Practice Guidelines

Pharmacologic Management of COPD Exacerbations: A Clinical Practice Guideline from the AAFP

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**Purpose**: To review the evidence and provide clinical recommendations for the management of acute exacerbations of chronic obstructive pulmonary disease (COPD).

**Methods**: This guideline is based on a systematic review of randomized controlled trials from database inception to January 2, 2019. The target audience for the guideline includes all primary care clinicians, and the target patient population includes adults who are experiencing acute exacerbations of COPD. This guideline was developed using a modified version of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, a transparent approach to evaluating the certainty of the evidence and determining the strength of recommendations.

**Recommendation 1**: The American Academy of Family Physicians (AAFP) recommends that clinicians prescribe systemic antibiotics for adults with acute exacerbations of COPD to improve clinical cure and reduce clinical failure (weak recommendation, moderate quality of evidence). Choice of antibiotic should be based on local resistance patterns, affordability, and patient history and preferences because there is insufficient evidence to support a preferential recommendation.

**Recommendation 2**: The AAFP recommends that clinicians prescribe corticosteroids for adults with acute exacerbations of COPD to reduce clinical failure (weak recommendation, low quality of evidence). There is insufficient evidence to guide the dose, route of administration, or duration of treatment.

**Good Practice Point**: Short-acting bronchodilators are routinely used to improve symptoms in patients with acute exacerbations of COPD (ungraded).

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**Guideline Scope and Purpose**
The purpose of this guideline is to provide primary care–relevant recommendations for the management of acute exacerbations of chronic obstructive pulmonary disease (COPD). The target audience includes family physicians and other primary care clinicians. The target patient population is adults with acute exacerbations of COPD.

**Introduction**
COPD is characterized by airflow limitation and chronic respiratory symptoms, including cough and shortness of breath. It affects around 15 million people in the United States and costs more than $32 billion annually.1,2 Chronic lower respiratory tract diseases, including COPD, are the fourth leading cause of death in the United States and the third leading cause of death worldwide.3,4 Patients with COPD are at risk of acute exacerbations of symptoms.
resulting in the need for additional treatment. Acute exacerbations of COPD are generally characterized by increased dyspnea, increased frequency and severity of cough, and increased frequency and severity of sputum production. Patients experiencing acute exacerbations of COPD are at increased risk of mortality and morbidity, lower quality of life, increased hospital admissions, and a progressive decline in lung function. The Mayo Clinic Evidence-Based Practice Center worked with key informants and a technical expert panel consisting of stakeholders, including physician and patient representatives. Family physicians served in both groups. The report included the following key questions represented by the analytic framework in Figure 1.

Key Question 1. In adults with exacerbations of COPD, what are the benefits and harms of systemic corticosteroids and antibiotics compared with placebo or standard care?

Key Question 2. In adults with exacerbations of COPD, what are the benefits and harms of systemic corticosteroids and antibiotics, with or without concurrent inhaled bronchodilators, and supplemental oxygen.

Key Question 3. In adults with exacerbations of COPD, what are the benefits and harms of combinations of treatments that are individually effective (based on empirical evidence) in stable COPD?

Key Question 4. In adults with exacerbations of COPD, what is the comparative effectiveness of different regimens of antibiotics and corticosteroids? Are different regimens of antibiotics and corticosteroids more effective than placebo?

Constructing the Guideline

The AAFP’s Commission on Health of the Public and Science appointed a group to develop the guideline. Members of the guideline development group included physicians with expertise in guideline development, family medicine, internal medicine, and pulmonary medicine, in addition to a consumer representative. This group followed the guideline development process that can be found in the AAFP Clinical Practice Guideline Manual. The group reviewed the evidence from the AHRQ evidence report and used a modified version20 of the GRADE system to rate the quality of the evidence for each outcome and the overall strength of each recommendation. The strength of recommendation reflects the extent to which one can be confident that the desirable effects of an intervention outweigh the undesirable effects and reflects the degree to which there is evidence of improved patient-oriented health outcomes (Table 1).

The quality of evidence is based on the certainty of the evidence. High-quality evidence means the authors have high certainty in the estimate of effect, and additional studies most likely will not change the outcome. Low-quality evidence means that the authors have lower certainty in the estimate of effect, and additional studies will likely change the result.

The AAFP also issues guideline recommendations with a rating system to reflect the certainty of the evidence. The ratings range from “strong recommendation, moderate certainty of effect” to “weak recommendation, low certainty of effect.” The AAFP clinical practice guidelines are intended to support the recommendation. The AAFP labels these as “good practice points.”

TABLE 1. GRADE evidence to decision frameworks, which enabled consideration of the strength of the evidence in addition to issues of feasibility, acceptability, equity, and patient preferences and values (Table 2).

The qualities of evidence include symptom resolution and recovery from the exacerbation event. The AHRQ publishes a consumer guide to support the recommendation. The patient representative assisted in developing the supporting text for the guideline. Patient representatives were also included in the peer-review process.

Conflict of Interest

The AAFP considers both financial and intellectual conflicts of interest (COI), which were solicited in writing at the beginning of the guideline process and updated verbally at each subsequent call. No panel member disclosed any COI. Policies for disclosures and management of COI are outlined in the AAFP Clinical Practice Guideline Manual.
Low quality of evidence demonstrated that systemic corticosteroids decreased the clinical failure rate in adults with acute exacerbations of COPD (Table 4).14,15 Two RCTs with a total of 217 patients showed less treatment failure for acute exacerbations with systemic corticosteroids compared with placebo (OR = 0.01; 95% CI, 0.00 to 0.13).14,15

One RCT conducted in the Veterans Affairs health system randomized 190 patients to receive a course of intravenous methylprednisolone and oral prednisone or to receive placebo for eight weeks.14 A third group, which was not included in the analysis, received corticosteroids for two weeks. Patients receiving placebo had significantly higher rates of clinical failure than those receiving corticosteroids (33% vs. 0%). The second study looked at 26 patients who received oral prednisolone or placebo.11 No treatment failures were observed in the treatment group (n = 13) compared with 61% of those in the placebo group (n = 14). There was no significant difference at longest follow-up (one month) for clinical failure as reported in the AHRQ evidence review.16 This evidence was rated as low quality because of the risk of bias and imprecision in both studies.14 The improvement was observed independent of severity of exacerbation episode and treatment setting.

There were no differences observed for other outcomes of interest, including mortality and rehospitalization. An increase in the number of adverse events was observed with systemic corticosteroid treatment, but it was not statistically significant.14,15 Three studies compared the effectiveness of different durations of systemic corticosteroids (three vs. 10 days, five vs. 14 days, and two vs. eight weeks) in the inpatient setting. No statistically significant differences in outcomes of interest were observed. Interestingly, these data suggest that five days of treatment is not inferior to 14 days of treatment.14 This is consistent with a large observational study that was published after the search dates for the evidence review.22 This study used administrative data and included 10,512 patients. These data showed small increases in rates of pneumonia-associated hospitalization and mortality associated with longer courses of corticosteroids.22

There was insufficient evidence to guide decisions about routes of administration (oral, inhaled, or intravenous) of corticosteroids in this population.18 One study examining oral with intravenous administration showed no differences in outcomes; however, this study was found to have a high risk of bias and severe imprecision and was deemed to provide insufficient evidence.15

**GOOD PRACTICE POINT**

Short-acting bronchodilators are routinely used to improve symptoms in patients with acute exacerbations of COPD (ungraded).

The evidence report evaluated other pharmacologic treatments and dietary supplements for acute exacerbations of COPD. However, there was insufficient evidence for all therapies other than antibiotics and corticosteroids for the outcomes of interest.

### RECOMMENDATION 2

The AAPF recommends that clinicians prescribe corticosteroids for adults with acute exacerbations of COPD to improve clinical cure and reduce clinical failure (weak recommendation, moderate quality of evidence). Choice of antibiotic should be based on local resistance patterns, affordability, and patient history and preferences because there is insufficient evidence to support a preferential recommendation.

Moderate quality of evidence showed that treatment of acute exacerbations with antibiotics improved the rate of clinical cure and decreased the rate of clinical failure in adult patients with COPD (Table 3).25-29 Clinical cure was defined as the complete improvement of clinical signs and symptoms following treatment. Clinical failure was defined as the lack of a significant improvement of clinical signs and symptoms and/or the requirement for additional or alternate treatment for an acute exacerbation event. Three randomized controlled trials (RCTs) with 633 patients examined the effectiveness of systemic antibiotics in the resolution (clinical cure) of an acute exacerbation of COPD compared with placebo.25-27 The pooled effect size showed increased rates of clinical cure at the end of the intervention (odds ratio [OR] = 2.03; 95% CI, 1.47 to 2.80) compared with placebo.26 Patients treated with amoxicillin had a significantly longer time to subsequent exacerbations than those receiving placebo, which was considered a measure of clinical cure.28,29

Two RCTs with a total of 505 patients showed less treatment failure for acute exacerbations with systemic antibiotics compared with placebo (OR = 0.54; 95% CI, 0.34 to 0.86).14,15 The evidence for these outcomes was rated as moderate quality because of the risk of bias for four out of the five included studies.25-27 There were no statistically significant differences in other outcomes of interest, including mortality, quality of life, and adverse events. Although studies were found that examined different types and dosages of antibiotics, there was insufficient evidence to estimate an effect on most of the outcomes of interest.14 Similarly, no studies were found that examined the effectiveness of systemic antibiotics in the resolution (clinical cure) of an acute exacerbation of COPD compared with placebo.14-15

### TABLE 2

**Should Corticosteroids or Antibiotics vs. Placebo Be Used for Adults with Acute Exacerbations of COPD?**

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Main outcomes</th>
<th>Setting</th>
<th>Antibiotics</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with acute exacerbations of COPD</td>
<td>Corticosteroids or antibiotics</td>
<td>Placebo</td>
<td>Clinical failure: clinical cure</td>
<td>Inpatient/outpatient</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Problem (COPD exacerbations)</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desirable effects</td>
<td>Large</td>
<td>Large</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undesirable effects</td>
<td>Small</td>
<td>Small</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certainty of evidence</td>
<td>Moderate</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Values</td>
<td>Probably no important</td>
<td>Probably no important</td>
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<tr>
<td>Uncertainty in how people would value the outcome</td>
<td>Uncertainty in how people would value the outcome</td>
<td></td>
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<td></td>
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<tr>
<td>Balance of effects</td>
<td>Favors the intervention</td>
<td>Favors the intervention</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Resources required</td>
<td>No studies included</td>
<td>No studies included</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost effectiveness</td>
<td>No costs</td>
<td>No costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Equity</td>
<td>Probably no impact</td>
<td>Probably no impact</td>
<td></td>
<td></td>
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<tr>
<td>Acceptability</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Feasibility</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>

*PROSTATE GUIDELINES*
There are limited data, specifically placebo-controlled trials, supporting the role of short-acting bronchodilators for acute exacerbations of COPD. However, these agents, specifically beta-2 agonists, anticholinergic agents, or combinations, are routinely recommended, primarily for symptom control.26–29 Because of the widespread recommendation and use of these medications, the AAFP identifies the use of short-acting bronchodilators for acute exacerbations of COPD as a good practice point. As discussed later, this area has been identified as a research gap, and the AAFP calls for additional research to address the role of these medications.

A list of other primary care–relevant pharmacologic treatments and outcomes is shown in Table 5.24

In particular, there were no high-quality RCTs demonstrating the benefit of short-acting bronchodilators for the treatment of acute exacerbations of COPD. Three studies were included in the review that looked at the comparative effectiveness of bronchodilators. One study compared ipratropium (Atrovent) with salbutamol (albuterol),34 two studies compared ipratropium/salbutamol (Combivent) with salbutamol alone,35,36 and a third study compared salbutamol plus inhaled corticosteroids with fenoterol (not available in the United States).37 None of the studies looked at patient-oriented outcomes, and no significant differences were observed in forced expiratory volume in one second (FEV1) or adverse events.38

Nonpharmacologic Treatments

The evidence review found only a few studies evaluating nonpharmacologic treatments for acute exacerbations of COPD, resulting in insufficient evidence for patient-oriented outcomes prioritized by the guideline development group.39 The review included a fairly large trial with 214 patients comparing titrated oxygen with high-flow oxygen, which found a reduction in mortality in patients with acute exacerbations of COPD who were given titrated oxygen.40

This study was rated as high risk of bias resulting in a low strength of evidence for this outcome. However, this result is similar to other observations associating increased risk of harms with high-flow oxygen when used to maintain higher saturation levels.41 Various dietary modifications and supplements were also included in the evidence review, but there was limited evidence to recommend for or against these treatments.

Implementations of Recommendations

BARRIERS TO IMPLEMENTATION OF THE GUIDELINE INTO CLINICAL PRACTICE

Most studies included in the evidence report evaluated patients who were hospitalized and experiencing severe acute exacerbations of COPD, limiting the applicability to outpatient settings and patients with less severe disease. Additionally, although there was insufficient evidence to draw conclusions among different antibiotics, the choice of treatment will depend on local antibiotic resistance patterns, which vary among patients, locations, and points in time.42 Shared decision-making is important in determining treatment plans. Any patient education materials should be written at an appropriate literacy level with risks and benefits of treatment conveyed adequately.

Addressing potential disparities that exist across racial, socioeconomic, and geographic demographics should be considered when implementing any guideline recommendations. Racial and gender disparities have been observed in frequency of exacerbations, health outcomes, and use of health care services. Lack of access to health care services, in addition to other social determinants of health that affect patients’ ability to obtain services, could be a significant impediment to implementation of these recommendations. Practices should consider screening for social determinants of health and help address those issues by developing and maintaining a directory of resources for patients.43 Increasingly, private and governmental insurers are employing case/care managers to assist patients and clinicians in obtaining the additional resources needed for supporting patients who face challenging situations. Clinicians may also consider the availability of telemedicine resources for counseling and follow-up for patients with acute exacerbations of COPD.

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**TECHNIQUES FOR IMPLEMENTATION**

Chronic care management can be effectively implemented in primary care practices to manage patients with chronic conditions, such as diabetes mellitus, cardiovascular disease, and COPD. It is a model that has been used to educate and empower patients to track, prevent, and self-manage symptoms, leading to earlier reporting of COPD exacerbations to primary care physicians and reducing use of the emergency department.63

Telemedicine may provide additional assistance in management of patients with COPD exacerbations. More studies are needed to determine the full impact on outcomes for patients with COPD. To date, only one study has been found that included patients with acute exacerbations who were managed using telemedicine. However, given the onset of widespread use of telemedicine in 2020, there may be additional support for its use in this patient population.64

Another study assessed the effectiveness of an integrative approach with both telemedicine and discharge bundles.65 Additional support for its use in this patient population.62

**TABLE 5**

<table>
<thead>
<tr>
<th>Insufficient Evidence for Other Pharmacologic Treatments for Acute Exacerbations of Chronic Obstructive Pulmonary Disease</th>
<th>Treatment</th>
<th>Outcome</th>
<th>No. of RCTs</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminophyllines</td>
<td>Mortality</td>
<td>2 (n = 132)</td>
<td>No difference between treatment and placebo; insufficient evidence</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>Dyspnea</td>
<td>1 (n = 72)</td>
<td>No difference between treatment and placebo; insufficient evidence</td>
<td></td>
</tr>
<tr>
<td>Mucolytics</td>
<td>Dyspnea</td>
<td>1 (n = 44)</td>
<td>No difference between treatment and placebo or management without mucolytics; insufficient evidence</td>
<td></td>
</tr>
</tbody>
</table>

**Repeat exacerbations**

<table>
<thead>
<tr>
<th>RCTs = randomized controlled trials</th>
<th>Information from reference 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 40)</td>
<td>Low strength of evidence for reduced number of exacerbations at one month and insufficient evidence for benefit at three months</td>
</tr>
</tbody>
</table>

**Variability in the reporting of outcomes with a limited number that were considered patient-oriented**

Most studies were in hospital settings and in patients with severe acute exacerbations of COPD, limiting applicability to outpatient settings and patients with mild or moderate events.

**Conclusions and Future Research**

The purpose of this updated guideline is to provide clinical recommendations for primary care physicians to treat patients who are experiencing acute exacerbations of COPD. The management of stable COPD was considered outside the scope of this guideline but is addressed elsewhere.66,67

The AAFP recommendations for managing acute exacerbations of COPD are consistent with guidance from others.68

Both systemic antibiotics and corticosteroids were observed to be beneficial for improving symptom resolution in this population as measured by increased clinical cure rates. Treatment with antibiotics also decreased clinical failure rate. Treatment decisions should be based on clinical judgment and patient preferences and values, and involve shared decision-making by the patient and clinician.

This guideline was developed using available evidence; however, significant gaps were identified in the AHRQ systematic review and by members of the guideline development group. New research into these areas may affect the recommendations, at which time the guideline will be updated accordingly. Research that would provide important information for the clinical questions discussed in this guideline includes the following:

- Studies to determine which patients with acute exacerbations of COPD benefit from oxygen therapy, as well as the best delivery mechanism(s) and optimal titration for oxygen therapy.
- Studies that are needed to determine the appropriate methods for oxygen therapy.
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- Additional studies to determine the optimal type of antibiotic and route and duration of corticosteroid treatment.
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1. Dr. Stevermer is a member of the U.S. Preventive Services Task Force (USPSTF). This article does not necessarily represent the views and policies of the USPSTF. Dr. Lin is deputy editor for AFP. All costs associated with the development of this guideline came exclusively from the operating budget of the AAFP.

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Disclaimer: These recommendations are provided only as assistance for clinicians making clinical decisions during the care of their patients. As such, they cannot substitute for the individual judgment brought to each clinical situation. As with all medical reference resources, they reflect the best understanding of the science of medicine at the time of publication, but they should be used with the clear understanding that continued research may require modification of these recommendations. All AAFP guidelines are scheduled for review five years after publication. Additional, or updated clinical practice guidelines with recommendations for acute exacerbations was identified and acknowledged in the supporting text.

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