation of Chronic Obstructive Pulmonary Disease: American College of Chest Physicians and Canadian Thoracic Society Guideline

Gerard J. Criner, MD, FCCP; Jean Bourbeau, MD, FCCP, FRCPC; Rebecca L. Diekemper, MPH; Daniel R. Ouellette, MD, FCCP; Donna Goodridge, RN, PhD; Paul Hernandez, MDCM, FRCPC; Kristen Curren, MA, Meyer S. Balter, MD, FCCP, FRCPC; Mohit Bhutani, MD, FCCP, FRCPC; Pat G. Camp, PT, PhD; Bartolome R. Celli, MD, FCCP; Gail Dechman, PT, BScPT, PhD; Mark T. Dransfield, MD; Stanley B. Fiel, MD, FCCP; Marilyn G. Foreman, MD, FCCP; Nicola A. Hanania, MBBS, FCCP; Belinda K. Ireland, MD, MSc; Nathaniel Marchetti, DO, FCCP; Darcy D. Marciniuk, MD, FCCP; Richard A. Mularski, MD, FCCP; Joseph Ornelas, MS, PhD(c);Jeremy D. Road, MD, FRCPC; Michael K. Stickland, PhD

Affiliations: From Temple University School of Medicine (Dr Criner), Philadelphia, PA; Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University Health Centre (Dr Bourbeau), Montreal, QC; American College of Chest Physicians (Ms Diekemper), Glenview, IL; Henry Ford Health System (Dr Ouellette), Detroit, MI; College of Nursing, University of Saskatchewan (Dr Goodridge), Saskatoon, SK; Dalhousie University (Dr Hernandez), Halifax, NS. Canadian Thoracic Society (Ms Curren), Ottawa, ON; Mount Sinai Hospital (Dr Balter) Toronto, ON; University of Alberta (Dr Bhutani), Edmonton, AB; Department of Physical Therapy, University of British Columbia (Dr Camp), Vancouver, BC; Harvard Medical School, Brigham and Women's Hospital (Dr Celli), Boston, MA; School of Physiotherapy, Dalhousie University (Dr Dechman), Halifax, NS; University of Alabama at Birmingham (Dr Dransfield), Birmingham, AL; Morristown Memorial Hospital (Dr Fiel), Morristown, NJ; Morehouse School of Medicine (Dr Foreman), Atlanta, GA; Baylor College of Medicine(Dr Hanania), Houston, TX; TheEvidenceDoc, LLC (Dr Ireland), Pacific, MO; Temple University School of Medicine (Dr Marchetti), Philadelphia, PA; Division of Respirology, Critical Care and Sleep Medicine, Royal University Hospital, University of Saskatchewan (Dr Marciniuk),, Saskatoon, SK; Kaiser Permanente Center for Health Research (Dr Mularski), Portland, OR; American College of Chest Physicians (Dr Ornelas), Glenview, IL; Respiratory Clinic, Vancouver General Hospital (Dr Road), Vancouver, BC; Division of Pulmonary Medicine, University of Alberta (Dr Stickland), Edmonton, AB

Endorsements: This guideline is endorsed by the U.S. COPD Coalition, the International Primary Care Respiratory Group, and the Canadian Respiratory Health Professionals.

Correspondence to: Gerard J. Criner, MD, FCCP, Temple University School of Medicine, 3401 North Broad St, Philadelphia, PA 19140; e-mail: Gerard.Criner@tuhs.temple.edu

DOI: XX.XXXX/chest.XX-XXXX

CONFLICTS OF INTEREST

GJC - no disclosure

JB - received grants (for conducting the longitudinal population-based Canadian Cohort Obstructive Lung Disease (CanCOLD) study from: Government grants: Canadian Institute of Health Research Rx&D collaborative program (Astra Zeneca, Boehringer-Ingelheim, GlaxoSmithKline, Merck, Nycomed, Novartis), Canadian Respiratory Research Network (CRRN), Respiratory Health Network of the FRQS and Research Institute of the MUHC.

RLD - I am a co-developer of the DART tool, which was used in the AECOPD Guideline to assess the quality of the systematic reviews that informed some of the recommendations.

DRO – no disclosure

DG – no disclosure

PH - institution has received pharmaceutical company grant monies for research studies on which I have been an investigator: CSL Behring; Boehringer Ingelheim; Grifols. My institution has received grant monies for research studies on which I have been an investigator: CIHR; Lung Association of Nova Scotia. I have participated in speaking activities, industry advisory committees, or other activities related to industry sources with the following pharmaceutical companies: Actelion; Almirall; AstraZeneca; Boehringer Ingelheim; GlaxoSmithKline; Merck; Novartis.

KC – no disclosure

MSB - over the past 3 years I have served on Advisory Boards for Almirall, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, MerckFrosst, Novartis, and

Takeda. I have presented at Continuing Education Meetings supported by Almirall, AstraZeneca, Boehringer-Ingelheim, MerckFrosst, Novartis, and Takeda.

MB - receives university grant money, pharmaceutical grant money, grant money from government organizations in Canada, participates in speakers bureaus and speaks publicly on the topic of AECOPD.

PGC - has received operating grant funding from the Canadian Institutes of Health Research, the Canadian Lung Association and the Physiotherapy Foundation of Canada. She has received research infrastructure funding from the Canadian Foundation of Innovation and the BC Lung Association. She has received a Scholar Award from the Michael Smith Foundation of Health Research. She has received honoraria for speaking engagements from the Canadian Lung Association and the UBC Respiratory Division.

BRC - Division has received grants from Astra Zeneca to complete research studies. Has been on an Advisory Board or served as a consultant to Glaxo Smith Kline, Boehringer-Ingelheim, Almirall, Astra Zeneca, Takeda, Novartis. I do not have shares or interest in any company, neither does any member of my family. I have not received or had any relationship with tobacco money.

GD - has no financial conflict of interest related to the content or publication of this manuscript. Speaks to health professionals about the management of COPD, including AECOPD

MTD - has served as a consultant for GSK, BI, and Ikaria. His institution has received research grant support from AHA, NHLBI, GSK and Forest and has received contracted support for enrollment in clinical trials from Aeris, BI, Boston Scientific, Centocor, GSK, Forest, Otsuka, Pearl, Pfizer, PneumRx, and Pulmonx.

SBF – has received grant support from the Cystic Fibrosis Foundation and grants for clinical trials from Vertex, Gilead, Novartis and PTC Therapeutics.

MGF – no disclosures

NAH - consultant to Boehringer Ingelheim, Sunovion, Novartis, Mylan, Pearl and Pfizer. Institution receives grant support on my behalf from GSK, Boehringer, Pfizer, Pearl,Sunovion and Pfizer

BKI - no disclosure

NM - served as PI for a pharmaceutical funded clinical trial with GSK.

DDM - in the last 3 years, Dr. Marciniuk has provided consultation for Health Canada, the Public Health Agency of Canada, and the Saskatoon Health Region. He has received research funding (all held and managed by the University of Saskatchewan) from AstraZeneca, Boehringer Ingelheim, the Canadian Institutes of Health Research, Forest,

Lung Association of Saskatchewan, Novartis, Pfizer, Saskatchewan Health Research Foundation, and Schering-Plough. He holds Fiduciary Positions with the American College of Chest Physicians, the Chest Foundation, and the Lung Health Institute of Canada.

RAM - no disclosure

JO – no disclosure

JDR – no disclosure

MKS - no disclosure

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease with substantial associated morbidity and mortality. Patients with COPD usually have a progression of airflow obstruction that is not fully reversible and can lead to a history of progressive worsening breathlessness that can impact daily activities and health-related quality of life.[1-3] COPD is the fourth leading cause of death in Canadian men and women[4] and the third in the U.S., it claimed 133,965 U.S. lives in 2009.[5] In 2011, 12.7 million U.S. adults were estimated to have COPD.[6] However, approximately 24 million U.S. adults have evidence of impaired lung function, indicating an under diagnosis of COPD.[7] While 4% of Canadians aged 35 to 79 self-reported being diagnosed with COPD, direct measurements of lung function from the Canadian Health Measures Survey (CHMS) indicate that 13% of Canadians had a lung function score indicative of COPD.[4]

COPD is also costly. In 2009, COPD caused 8 million office visits, 1.5 million emergency department visits, 715,000 hospitalizations, and 133,965 deaths in the United States.[8] In 2010, U.S. costs for COPD was projected to be approximately $49.9 billion, including $29.5 billion in direct health care expenditures, $8.0 billion in indirect morbidity costs and $12.4 billion in indirect mortality costs.[9] Exacerbations account for

most of the morbidity, mortality, and costs associated with COPD. The economic burden associated with moderate and severe exacerbations in Canada has been estimated in the range of $646 million to $736 million per annum.[10] This value may be an underestimate given that the prevalence of moderate exacerbations is not well documented, COPD is under-diagnosed and prevalence of hospitalization due to COPD is increasing.[11]

Exacerbations are to COPD what myocardial infarctions are to coronary artery disease: they are acute, trajectory-changing, and often deadly manifestations of a chronic disease. Exacerbations cause frequent hospital admissions, relapses, and readmissions;[12] contribute to death during hospitalization or shortly thereafter;[12] dramatically reduce the quality of life;[12,13] consume financial resources;[12,14] and hasten a progressive decline in pulmonary function, a cardinal feature of COPD. Hospitalization due to exacerbations accounts for more than 50% of the cost of managing COPD in North America and Europe.[15,16]

COPD exacerbation has been defined as "an event in the natural course of the disease characterized by a baseline change in the patient's dyspnea, cough and/or sputum that is beyond the normal day to day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD."[17,18] Exacerbation in clinical trials has been defined for operational reasons based on whether there is an increase in treatment beyond regular treatment or urgent treatment is required in an emergency room or hospital. Exacerbation treatment in clinical trials is usually defined by the use of antibiotics and/or systemic corticosteroids.[19] The severity of the exacerbation is then ranked or stratified according to the outcome: mild, when the clinical symptoms are present but no change in treatment or outcome is recorded; moderate when the event results in a change in medication such as the use of antibiotics and/or systemic corticosteroids; or severe when the event leads to a hospitalization.[1]

Two-thirds of exacerbations are associated with respiratory tract infections or air pollution, but one-third present without an identifiable cause.[17] Exacerbations remain poorly understood in terms of cause but also in terms of treatment and prevention.

Although the management of an acute exacerbation has been the primary focus of clinical trials, the prevention of acute exacerbations has not been a major focus until recently. Most current COPD guidelines focus on the general diagnosis and evaluation of the COPD patient, the management of stable disease and the diagnosis and management of acute exacerbations.[1,20] Although current COPD guidelines state that prevention of exacerbations is possible, little guidance is provided to the clinician regarding current available therapies for prevention of COPD exacerbations.[1,20] Moreover there are recent new therapies that have promise in preventing acute exacerbations, and would benefit from critical review of their efficacy in the exacerbation prevention management of the COPD patient.[21-23] The ACCP and CTS jointly commissioned this evidence-based guideline on the prevention of COPD exacerbations to fill this important void in COPD management.

The overall objective of this American College of Chest Physicians (CHEST) and Canadian Thoracic Society (CTS) joint evidence-based guideline (AECOPD Guideline) was to create a practical, clinically useful document to describe the current state of knowledge regarding the prevention of acute exacerbations according to major categories of prevention therapies. We accomplished this by utilizing recognized document evaluation tools to allow us to assess and choose the most appropriate studies and evidence to extract meaningful data and grade the level of evidence to support the recommendation in a balanced and unbiased fashion. The AECOPD Guideline is unique not only for the topic of the guideline, prevention of acute COPD exacerbations, but also for the first-in-kind partnership between two of the largest thoracic societies of North America. The Guidelines Oversight Committee (GOC) of the American College of Chest Physicians in partnership with the COPD Clinical Assembly of the Canadian Thoracic Society launched this project with the objective that a systematic review and critical evaluation of the published literature that was conducted by clinical experts and researchers in the field of COPD would lead to a series of recommendations to assist clinicians in their management of the COPD patient. This guideline is unique because a group of interdisciplinary clinicians who have special expertise in COPD clinical

research and care led the development of the guideline process with the assistance of methodologists.

METHODS

Members from the American College of Chest Physicians (CHEST, formerly known as ACCP) and Canadian Thoracic Society (CTS) were selected to participate on the AECOPD Guideline Panel based on their expertise in the field. Panelists were assigned to 1 of 3 writing groups that addressed each key question. The groups were referred to as PICO groups since the key questions were developed using the PICO format, which defines the population, intervention, comparator, and outcome of interest. The 3 PICO questions that addressed the prevention of acute exacerbations of COPD were non-pharmacologic therapies, inhaled therapies, and oral therapies. Systematic reviews were conducted to inform the evidence-base for the recommendations developed by each PICO group. Recommendations were graded using the CHEST Grading System.[24,25] Panelists who did not report any substantial conflicts of interest were permitted to vote on all of the recommendations. Controversial recommendations went through up to 3 rounds of voting before being improved for inclusion in the AECOPD Guideline.

RECOMMENDATIONS

PICO 1: Do non-pharmacologic treatments and vaccinations prevent/decrease acute exacerbations of COPD?

Background

Effective support and management of individuals at risk to develop AECOPD demands a comprehensive and patient-centered approach. The widely adopted Chronic Care Model (CCM)[26,27] recognizes that improvements in care require approaches incorporating patient, provider and system level interventions. Key elements of the CCM include: the health system; delivery system design (including case management); decision support; clinical information systems; self-management support (including assessment, goal-

setting, action planning, problem solving and follow-up) and the community. The importance of incorporating non-pharmacological approaches into the care of this population is reflected in international guidelines for COPD management.[20,28,29]

PICO question 1 addresses the following categories: a) pneumococcal vaccinations; b) influenza vaccinations; c) smoking cessation programs; d) pulmonary rehabilitation; e) education/action plans/case management; and f) telemonitoring.

These topics may be considered "complex interventions"[30] in that they contain multiple interacting components and possess non-linear causal pathways subject to a host of variables.[31] Rigorous evaluation of complex interventions can be complicated by numerous factors, including the need to adapt interventions to local contexts and issues of feasibility and acceptability.[32] Many of the non-pharmacological trials have limitation with respect to methodological aspects such as how the intervention was standardized, and the details of the experimental treatment and comparator as they were implemented. Prevention of exacerbations was often not the primary outcome for many studies examining the efficacy and effectiveness of non-pharmacological interventions, thus limiting our ability to make definitive recommendations. We recognize that some interventions may have beneficial outcomes relevant to overall health and quality of life but insufficient to recommend their use to prevent exacerbations.

PICO 1 Recommendations

1. In patients with COPD, we suggest administering the 23-valent pneumococcal vaccine as part of overall medical management but did not find sufficient evidence that pneumococcal vaccination prevents acute exacerbations of COPD (Grade 2C).

Underlying values and preferences: This recommendation places high value on the benefits of pneumococcal vaccine for general health and we endorse existing guidelines that recommend it for COPD patients. Although evidence does not specifically support using the vaccine for the prevention of acute exacerbations, multiple bodies including the CDC and WHO recommend the use of pneumococcal

vaccine for all adults aged ≥ 65 and in all those 19-64 years with underlying medical conditions such as COPD that put them at greater risk of serious pneumococcal infection.

2. In patients with COPD, we recommend administering the influenza vaccine annually to prevent acute exacerbations of COPD (Grade 1B).

Underlying values and preferences: This recommendation places high value on the benefits of influenza vaccination for general health, the low risk of side effects, and existing guidelines that recommend it for COPD patients. Although the effect and evidence is moderate for the prevention of acute exacerbations in COPD, multiple bodies including the CDC and WHO recommend the use of yearly influenza vaccine for all adults, including those with COPD.

3. In patients with COPD, we suggest including smoking cessation counseling and treatment using best practices as a component of a comprehensive clinical strategy to prevent acute exacerbations of COPD (Grade 2C).

Underlying values and preferences: This recommendation places high value on the benefits of smoking cessation for all individuals. In particular, it is the only evidence-based intervention that improves prognosis in COPD by mitigating lung function decline and reduces symptoms. Although the effect and evidence for smoking cessation in the prevention of acute exacerbations of COPD is low, evidence exists to support smoking cessation for many reasons: smokers with mild COPD who produce cough and phlegm achieve substantial symptom reductions in the first year after smoking cessation with less lung function decline and less symptoms upon sustained cessation; cigarette smoking may be associated with infections such as pneumonia; among other general health benefits. The benefit from smoking cessation outweighs the risks and a myriad of strategies have been summarized by other guidelines and reviews; in general, effective smoking cessation programs include behavioral, physiological, and psychological components composed of acknowledging current smoking followed by advice to quit, pharmacological therapies (nicotine replacement therapy, antidepressants, nicotine receptor modifier therapy), and counseling (in-

person counseling or by telephone) with cessation rates that range from 8.8 – 34.5%. Smoking cessation that includes counseling and pharmacological interventions are cost-effective.

4. In patients with moderate, severe or very severe COPD who have had a recent exacerbation (i.e., < 4 weeks), we recommend pulmonary rehabilitation to prevent acute exacerbations of COPD (Grade 1C).

5. In patients with moderate, severe or very severe COPD who have had an exacerbation > than the past 4 weeks, we do not suggest pulmonary rehabilitation to prevent acute exacerbations of COPD (Grade 2B).

Underlying values and preferences: The pulmonary rehabilitation recommendations place high value on pulmonary rehabilitation reducing the risk of hospitalizations in COPD patients who have had a recent COPD exacerbation (i.e., < 4 weeks post hospitalization**)**. While it has been well established that pulmonary rehabilitation improves quality of life, exercise tolerance and dyspnea, these recommendations do not support pulmonary rehabilitation for the prevention of hospitalizations in COPD patients > 4 weeks post recent hospitalization.

6. In patients with COPD, we suggest that education alone should not be used for prevention of acute exacerbations of COPD (CB).

Underlying values and preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality. A lower value was placed on the motivational educational intervention as it is labor intensive compared to traditional education techniques.

7. In patients with COPD, we suggest that case management alone should not be used for prevention of acute exacerbations of COPD (CB).

Underlying values and preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality. A lower value was placed on the lack of change in

quality of life in either group since this information was present for only a small proportion of the entire sample.

8. In patients with COPD with a previous or recent history of exacerbations, we recommend education and case management that includes direct access to a health care specialist at least monthly, to prevent severe acute exacerbations of COPD, as assessed by decreases in hospitalizations (Grade 1C).

Underlying values and preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality.

9. In patients with moderate to severe COPD, we suggest education together with an action plan but without case management does not prevent severe acute exacerbations of COPD, as assessed by a decrease in emergency department visits or hospitalizations over a 12 month period (Grade 2C).

Underlying values and preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality.

10. For patients with COPD, we suggest education with a written action plan and case management for the prevention of severe acute exacerbations of COPD, as assessed by a decrease in hospitalizations and emergency department visits (Grade 2B).

Underlying values and preferences: This recommendation places high value on reducing COPD related hospitalizations, as these are associated with increased morbidity and mortality. Hospitalizations were felt to best reflect exacerbations as increased physician visits or increased medication use could be a result of the intervention to prevent an exacerbation. High value was also placed on changes in individuals with a history of exacerbations and on outcomes that specifically identified COPD related hospitalizations. The recommendation reflects the fact that one study reported increased mortality in the intervention group. Although we don't

know the reason for increased mortality in this one study, patients with underlying severe disease and clinical instability need close attention and careful followup. This point emphasizes that specially trained staff is required to supervise this intervention and patient selection must be individualized.

11. For patients with COPD, we suggest that telemonitoring compared to usual care does not prevent acute exacerbations of COPD, as assessed by decreases in emergency room visits, exacerbations or hospitalizations over a 12-month period (Grade 2C).

Underlying values and preferences: There is insufficient evidence at this time to support the contention that telemonitoring prevents COPD exacerbations.

PICO 2: Does maintenance inhaled therapy prevent/decrease acute exacerbations of COPD?

Background

An extensive amount of data is available regarding the effects of inhaled therapy on the treatment and prevention of acute exacerbation of COPD. To examine this area in a systematic fashion we organized the analysis of the efficacy of inhaled therapy to prevent COPD exacerbations into separate analyses of short-acting β_2-agonists and short-acting muscarinic antagonists vs. placebo and long-acting β_2-agonists and long-acting muscarinic antagonists vs. placebo to each other, and, in combination. Similarly we compared inhaled corticosteroids to placebo and the combination of long-acting β_2-agonists plus inhaled corticosteroids to placebo and vs. long-acting muscarinic antagonists and the combination of all three inhaled agents to placebo to prevent COPD exacerbations.

PICO 2 Recommendations

12. In patients with moderate to severe COPD, we recommend the use of long-acting β_2-agonist compared to placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1B).

Underlying values and preferences: This recommendation places high value on long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids and/or antibiotics) and severe (required hospitalization) together with the comparative benefit of long-acting β_2-agonist therapy improving quality of life and lung function compared to placebo. This recommendation also acknowledges that there are no significant differences in serious adverse events or incidence of mortality between long-acting β_2-agonist therapy vs. placebo in this patient group.

13. In patients with moderate to severe COPD, we recommend the use of a long-acting muscarinic antagonist compared to placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1A).

Underlying values and preferences: This recommendation places high value on long-acting muscarinic antagonists on reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids and/or antibiotics) and severe together with the comparative benefit of a long-acting muscarinic antagonist improving quality of life and lung function compared to placebo. Although pooled analyses show a reduction in COPD hospitalization with use of a long acting muscarinic antagonist compared to placebo, it does not reach statistical significance for all-cause hospitalization. This recommendation also acknowledges that there are no significant differences in serious adverse events or incidence of mortality between long-acting muscarinic antagonists vs. placebo in this patient group.

14. In patients with moderate to severe COPD, we recommend the use of long-acting muscarinic antagonists compared to long-acting β_2-agonist to prevent moderate to severe acute exacerbations of COPD (Grade 1C).

Underlying values and preferences: This recommendation places high value on long-acting muscarinic antagonists to reduce the risk of acute exacerbations of

COPD, both moderate (required course of oral steroids and/or antibiotics) and severe (required hospitalization) together with the comparative benefit of long-acting muscarinic antagonists having a lower rate of non-fatal serious adverse events compared with long-acting β_2-agonist. This comparative benefit may not apply with the new ultra-long-acting β_2-agonists that are once daily medication. Although pooled analyses show a reduction in COPD hospitalization with use of a long acting muscarinic antagonist compared to placebo, it does not reach statistical significance for all-cause hospitalization. A lower value was placed on the lack of statistically significant differences in changes in lung function, quality of life or patient symptoms between the two drug groups.

15. In patients with moderate to severe COPD, we suggest the use of a short-acting muscarinic antagonist compared to short acting β_2-agonist monotherapy to prevent acute mild-moderate exacerbations of COPD (Grade 2C).

Underlying values and preferences: This recommendation places value on a short-acting muscarinic antagonist to reduce the risk of acute exacerbations of COPD together with the comparative benefit of a short-acting muscarinic antagonist to improve quality of life and lung function compared to short-acting β2-agonist monotherapy. There is no data that favors one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that medication related adverse events were less in the short-acting muscarinic antagonist compared to the short-acting β_2-agonist group.

16. In patients with moderate to severe COPD, we suggest the use of short-acting muscarinic antagonist plus short-acting β_2-agonist compared to short-acting β_2-agonist alone to prevent acute moderate exacerbations of COPD (Grade 2B).

Underlying values and preferences: This recommendation places value on short-acting muscarinic antagonist plus short acting β_2-agonist reducing the risk of acute exacerbations of COPD together with the comparative small benefits of short-acting muscarinic antagonist plus short-acting β_2-agonist improving quality of life, exercise tolerance and lung function compared to short-acting beta agonist alone. This

recommendation also acknowledges that there are no significant differences in serious adverse events with the use of short-acting muscarinic antagonist plus short-acting β_2-agonists vs. short-acting β_2-agonist alone.

17. In patients with moderate to severe COPD, we suggest the use of long-acting β_2-agonist monotherapy compared to short-acting muscarinic antagonist monotherapy to prevent acute exacerbations of COPD (Grade 2C).

Underlying values and preferences: This recommendation places value on long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD in patients treated with long-acting β_2-agonist monotherapy over short- acting muscarinic antagonist monotherapy and the comparative value of long acting β_2-agonist monotherapy improving lung function, quality of life and dyspnea scores to short-acting muscarinic antagonist monotherapy. There is no data that favors one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that there are no significant differences in serious adverse events with the use of long-acting β_2-agonist monotherapy over short- acting muscarinic antagonist monotherapy.

18. In patients with moderate to severe COPD, we recommend the use of a long–acting muscarinic antagonist compared to a short acting muscarinic antagonist to prevent acute moderate to severe exacerbations of COPD (Grade 1A).

Underlying values and preferences: This recommendation places high value on a long–acting muscarinic antagonist reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids and/or antibiotics) and severe (required hospitalization) together with the comparative benefit of long–acting muscarinic antagonist improving quality of life and lung function compared to short-acting muscarinic antagonist. This recommendation also acknowledges that there were fewer nonfatal serious adverse events in subjects treated with long-acting muscarinic antagonist compared to short-acting muscarinic antagonist.

19. In patients with moderate to severe COPD, we suggest the combination use of a short-acting muscarinic antagonist plus long acting β2-agonist compared to long acting β2-agonist monotherapy to prevent acute mild to moderate exacerbations of COPD (Grade 2C).

Underlying values and preferences: This recommendation places value on the combination of a short-acting muscarinic antagonist plus long-acting β_2-agonist therapy on reducing the risk of acute exacerbations of COPD in patients compared to the use of long-acting β_2-agonist therapy alone and the comparative value of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy improving lung function, quality of life and dyspnea scores compared to long-acting β_2-agonist monotherapy. There is no data that favors one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that there are no significant differences in serious adverse events with the combination use of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy vs. long-acting β_2-agonist therapy alone.

20. For patients with stable moderate, severe and very severe COPD, we recommend maintenance inhaled, combination ICS/LABA therapy (and not ICS monotherapy) compared to placebo to prevent acute exacerbations of COPD (Grade 1B).

Underlying values and preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with slowing of the rate of decline in health-related quality of life; and a relatively lower value on the risk/consequences of oral candidiasis, hoarseness/dysphonia, bruising and pneumonia.

21. For patients with stable moderate, severe and very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting β_2-agonist therapy compared to long-acting β_2-agonist monotherapy to prevent acute exacerbations of COPD (Grade 1C).

Underlying values and preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with improved health-

related quality of life, reduced dyspnea, less rescue medication use, and improved lung function; and a relatively lower value on the risk/consequences of oral candidiasis, upper respiratory tract infections and pneumonia.

22. For patients with stable moderate, to very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting β_2-agonist therapy compared to inhaled corticosteroid monotherapy to prevent acute exacerbations of COPD (Grade 1B).

Underlying values and preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with the comparative mortality benefit of combination inhaled corticosteroid/long-acting β_2-agonist therapy, acknowledging there are no significant differences in serious adverse events or incidence of pneumonia between the groups. This recommendation does not support the use of inhaled corticosteroid monotherapy in COPD.

23. For patients with stable COPD, we recommend inhaled long-acting anticholinergic/long-acting β2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).

Underlying values and preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD.

24. For patients with stable COPD, we recommend maintenance combination of inhaled corticosteroid/long-acting β2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).

Underlying values and preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD, and a relatively lower value on the risk/consequences of pneumonia.

25. For patients with stable COPD, we suggest maintenance combination of inhaled long-acting anticholinergic/corticosteroid/long-acting β2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 2C).

Underlying values and preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD.

PICO 3: In patients greater than 40 years of age who are previous or current smokers diagnosed with COPD, does oral therapy prevent/decrease acute exacerbation of COPD?

Background

In the administration of treatment medication for COPD, the inhalation route has been favored for the last 30 years. This technique enables the drugs to act directly on the airways, provided that the inhalation device is used correctly. Although inhaled medications are not without adverse effects, they are often seen as having a better tolerability and safety profile than oral medications. Some medication can only be administered orally. Selecting drugs that are orally administered could depend on the type of drug and the patient. Furthermore, poor access to inhaled medications can be a problem in some countries. We chose to organize our review of oral therapy using the following categories: antibiotics, oral corticosteroids, phosphodiesterase inhibitors (roflumilast, theophylline), mucolytic agents (N-acetylcysteine, erdosteine, and carbocysteine) and statins.

Some of the oral medications, e.g., antibiotics and corticosteroids, are primarily prescribed to treat acute exacerbations of COPD. In this review, we did not assess the interventions used to treat acute exacerbations; we evaluated the evidence around the use of the interventions to prevent/decrease acute exacerbations.

PICO 3 Recommendations

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

Underlying values and preferences: This recommendation places high value on the prevention of COPD exacerbations. However, clinicians prescribing macrolides need to consider in their individual patients the potential for prolongation of the QT interval and hearing loss as well as bacterial resistance. The duration and exact dosage of macrolide therapy is unknown.

27. For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, we suggest that systemic corticosteroids be given orally or intravenously to prevent hospitalization for subsequent acute exacerbations of COPD in the first 30-days following the initial exacerbation (Grade 2B).

Underlying values and preferences: We place high value on reducing recurrent exacerbations in the first 30-days following an initial acute exacerbation of (AECOPD) by treating the AECOPD with systemic corticosteroids. This recommendation takes into consideration the risks associated with short-term use of systemic corticosteroids, which include hyperglycemia, weight gain and insomnia, but the benefits of this intervention are felt to outweigh the risks. The use of systemic corticosteroids to treat an acute exacerbation has not been shown to reduce acute exacerbations beyond the 30-day window. Furthermore, there is no evidence to support the use of chronic corticosteroids to reduce AECOPD and the risks of hyperglycemia, weight gain, infection, osteoporosis, and adrenal suppression far outweigh any benefits.

28. For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, we recommend that systemic corticosteroids not be given orally or intravenously for the sole purpose of preventing hospitalization due to subsequent acute exacerbations of COPD beyond the first 30-days following the initial acute exacerbation of COPD (Grade 1A).

Remark: This does not preclude the use of systemic corticosteroids for the treatment of acute exacerbation of COPD (AECOPD).

Underlying values and preferences: We place high value on reducing recurrent exacerbations in the first 30-days following an initial AECOPD by treating the AECOPD with systemic corticosteroids. This recommendation takes into consideration the risks associated with short-term use of systemic corticosteroids, which include hyperglycemia, weight gain and insomnia, but the benefits of this intervention are felt to outweigh the risks. The use of systemic corticosteroids to treat an acute exacerbation has not been shown to reduce acute exacerbations beyond the 30-day window. Furthermore, there is no evidence to support the use of chronic corticosteroids to reduce AECOPD and the risks of hyperglycemia, weight gain, infection, osteoporosis, and adrenal suppression far outweigh any benefits.

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

Underlying values and preferences: Clinicians prescribing this medication need to advise their patients of the potential side effects of weight loss and diarrhea. Patients may have to discontinue the therapy because of side effects. The decision to prescribe this medication should also be informed by the fact that there is limited data for supplemental effectiveness in patients concurrently using inhaled therapies.

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

Underlying values and preferences: Physicians should inform their patients that theophylline may reduce the number of exacerbations in patients with COPD who are being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations. Patient decisions may also be informed by the relatively narrow therapeutic window with respect to adverse effects of treatment with theophylline. Physicians should use the lowest effective dose in

prescribing theophylline in order to avoid adverse effects. Theophylline use requires vigilance on the part of the physician in order to avoid serious drug interactions, which lead to changes in serum theophylline levels. Patients should be advised that changes in tobacco use habits will affect serum theophylline levels, and that their physicians should be advised if they stop smoking while taking theophylline.

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

Underlying values and preferences: Physicians should inform their patients that N-acetylcysteine may reduce the number of exacerbations in patients with COPD who are being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations. Patient decisions may also be informed by the low risk of adverse effects of treatment with N-acetylcysteine.

32. For stable outpatients with COPD who continue to experience acute exacerbations of COPD despite maximal therapy designed to reduce acute exacerbations of COPD, we suggest that oral carbocysteine could be used to prevent acute exacerbations where this therapy is available (CB).

Underlying values and preferences: This suggestion places high value on prevention of acute exacerbations of COPD with minimal risks associated with carbocysteine. The main adverse events reported in the studies were mild gastrointestinal symptoms.

33. For patients with moderate to severe COPD who are at risk for COPD exacerbations, we do not recommend using statins to prevent acute exacerbations of COPD (Grade 1B).

Underlying values and preferences: We place high value on reducing exacerbations in patients with COPD and thus do not recommend statins for prevention of acute

exacerbations. However, patients with COPD may meet accepted criteria for initiation of statins due to the presence of cardiovascular risk factors.

CONCLUSIONS

These guidelines provide the clinician evidence-based information on therapies to prevent COPD exacerbations using an objective rigorous evidence-based approach to the assessment of the existing literature regarding non-pharmacologic, inhaled and oral therapies. We have avoided providing opinions but rather provide objective assessment of each recommendation where the data is robust enough to provide a meaningful conclusion based on the available data. This assessment also highlights areas where more research is needed as demonstrated by consensus-based recommendations as well as recommendations that were given a grade of C. It is clear that large gaps in knowledge currently exist about exacerbation prevention that limits our ability to prioritize one type of therapy over another or make recommendations about combinations of therapy to prevent exacerbations. Hopefully future research will evaluate combinations of therapies across PICO groups and their impact on exacerbation prevention.

Newer therapies that are soon to be released for clinical use or that are currently under investigation that focus on the prevention of COPD exacerbations, also promise to rapidly improve the future armamentarium for the treatment of the patient with COPD.

Figure 1. Decision tree for prevention of acute exacerbations of COPD (see attached file)

Acknowledgements

Author Contributions:

Financial/Nonfinancial Disclosures:

Role of Sponsors: The American College of Chest Physicians and the Canadian Thoracic Society supported the development this article and the innovations addressed within.

Other Contributions: This process spanned over 18 months and required the dedicated efforts of many from both CHEST and CTS in selecting panelists, organizing the systematic reviews and the regular executive and panelist conference calls, in person meetings and the extraction of information from the systematic reviews. We are indebted to Rebecca Diekemper, Kristen Current, Belinda Ireland, Joe Ornelas, Joyce Bruno, Nanette Umphrey, Sandra Zelman Lewis and Marianne Wright (Dr. Lewis and Ms. Wright helped in the early stages of the guideline) for their tireless efforts to make this guideline a current and valuable addition to the management of the COPD patient.

REFERENCES

1 Global strategy for the diagnosis, management n prevention of chronic obstructive pulmonary disease. Updated 2103.http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf.

2 Brusasco V. Reducing cholinergic constriction: the major reversible mechanism in COPD. European Respiratory Review 2006; 15:32-36

3 Cooper CB. Airflow obstruction and exercise. Respir Med 2009; 103:325-334

4 Public Health Agency of Canada. Chronic Pulmonary Obstructive Disease (COPD). Ottawa: Public Health Agency of Canada. Available at: http://www.phac-aspc.gc/cd-mc/crd-mrc/copd-mpoc-eng.php, Accessed June 28, 2012

5 Centers for Disease Control and Prevention. National Center for Health Statistics. National Vital Statistics Report. Deaths: Final Data for 2009. June 2012; 60(03).

6 Centers for Disease Control and Prevention. National Center for Health Statistics. National Health Interview Survey Raw Data, 2011. Analysis performed by the American Lung Association Research and Health Education Division using SPSS and SUDAAN software.
7 Centers for Disease Control and Prevention. Chronic Obstructive Pulmonary Disease Surveillance – United States, 1971-2000. Morbidity and Mortality Weekly Report. August 2, 2002; 51(SS06):1-16.
8 Centers for Disease Control and Prevention. National Center for Health Statistics. National Hospital Discharge Survey raw data, 2010. Analysis performed by the American Lung Association Research and Health Education Division using SPSS software.
9 Confronting COPD in America, 2000. Schulman, Ronca and Bucuvalas, Inc. (SRBI) Funded by Glaxo Smith Kline.
10 Mittmann N, Kuramoto L, Seung SJ, et al. The cost of moderate and severe COPD exacerbations to the Canadian healthcare system. Respir Med 2008; 102:413-421
11 Chapman KR, Bourbeau J, Rance L. The burden of COPD in Canada: results from the Confronting COPD survey. Respir Med 2003; 97 Suppl C:S23-31
12 Connors AF, Jr., Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). American journal of respiratory and critical care medicine 1996; 154:959-967
13 Seemungal TA, Donaldson GC, Paul EA, et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine 1998; 157:1418-1422
14 EPOC DSGDsAyFel. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. Chest 2002; 121:1449-1455
15 Miravitlles M, Garcia-Polo C, Domenech A, et al. Clinical outcomes and cost analysis of exacerbations in chronic obstructive pulmonary disease. Lung 2013; 191:523-530
16 Wouters EF. Economic analysis of the Confronting COPD survey: an overview of results. Respir Med 2003; 97 Suppl C:S3-14
17 Celli BR, MacNee W, Force AET. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. The European respiratory journal 2004; 23:932-946
18 Maltais F, Celli B, Casaburi R, et al. Aclidinium bromide improves exercise endurance and lung hyperinflation in patients with moderate to severe COPD. Respiratory medicine 2011; 105:580-587
19 Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. Chest 2000; 117:398S-401S
20 Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Annals of Internal Medicine 2011; 155:179-191

21 Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. The New England journal of medicine 2011; 365:689-698
22 Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003; 361:449-456
23 Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. The New England journal of medicine 2008; 359:1543-1554
24 Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. Chest 2006; 129:174-181
25 Lewis SZ, Diekemper R, Ornelas J, et al. Methodologies for the development of CHEST guidelines and expert panel reports. Chest 2014; 146:182-192
26 Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. JAMA 2002; 288:1775-1779
27 Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness: the chronic care model, Part 2. JAMA 2002; 288:1909-1914
28 National Clinical Guideline Centre (2010) Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English
29 O'Donnell DE, Aaron S, Bourbeau J, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. Can Respir J 2007; 14 Suppl B:5B-32B
30 Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008; 337
31 Petticrew M. When are complex interventions 'complex'? When are simple interventions 'simple'? The European Journal of Public Health 2011; 21:397-398
32 Weightman A ES, Cullum A, Sander L, Turley R. Grading evidence and recommendations for public health interventions: developing and piloting a framework. Retrieved from http://www.nice.org.uk/nicemedia/docs/grading_evidence.pdf

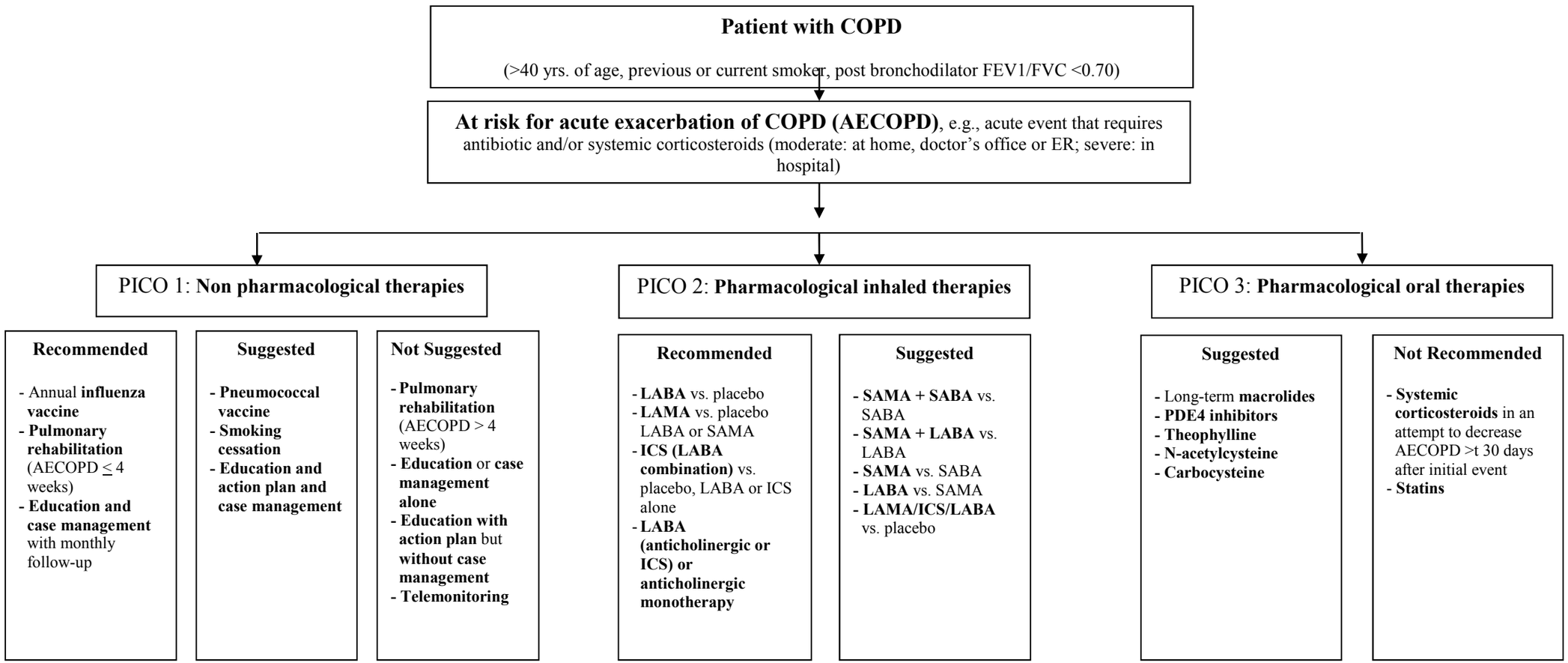

Figure 1

Decision tree for prevention of acute exacerbations of COPD according to 3 key clinical questions using the PICO format: non-pharmacologic therapies, inhaled therapies, and oral therapies.

Note: The wording used is "Recommended or Not Recommended" when the evidence was strong (Level 1) or "Suggested or Not Suggested" when the evidence was weak (Level 2).

Abbreviations: LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroids; SAMA short-acting muscarinic antagonist; SABA, short-acting beta agonist.