

Executive Summary

Prevention of Acute Exacerbation of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline

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ABBREVIATIONS: AECOPD = acute exacerbation of COPD; CDC = US Centers for Disease Control and Prevention; CHEST = American College of Chest Physicians; CTS = Canadian Thoracic Society; WHO = World Health Organization

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 progressively worsening breathlessness, affecting daily activities and health-related quality of life.¹⁻³ COPD is the fourth leading cause of death in Canada⁴ and the third leading cause of death in the United States where it claimed

133,965 lives in 2009.⁵ In 2011, 12.7 million US adults were estimated to have COPD.⁶ However, approximately 24 million US adults have evidence of impaired lung function, indicating an underdiagnosis of COPD.⁷ Although 4% of Canadians aged 35 to 79 years self-reported having been given a diagnosis of COPD, direct measurements of lung function from the Canadian Health Measures Survey indicate that 13% of Canadians have a lung function score indicative of COPD.⁴

COPD is also costly. In 2009, COPD caused 8 million office visits, 1.5 million ED visits, 715,000 hospitalizations, and 133,965 deaths in the United States.⁸ In 2010, US costs for COPD were projected to be approximately \$49.9 billion, including \$29.5 billion in direct

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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 to be 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 underdiagnosed, and the rate 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 readmissions¹²; contribute to death during hospitalization or shortly thereafter¹²; reduce quality of life dramatically^{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 > 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 on the basis of whether an increase in treatment beyond regular or urgent care is required in an ED or a hospital. Exacerbation treatment in clinical trials usually is defined by the use of antibiotics, systemic corticosteroids, or both.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 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 not only cause

but also 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 patient with COPD, 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 the prevention of COPD exacerbations.^{1,20} Moreover, new therapies have promise in preventing acute exacerbations of COPD (AECOPD) and would benefit from critical review of their efficacy in the exacerbation prevention management.²¹⁻²³ The American College of Chest Physicians (CHEST) and Canadian Thoracic Society (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 CHEST and CTS joint evidence-based guideline (AECOPD Guideline) was to create a practical, clinically useful document describing the current state of knowledge regarding the prevention of AECOPD according to major categories of prevention therapies. We accomplished this by using recognized document evaluation tools to assess and choose the most appropriate studies and evidence to extract meaningful data and to grade the level of evidence supporting the recommendations in a balanced and unbiased fashion. The AECOPD Guideline is unique not only for its topic but also for the first-in-kind partnership between two of the largest thoracic societies in North America. The CHEST Guidelines Oversight Committee in partnership with the CTS COPD Clinical Assembly launched this project with the objective that a systematic review and critical evaluation of the published literature 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 patient with COPD. 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.

Materials and Methods

Members from CHEST and CTS were selected to participate on the AECOPD Guideline panel based on their expertise in the field. Panelists were assigned to one of three writing groups that addressed each key question. The groups were referred to as PICO groups because the key questions

were developed using the PICO format, which defines the population, intervention, comparator, and outcome of interest. The three PICO questions that addressed the prevention of AECOPD were nonpharmacologic 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 recommendations. Controversial recommendations went through up to three rounds of voting before being approved for inclusion in the AECOPD Guideline.

Recommendations

PICO 1: Do Nonpharmacologic Treatments and Vaccinations Prevent/Decrease Acute Exacerbations of COPD?

Background: Effective support and management of individuals at risk for an acute exacerbation of COPD demands a comprehensive and patient-centered approach. The widely adopted Chronic Care Model^{26,27} recognizes that improvements in care require approaches incorporating patient-, provider-, and system-level interventions. Key elements of the Chronic Care Model are 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 community. The importance of incorporating nonpharmacologic 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: (1) pneumococcal vaccinations; (2) influenza vaccinations; (3) smoking cessation programs; (4) pulmonary rehabilitation; (5) education, action plans, and case management; and (6) telemonitoring. These topics may be considered complex interventions³⁰ in that they contain multiple interacting components and possess nonlinear 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 nonpharmacologic trials have limitations with respect to such methodologic aspects as how the intervention was standardized and the details of the experimental treatment and comparator as they were implemented. Prevention of exacerbations often was not the primary outcome for many studies examining the efficacy and effectiveness of nonpharmacologic 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 are 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 patients with COPD. Although evidence does not specifically support using the vaccine for the prevention of acute exacerbations, multiple bodies, including the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO), recommend the use of pneumococcal vaccine for all adults aged ≥ 65 years and in those aged 19 to 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 the existing guidelines that recommend it for patients with COPD. Although the effect and evidence are moderate for the prevention of acute exacerbations of COPD, multiple bodies, including the CDC and WHO, recommend the use of a 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 COPD prognosis by mitigating lung function decline and reduces symptoms. Although the effect and evidence for smoking cessation in the prevention of acute exacerbations of COPD are low, evidence supports 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, physiologic, and psychologic components comprising an acknowledgment of current smoking followed by advice to quit, pharmacologic therapies (nicotine replacement therapy, antidepressants, nicotine receptor modifier therapy), and counseling (in-person or telephone counseling), with cessation rates ranging from 8.8% to 34.5%. Smoking cessation that includes counseling and pharmacologic interventions are cost-effective.

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

Underlying Values and Preferences: The pulmonary rehabilitation recommendations place high value on pulmonary rehabilitation reducing the risk of hospitalizations in patients with COPD who have had a recent COPD exacerbation (ie, ≤ 4 weeks posthospitalization). Although 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 rehospitalizations in patients with COPD greater than 4 weeks after a recent hospitalization.

5. In patients with moderate, severe, or very severe COPD who have had an exacerbation greater 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 patients with COPD who have had a recent COPD exacerbation (ie, ≤ 4 weeks posthospitalization). Although 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 rehospitalizations in patients with COPD greater than 4 weeks after a recent hospitalization.

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

exacerbations of COPD (Ungraded Consensus-Based Statement).

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 because it is labor intensive compared with 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 (Ungraded Consensus-Based Statement).

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 because 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 ED 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 ED 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 believed to best reflect exacerbations because 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 do not know the reason for increased mortality in this one study, patients with underlying severe disease and clinical instability need close attention and careful follow-up. This point emphasizes that a specially trained staff is required to supervise this intervention and that patient selection must be individualized.

11. For patients with COPD, we suggest that telemonitoring compared with 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 AECOPD. 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 with each other and in combination. Similarly, we compared inhaled corticosteroids with placebo and the combination of long-acting β_2 -agonists plus inhaled corticosteroids with placebo and vs long-acting muscarinic antagonists and the combination of all three inhaled agents with 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 with 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, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of long-acting β_2 -agonist therapy improving quality of life and lung function compared with 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 and placebo in this patient group.

13. In patients with moderate to severe COPD, we recommend the use of a long-acting muscarinic antagonist compared with 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 reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of a long-acting muscarinic antagonist improving quality of life and lung function compared with placebo. Although pooled analyses show a reduction in COPD hospitalization with the use of a long-acting muscarinic antagonist compared with 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 and placebo in this patient group.

14. In patients with moderate to severe COPD, we recommend the use of long-acting muscarinic antagonists compared with 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 reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of long-acting muscarinic antagonists having a lower rate of nonfatal serious adverse events compared with long-acting β_2 -agonists. This comparative benefit may not apply with the new ultralong-acting β_2 -agonists that are a once-daily medication. Although pooled analyses show a reduction in COPD hospitalization with the use of a long-acting muscarinic antagonist compared with 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, and 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 with 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 reducing the risk of acute exacerbations of COPD together with the comparative benefit of a short-acting muscarinic antagonist improving quality of life and lung function compared with short-acting β_2 -agonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that medication-related adverse events were fewer in the short-acting muscarinic antagonist than in 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 with short-acting β_2 -agonist alone to prevent acute moderate exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: This recommendation places value on a 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 a short-acting muscarinic antagonist plus a short-acting β_2 -agonist improving quality of life, exercise tolerance, and lung function compared with a short-acting β_2 -agonist alone. This recommendation also acknowledges that there are no significant differences in serious adverse events with the use of a short-acting muscarinic antagonist plus a short-acting β_2 -agonist vs a 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 with 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 compared with short-acting muscarinic antagonist monotherapy. No data favor 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 with 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, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of a long-acting muscarinic antagonist improving quality of life and lung function compared with a short-acting muscarinic antagonist. This recommendation also acknowledges that there were fewer nonfatal serious adverse events in subjects treated with long-acting muscarinic antagonist than in those treated with a 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 β_2 -agonist compared with long-acting β_2 -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 short-acting muscarinic antagonist plus long-acting β_2 -agonist therapy reducing the risk of acute exacerbations of COPD compared with 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 with long-acting β_2 -agonist monotherapy. No data favor 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 combined 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 combination inhaled corticosteroid/long-acting

β_2 -agonist therapy (and not inhaled corticosteroid monotherapy) compared with 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 the rate of decline in health-related quality of life and a relatively lower value on the risks and consequences of oral candidiasis, hoarseness and 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 with 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 risks and 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 with 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 that there were 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 β_2 -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 β_2 -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 risks and consequences of pneumonia.

25. For patients with stable COPD, we suggest maintenance combination of inhaled long-acting anticholinergic/corticosteroid/long-acting β_2 -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 Aged > 40 Years Who Are Previous or Current Smokers With COPD, Does Oral Therapy Prevent/Decrease Acute Exacerbations of COPD?

Background: In the administration of treatment medication for COPD, the inhalation route has been favored for the past 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 often are seen as having a better tolerability and safety profile than oral medications. Some medications can only be administered orally. Selecting drugs that are orally administered depends 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 the review of oral therapy by the following categories: antibiotics, oral corticosteroids, phosphodiesterase inhibitors (roflumilast, theophylline), mucolytic agents (N-acetylcysteine, erdosteine, carbocysteine), and statins. Some of the oral medications (eg, antibiotics, corticosteroids) are primarily prescribed to treat AECOPD. 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 or 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 are 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 COPD by treating the exacerbation with systemic corticosteroids. This recommendation takes into consideration the risks associated with the short-term use of systemic corticosteroids, which include hyperglycemia, weight gain, and insomnia, but the benefits of this intervention are believed 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, no evidence supports the use of long-term corticosteroids to reduce acute exacerbations of COPD, 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 exacerbations of COPD.

Underlying Values and Preferences: We place high value on reducing recurrent exacerbations in the first 30 days following an initial acute exacerbation of COPD by treating the exacerbation with systemic corticosteroids. This recommendation takes into consideration the risks associated with the short-term use of systemic corticosteroids, which include hyperglycemia, weight gain, and insomnia, but the benefits of this intervention are believed 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, no evidence supports the use of long-term corticosteroids to reduce acute exacerbations of COPD, 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 roflumilast 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 are limited data for supplemental effectiveness in patients concurrently using inhaled therapies.

30. For stable patients with COPD, 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 with COPD who are being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations that theophylline may reduce the number of 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 they should inform their physicians if they stop smoking while taking theophylline.

31. For patients with moderate to severe COPD and a history of two or more exacerbations in the previous 2 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 with COPD who are being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations that N-acetylcysteine may reduce the number

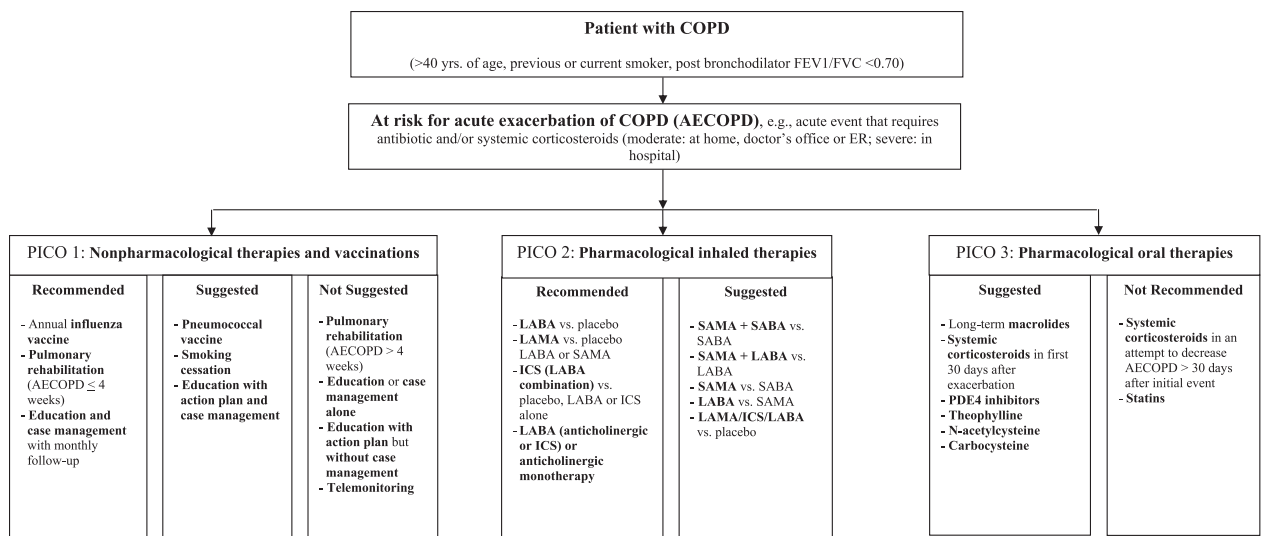


Figure 1 – Decision tree for prevention of AECOPD according to three key clinical questions using the PICO format: nonpharmacological therapies, inhaled therapies, and oral therapies. Note that the wording used is “recommended or not recommended” when the evidence was strong (level 1) or “suggested or not suggested” when the evidence was weak (level 2). ER = emergency room; ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; PDE4 = phosphodiesterase 4; PICO = population, intervention, comparator, outcome; SABA = short-acting β_2 -agonist; SAMA = short-acting muscarinic antagonist.

of exacerbations. Patient decisions may also be informed by the low risk of adverse effects from 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 (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This suggestion places high value on preventing acute exacerbations of COPD, with minimal risks associated with carbocysteine. The main adverse events reported in studies were mild GI 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 preventing acute exacerbations. However, patients with COPD may meet accepted criteria for initiating statins because of the presence of cardiovascular risk factors.

Conclusions

These guidelines provide the clinician with evidence-based information on therapies to prevent COPD

exacerbations using an objective, rigorous, evidence-based approach to the assessment of the existing literature regarding nonpharmacologic inhaled and oral therapies (Fig 1). We have avoided providing opinions, instead using objective assessment of each recommendation where the data are 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 given a grade of C. It is clear that large gaps in knowledge currently exist about exacerbation prevention that limit 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.

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Nonpharmacologic Therapies section, oversaw the systematic reviews for inhaled and oral therapies as well as advising all of the writing committees on drafting recommendations and supporting text, drafted the Methodology section, and reviewed and provided feedback on the entire manuscript; D. R. O. served as the liaison to the Guidelines Oversight Committee, drafted recommendations and supporting text for the Oral Therapies section, and reviewed and provided feedback on the entire manuscript; D. G. and P. H. led the nonpharmacologic therapies writing committee, drafted recommendations and supporting text for the section, and reviewed and provided feedback on the entire manuscript; K. C. coordinated all of the writing committee and executive committee meetings, facilitated the review of the entire manuscript, drafted the Knowledge Translation section, and reviewed and provided feedback on the entire manuscript; M. S. B. drafted supporting text for the Oral Therapies section and reviewed the entire manuscript; M. B., B. R. C., S. B. F., and N. A. H. drafted supporting text for the Inhaled Therapies section and reviewed the entire manuscript; P. G. C., G. D., M. G. F., R. A. M., and M. K. S. drafted recommendations and supporting text for the Nonpharmacologic Therapies section and reviewed the entire manuscript; M. T. D., N. M., and J. D. R. drafted recommendations and supporting text for the Oral Therapies section and reviewed the entire manuscript; B. K. I. conducted systematic reviews for the Inhaled Therapies section and reviewed the recommendations and supporting text for the Inhaled Therapies and Methodology sections; D. D. M. drafted recommendations and supporting text for the Inhaled Therapies section and reviewed the entire manuscript; and J. O. conducted systematic reviews for the Oral Therapies section and reviewed the recommendations and supporting text for the Oral Therapies and Methodology sections.

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