Evidence Base for Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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The American College of Physicians–American Society of Internal Medicine (ACP–ASIM) and the American College of Chest Physicians (ACCP) developed this evidence-based clinical practice guideline in collaboration. A joint expert panel examined the evidence and developed recommendations. The numbers in square brackets are cross-references to the numbered sections in the accompanying background paper, "Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Summary and Appraisal of Published Evidence," which is part 2 of this guideline (see pages 600-620). The guideline and background paper are based primarily on a systematic review compiled in an Agency for Healthcare Research and Policy evidence report prepared by the Evidence-Based Practice Center at Duke University (1). Our target audience is primary care physicians and specialists who care for patients with chronic obstructive pulmonary disease (COPD). Although most acute exacerbations of COPD take place and are treated on an outpatient basis, research studies focus on emergency department or inpatient settings. As a result, this guideline applies to exacerbations treated in those settings. The guideline presents the available evidence on risk stratification for relapse and 6-month mortality rates, diagnostic testing for acute exacerbations of COPD, and current treatment options for acute exacerbations of COPD.

In the United States, 16 million adults have COPD, which accounts annually for 110 000 deaths, more than 16 million office visits, 500 000 hospitalizations, and $18 billion in direct health care costs. The disease is characterized by chronic airflow obstruction and episodic increases in dyspnea, cough, and sputum production that are commonly called "exacerbations." After an acute exacerbation, most patients experience a transitory or permanent decrease in quality of life, and nearly 50% of patients discharged from hospitals after acute exacerbations are readmitted more than once in the following 6 months. Therefore, one of the main treatment goals for patients with COPD is reducing the number and severity of annual exacerbations.

There is no widely accepted definition of acute exacerbation of COPD, but most published definitions encompass some combination of three clinical findings: worsening dyspnea, increase in sputum purulence, and increase in sputum volume. A severity scale for acute exacerbations developed by Anthonisen and colleagues (2) is based on these findings as well as others. Type 1 exacerbations (severe) have all three clinical findings, and type 2 exacerbations (moderate) exhibit two. Type 3 exacerbations (mild) have one of these clinical findings plus at least one of the following: an upper respiratory tract infection in the past 5 days, fever without other apparent cause, increased wheezing, increased cough, or a 20% increase in respiratory rate or heart rate above baseline. We use this scale when referring to severity in this guideline. Acute exacerbations can be triggered by tracheobronchial infections or environmental exposures, and patients often have associated clinical conditions, such as heart failure, extrapulmonary infections, and pulmonary embolism. Therefore, acute exacerbation is mainly a clinical diagnosis.

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Despite the importance of this disease, the review of the evidence brings to light the paucity of high-quality studies on this subject. Nevertheless, recommendations in this guideline are based on the highest-quality evidence currently available. While the studies of "highest" quality were often randomized, controlled clinical trials, these were few in number and tended to enroll small numbers of patients. The clinician must consider this fact when basing management decisions on the guideline recommendations.

Current practices for the diagnosis and management of acute exacerbations of COPD are varied. Some commonly used tests and therapies are not supported by evidence, while others are. The Panel found enough evidence to make recommendations about the use of the following diagnostic and therapeutic methods in acute exacerbations of COPD: chest radiography, acute spirometry, bronchodilators, corticosteroids, antibiotics, oxygen, mucolytic agents, mucus-clearing strategies, and noninvasive positive-pressure ventilation (NPPV). Indirect evidence shows that arterial blood gases are helpful for determining the present need for oxygen therapy and the potential need for mechanical ventilatory support. We did not find enough evidence to make recommendations regarding the use of pulse oximetry, sputum smear, and culture.

Risk Stratification

Prediction of Outpatient Relapse

All of the studies included for analysis were performed in the emergency department. Relapse was defined as a return visit to the emergency department within 14 days of initial presentation. Identifying patients at high risk for relapse should help guide decisions about hospital admission and follow-up appointments. Several studies have confirmed what most clinicians intuitively know: Patients who have lower baseline FEV_1, low P_{O_2}, high P_{CO_2}, and low pH and who receive more bronchodilator treatments while in the emergency department are more likely to relapse within 14 days of initial presentation. Unfortunately, none of the predictive models perform well enough to justify their uniform use in clinical practice [2.1.1].

Prediction of 6-Month Mortality

The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) found a 180-day mortality rate of 33% in its cohort. Significant predictors of 180-day mortality were worse Acute Physiology and Chronic Health Evaluation (APACHE) III score, lower body mass index, older age, worse functional status 2 weeks before admission, lower ratio of P_{O_2} to fraction of inspired oxygen, history of congestive heart failure, lower serum albumin level, and presence of cor pulmonale. Other studies reported similar associations. Although these studies suggest that certain physiologic characteristics are associated with a higher likelihood of inpatient mortality, we conclude that there is currently no reliable method for identifying patients at high risk (>90%) for inpatient or 6-month mortality. Therefore, these measures should not influence decisions about instituting, continuing, or withdrawing life-sustaining therapies but should prompt a discussion regarding patient preferences for end-of-life care [2.1.2].

Diagnostic Testing: Chest Radiography and Spirometry

Three observational studies showed substantial rates of abnormalities in chest radiography among patients admitted for acute exacerbation of COPD. In one prospective study, which included patients with asthma, chest radiography results prompted change in management in 23.5% of patients, mostly because of new infiltrates. Observational studies showed that spirometric assessment at presentation or during treatment is not useful in judging severity or guiding management of patients with acute exacerbations of COPD. When measured at the time of an exacerbation, FEV_1 showed no significant correlation with P_{O_2} and only a weak (although statistically significant) correlation with P_{CO_2}. Peak expiratory flow rate is often used in the clinic to approximate FEV_1. One study found a correlation between peak expiratory flow rate and FEV_1. The clinical implication of this finding is not clear, however, because FEV_1 is a poor predictor. Despite this fact, many studies use changes in FEV_1 as the primary outcome rather than other, more clinically pertinent measures (such as degree of dyspnea or sputum production and quality), probably because the latter are much more difficult to quantify and evaluate [2.2.2, 2.2.3].

Therapeutic Interventions

Bronchodilators

Fourteen randomized trials show that inhaled short-acting β_2 agonists, such as albuterol, and anticholinergic bronchodilators, such as ipratropium, are equally efficacious in patients with acute exacerbations of COPD. They are also superior to all parenterally administered bronchodilators, including methylxanthines and sympathomimetic agents. Furthermore, some patients may experience additional benefit when a second inhaled bronchodilating agent is administered after the maximal dose of the initial agent is reached. Several studies examined patients receiving a short-acting β_2 agonist plus an anticholinergic bronchodilator. In general, patients in these studies had marginally shorter lengths of stay and proportionally larger increases in FEV_1, but hospital admission rates were similar to those of patients receiving one bronchodilator. Since anticholinergic bronchodilators are associated with fewer and milder side effects, it is advisable to start with them and then add a short-acting β_2 agonist. Studies are equivocal on the addition of a methylxanthine, such as aminophylline, to inhaled bronchodilators. More important, the potentially serious side effects of the methylxanthines make their use more problematic. In addition, some evidence shows that the efficacy of wet nebulization and dry aerosol delivery systems (metered-dose inhaler plus a spacer) are clinically equivalent. Therefore, the choice of a specific delivery method should be determined on an individual basis, depending on each patient's ability to use the different methods (3) [2.3.1].

Corticosteroids

Six randomized, placebo-controlled trials showed that for patients hospitalized with acute exacerbation of COPD, systemic corticosteroids given for up to 2 weeks are helpful. Dosage, length of treatment, administration, and setting varied greatly among the studies evaluated. In the largest trial (Systemic Corticosteroids in Chronic Obstructive Pulmonary Disease Exacerbations), patients received a 2-week or 8-week course. The 2-week course consisted of 3 days of intravenous methylprednisolone, 125 mg every 6 hours, followed by oral prednisone for 2 weeks (60 mg/d on days 4 to 7, 40 mg/d on days 8 to 11, and 20 mg/d on days 12 to 15). Outcome did significantly differ between the 2-week and 8-week courses. A statistically significant difference in FEV_1 was seen between the glucocorticoid group and the placebo group for the first 3 days of treatment; however, the difference was no longer significant after 2 weeks. The most common adverse effect associated with systemic corticosteroids was hyperglycemia; two thirds of cases occurred in patients with known diabetes mellitus. There is no evidence to show whether hyperglycemia is more severe in longer courses of treatment. Inhaled steroids are not appropriate in the treatment of acute exacerbation of COPD [2.3.2].

Antibiotics

Eleven randomized, placebo-controlled trials have shown that antibiotic treatment is beneficial in selected patients with acute exacerbation of COPD. In particular, the studies showed that patients with more severe exacerbations (type 1) are more likely to experience benefit than those whose exacerbations are less severe. Severity was assessed by using clinical judgment or the criteria developed by Anthonisen and colleagues (2). Typical administration periods ranged from 3 to 14 days, and tetracycline, amoxicillin, and trimethoprim–sulfamethoxazole were the most common antibiotics. Although most of these randomized, placebo-controlled trials were done before the emergence of multidrug-resistant organisms, they show only a minimal benefit with antibiotic treatment in the more severe exacerbations. On the basis of these data and the emergence over time of more resistant organisms, particularly *Streptococcus pneumoniae*, it has become common practice to use more broad-spectrum antibiotics in acute exacerbations of COPD. To date, however, no randomized, placebo-controlled trials have proved the superiority of the newer broad-spectrum antibiotics in such cases [2.3.3].

Oxygen Therapy

Ample evidence shows that oxygen therapy provides important benefits to inpatients with acute exacerbations of COPD and hypoxemia. The major concern with the administration of this therapy is the risk for resultant hypercarbia and respiratory failure. In three observational studies, most patients with acute exacerbations of COPD developed hypercarbia after oxygen administration (FiO_2 ranged from 24% to 28%). These studies seem to suggest that the relationship between pH and Po_2 at presentation is a good predictor of the risk for hypercarbia and subsequent failure. This relation was

translated into a discriminant function for predicting respiratory failure, which is shown in the Figure in the accompanying background paper. Although this model is not widely used, it underscores the fact that patients who present with altered gas exchange are at greatest risk for respiratory failure [2.3.4].

Mucolytic Agents and Mucus Clearance Strategies

Five randomized trials failed to show that mucolytic agents shorten disease course or improve patient outcomes. Three randomized trials showed that mechanical percussion of the chest as applied by a physical or respiratory therapist is ineffective (that is, does not increase FEV_1) in patients with acute exacerbations of COPD. In fact, one study showed a decrease in FEV_1 after physical therapy [2.3.5.1, 2.3.5.2].

Noninvasive Positive-Pressure Ventilation

Noninvasive positive-pressure ventilation is frequently used in the inpatient management of patients with acute exacerbations of COPD. It not only improves ventilation and decreases PCO_2 levels but, in many instances, is also a means of avoiding intubation. In five randomized, controlled trials and five observational studies, NPPV was a beneficial support strategy and decreased the likelihood of respiratory failure requiring invasive mechanical ventilation. Some data show that NPPV might improve survival of patients with acute exacerbations of COPD. These conclusions, however, are weakened by issues of study design, such as unclear selection criteria for patients receiving therapy, and the uncertain number of patients who were screened but excluded from the trials. Further studies are needed to provide information on which patients would benefit most from this intervention [2.4].

RECOMMENDATIONS

Recommendation 1. An admission chest radiography may be useful since it has been shown that up to 23% of patients admitted had changes in management related to findings on chest radiography. Chest radiography in patients visiting the emergency department may also useful. To date, there is no evidence for or against the utility of chest radiography in the office setting.

Recommendation 2. For patients hospitalized with an acute exacerbation of COPD, acute spirometry should not be used to diagnose an exacerbation or to assess its severity.

Recommendation 3. Inhaled anticholinergic bronchodilators or inhaled short-acting β_2 agonists are beneficial in the treatment of patients presenting to the hospital with acute exacerbation of COPD. Since the inhaled anticholinergic bronchodilators have fewer and more benign side effects, consider these agents first. Only after the initial bronchodilator is at maximum dose is the addition of a second inhaled bronchodilator beneficial.

Recommendation 4. In the treatment of patients presenting to the hospital with moderate or severe acute exacerbation of COPD, the following therapeutic options are beneficial: a) systemic corticosteroids given for up to 2 weeks in patients who are not receiving long-term therapy with oral steroids, b) NPPV administered under the supervision of a trained physician, and c) oxygen, with caution, in hypoxemic patients.

Recommendation 5. In patients with severe exacerbations of COPD, initial narrow-spectrum antibiotics are reasonable first-line agents. The superiority of newer, more broad-spectrum antibiotics has not been established.

Randomized, placebo-controlled trials favored amoxicillin, trimethoprim–sulfamethoxazole, and tetracycline. Most of these studies were done before the emergence of multidrug-resistant organisms, particularly *S. pneumoniae.* To date, however, no randomized, placebo-controlled trials have proved the superiority of newer broad-spectrum antibiotics in acute exacerbations of COPD. The trials also did not include nursing home residents or recently hospitalized patients.

Recommendation 6. In the treatment of patients with acute exacerbation of COPD, the following therapeutic options are not beneficial: mucolytic medications, chest physiotherapy, and methylxanthine bronchodilators. The latter two options may be harmful.

Recommendation 7. Currently, there are no reliable methods of risk stratification for relapse or inpatient mortality.

Recommendation 8. Future research should include efforts to develop a reproducible, transportable definition of "acute exacerbation" in order to provide more consistent and transparent inclusion and exclusion criteria for clinical trials studying this entity. There is a great need, in this age of antibiotic-resistant organisms, for randomized, placebo-controlled trials of the newer broad-spectrum antibiotics. More in-depth research on therapeutics and management

would greatly benefit patients with COPD, as would the recognition that nonphysiologic outcomes, such as symptoms, quality of life, and the interval before subsequent relapse, are all clinically important.

Appendix

The following people participated in the development of these guidelines.

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Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP–ASIM clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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References

1. Management of acute exacerbations of chronic obstructive pulmonary disease. Evidence Report/Technology Assessment # 19. Agency for Healthcare Research and Quality. AHRQ publication no. 00-E020. Available at: www.ahrq.gov/clinic/copdsum.htm.

2. **Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA.** Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med. 1987;106:196-204. [PMID: 0003492164]

3. **Turner MO, Patel A, Ginsburg S, FitzGerald JM.** Bronchodilator delivery in acute airflow obstruction. A meta-analysis. Arch Intern Med. 1997;157:1736-44. [PMID: 0009250235]