

Managing Acute Exacerbations of Chronic Obstructive Pulmonary Disease

a report by

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The Impact of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is complicated by recurrent acute exacerbations. These exacerbations are associated with poor quality of life, an accelerated decline in lung function, and significant mortality. Patients with an acute exacerbation of COPD (AECOPD) comprise a heterogeneous population and vary widely in their clinical course. The definition of an AECOPD is an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum beyond normal day-to-day variability sufficient to warrant a change in management.¹

Nationally AECOPD was responsible for over 725,000 hospitalizations and 1.5 million emergency department visits in 2000.^{2,3} Inpatient care for AECOPD is responsible for the majority of the \$37 billion total expenditure for COPD.^{3,4} Quality of life questionnaires offer complementary information to lung function and respiratory symptoms, which helps monitor the course of recovery following an exacerbation. Episodes of AECOPD negatively affect quality of life of patients with COPD for over six months after the acute event.^{5,6} Patients who suffer more frequent exacerbations have significantly worse quality of life scores than those with less frequent exacerbations.^{7,8} In addition to poorer quality of life, patients with recurrent AECOPD (particularly those who continue smoking tobacco) have an increased rate of decline of lung function over time (i.e. significant long-term adverse effects on lung function).⁹ Finally, mortality rates for patients with AECOPD are high (up to 22%), especially for those with frequent exacerbations and those requiring hospitalization.^{10,11} One study enrolled patients with acute hypercapnic respiratory failure due to severe AECOPD and reported an in-hospital mortality rate of 11%, a 180-day mortality rate of 33%, and a two-year mortality rate of 49%.⁵ The predictors of mortality include acute physiology and chronic health evaluation (APACHE III) score, body mass index (BMI), age, functional status two weeks prior to admission,

lower ratio of partial pressure (tension) of oxygen to fraction of inspired oxygen (PO_2 to FiO_2 ratio), congestive heart failure, serum albumin level, cor pulmonale, lower activities of daily living scores, and lower scores on the Duke Activity Status Index.⁵ Mortality rates may be significantly higher for people aged over 65 years, and in one study reached 59% at one year following an AECOPD episode that required treatment in the intensive care unit.¹² AECOPD is clearly associated with high cost, morbidity, and mortality, and place an enormous burden on patients and the healthcare system.

Management Strategies

There are several treatment methods that should always be applied to patients with AECOPD.

- Short-acting bronchodilators should be administered for acute symptoms of dyspnea in patients with AECOPD.
- Patients with symptoms of AECOPD who present to the emergency department or hospital should undergo chest radiography.^{13,14} This does not mean that a chest radiograph should not be obtained in patients who present to your clinic; however, data are not clear regarding the utility of obtaining radiographs in this setting. Chest radiography may be helpful in an outpatient clinic setting if the patient appears ill or has fever, pleuritic chest pain, or crackles or egophony on lung exam (suggesting possible pneumonia).
- Systemic corticosteroids (e.g. prednisone) should be prescribed for patients with moderate to severe episodes of AECOPD.^{13,14} The optimal dose and duration of therapy have not been clearly defined because most of the trials in this area have been performed in hospitalized patients. However, a randomized controlled trial (RCT) of outpatients with AECOPD demonstrated improved outcomes for patients treated with 40mg of prednisone for 10 days.¹⁵ We know that a prolonged treatment period (eight weeks) of systemic steroids is as effective as a two-week treatment period, but the longer course is associated with significantly more side effects.¹⁶ Therefore, many experts recommend prescribing relatively low doses of prednisone (30–40mg) for seven to 14 days.¹⁷
- Oxygen should be administered to hypoxic patients. For most patients, an oxygen saturation goal of 90% or greater is appropriate (although >95% saturation is recommended for patients with underlying ischemic heart disease). However, a patient who has chronic hypercapnia with an elevated serum bicarbonate should receive just enough oxygen to raise oxygen saturation to between 88 and 92%. Administering high levels of oxygen (which raise the oxygen saturations near to 100%) to patients with hypercapnia may cause or worsen the respiratory acidosis, resulting in a reduced pH and markedly increased arterial carbon dioxide pressure

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(PaCO₂). However, despite this risk, oxygen must be administered to patients who are hypoxemic (saturations <88%), even if respiratory acidosis occurs. In other words, the oxygen must not be taken away if respiratory acidosis develops/worsens. However, other interventions, such as the non-invasive ventilation method bilevel positive airway pressure (BiPAP) or mechanical ventilation, must be added to the oxygen to reverse the respiratory acidosis.

- Patients with progressive respiratory acidosis, impending respiratory failure, or markedly increased difficulty breathing due to AECOPD benefit from BiPAP. There have been several RCTs and multiple uncontrolled trials that have shown that BiPAP reduces intubation rates, lowers the occurrence of nosocomial infections, and improves mortality in approximately 80–85% of patients with AECOPD.^{13,14,18} However, BiPAP should not be used in patients with respiratory failure associated with severe multilobar pneumonia, acute respiratory distress syndrome, or sepsis, because these patient populations have higher mortality if invasive mechanical ventilation is postponed. However, BiPAP reduces mortality and is an excellent option for patients with respiratory failure associated with AECOPD (with or without concomitant congestive heart failure).¹⁸

A few management strategies are not helpful in patients with AECOPD.

- Measuring peak expiratory flow rates (PEFRs) and/or spirometry acutely in patients with AECOPD is not indicated and is not helpful in assessing the severity of these exacerbations or the response to therapy.^{13,14} In contrast, these measurements are critical and very important in patients with acute exacerbations of asthma.
- Mucolytics such as N-acetylcysteine (Mucomyst) are not beneficial in patients with AECOPD and may be associated with bronchospasm.^{13,14}
- Chest physiotherapy (percussion and postural drainage) has no role in patients with AECOPD unless they have documented areas of atelectasis on chest radiograph.^{13,14}

Controversial Management Strategies for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Antibiotics

Bacterial infections can be identified in approximately 50% of patients with AECOPD.¹⁹ Other factors, such as pollutants, viruses, allergens, atypical infections, and other noxious stimuli, also contribute to episodes of AECOPD. Some episodes of AECOPD will resolve spontaneously and do not require treatment with antibiotics.¹⁹ Therefore, one of the major questions in the treatment of patients with AECOPD is: 'Who should be treated with antibiotics?' Unfortunately, the literature does not provide a definitive answer to this question. However, the evidence generally supports the use of antibiotics in patients with two or three symptoms of AECOPD (increased shortness of breath, increased sputum production, and/or sputum purulence).^{13,14,20} Due to the paucity of evidence-based data in this area, most of the recommendations regarding the use of antibiotics are based on expert opinion.^{1,21,22} The Global Initiative for Obstructive Lung Disease (GOLD) and the American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines recommend antibiotic choices on the basis of local sensitivity patterns of the most common pathogens associated with this condition.^{1,23} The most common bacterial 'core' organisms associated with AECOPD include *Streptococcus pneumoniae*,

Haemophilus influenzae, and *Moraxella catarrhalis*. However, some data suggest that patients with severe and very severe COPD have a higher risk for infections with Gram-negative organisms (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Stenotrophomonas*, etc.).^{24,25}

One potential benefit of antibiotic therapy for patients with AECOPD is that antibiotics can reduce the burden of bacteria in the airways.^{26–30} Most of the antibiotic trials in AECOPD were designed to compare a new antibiotic with an established compound for the purpose of new product registration and licensing. Equivalence is the desired outcome of such trials and, therefore, the agent chosen for comparison is not considered important. In addition, these trials frequently include patients with poorly defined disease severity (often without any obstructive lung disease) and acute illness of minor severity. One known factor is that relapses (treatment failures requiring a return visit or hospitalization within 14–28 days of index visit) occur in up to 26% of patients and are associated with high morbidity.^{7,31–36} Patients who fail their initial outpatient therapy use the largest percentage of total resources spent on COPD, especially when they subsequently require hospitalization.^{32,33,37,38} Although definitive data are lacking, some studies suggest that appropriate antibiotic selection is important in patients with AECOPD, particularly with widespread reports of increasing antimicrobial resistance to the common pathogens isolating this population. Two retrospective studies evaluating specific antibiotic choices in outpatients with AECOPD demonstrated that antibiotics such as amoxicillin,^{31,39} trimethoprim-sulfamethoxazole,³⁹ and erythromycin³⁹ were associated with higher relapse rates and worse outcomes compared with other antibiotics. One prospective RCT demonstrated that patients who received moxifloxacin had a significantly lower failure rate compared with those taking a macrolide or amoxicillin/clavulanic acid.⁴⁰ These studies suggest that the specific antibiotic choice may be important for some patients with AECOPD.

Risk Stratification

As relapse after initial therapy for AECOPD may lead to prolonged disability, an emergency visit, or even an admission to the hospital, it is important to identify patients most at risk for relapse. Wilson and colleagues found that differences observed in outcomes of antibiotic treatment could be confounded by factors related to medical history, severity of disease, and use of concomitant medications such as bronchodilators.⁴¹ There are many approaches to managing patients with AECOPD, but it is important to note that the available recommendations are largely based on expert opinion and have not been prospectively evaluated in clinical trials.^{1,21,22,42} An important first step in managing patients with AECOPD is to identify those who require hospitalization. The ATS/ERS guidelines recommend that patients with the following criteria should be hospitalized:

- presence of high-risk comorbid conditions, including pneumonia, cardiac arrhythmia, congestive heart failure, diabetes mellitus, and renal or liver failure;
- inadequate response of symptoms to outpatient management;
- marked increase in dyspnea;
- inability to eat or sleep due to symptoms;
- worsening hypoxemia;
- worsening hypercapnia;
- changes in mental status;
- inability of the patient to care for her/himself (lack of home support);

- uncertain diagnosis; or
- inadequate home care.¹

Among the risk factors for relapse, severity of the underlying disease is one of the most important. In addition to severe airflow obstruction, older age, frequent exacerbations, increased number of unscheduled/emergency visits within the prior year, chronic prednisone therapy, cardiopulmonary comorbidity, hypoxemia, and the presence of hypercapnia are all risk factors leading to poor outcomes.^{31,36,40,43-47} One proposed approach to managing patients with AECOPD is based on utilizing certain clinical criteria to risk-stratify patients.^{21,22,42} Group 1 includes previously healthy patients without significant underlying lung disease—who present with acute respiratory symptoms—demonstrating near-normal forced expiratory volume in one second (FEV₁). These patients most likely have a post-viral tracheobronchitis and usually do not require treatment with any antibiotics. One study in the Group 1 patient population evaluated azithromycin versus vitamin C and demonstrated no differences in time to return to normal activities or health-related quality of life.⁴⁸ Therefore, antibiotics are not indicated for patients stratified to Group 1.^{21,22,42} Patients in Group 2 comprise the majority of patients seen by primary care providers (>70% of patients who present with AECOPD) and include those with fewer than four episodes of AECOPD within the previous year, no significant cardiovascular comorbidities, and a predicted FEV₁ ≥50%. These patients most likely have one of the ‘core’ organisms and may be treated with one of the newer macrolides (azithromycin or clarithromycin), a newer cephalosporin, or doxycycline.^{21,22,42} Patients in Groups 3 and 4 include those with four or more exacerbations within the previous year, predicted FEV₁ <50%, or the presence of one of the significant cardiac comorbidities (congestive heart failure or ischemic heart disease). These patients are at higher risk for relapse and, therefore, treatment with either amoxicillin-clavulanate or a fluoroquinolone may be considered.^{21,22,42} Although this

management strategy is reasonable, it has not been prospectively evaluated in clinical trials.

Prevention

Finally, because episodes of AECOPD are associated with such high morbidity and mortality, significant attention should be focused on preventing exacerbations. The two most important preventive measures are smoking cessation and active immunizations, including influenza and pneumococcal vaccinations.⁴⁹⁻⁵² In addition to smoking cessation and vaccinations, clinical studies have demonstrated that chronic maintenance therapy in patients with COPD can significantly decrease the frequency of exacerbations. A recent meta-analysis demonstrated reductions of episodes of AECOPD by 21% for patients treated with a long-acting beta-2 agonist (formoterol or salmeterol), by 23–26% for those treated with a long-acting anticholinergic agent (tiotropium), by 24% for those treated with an inhaled corticosteroid (budesonide, beclomethasone, fluticasone, or triamcinolone), and by 20–30% for patients treated with a combination agent (budesonide/formoterol or fluticasone/salmeterol).^{53,54} Despite the evidence of the use of long-acting inhaled medications being associated with reductions of episodes of AECOPD, the US Food and Drug Administration (FDA) has not approved any inhaled medication for this indication.

Summary

AECOPD are important events in the natural history of the disease and are associated with high cost, morbidity, and mortality. Patients with frequent exacerbations often experience impaired quality of life and faster decline of lung function over time. Acute exacerbations, particularly those requiring hospitalization, are responsible for the largest proportion of direct costs expended for COPD management. Therefore, aggressively managing AECOPD and implementing measures to prevent future episodes are crucial for improving outcomes in these patients. ■

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