

SPECIAL CONTRIBUTIONS

Research Opportunities in the Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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Abstract

Acute exacerbations of chronic obstructive pulmonary disease are a common problem in the emergency department. Despite considerable research involving the management of this disease over the past decade, much remains unclear from an emergency medicine perspective. Increased research would better guide the management of these complex patients from the perspectives of the patient, the caregiver, and society. The major areas of research can be divided into diagnosis, therapy, and education. The reliability and validity of different definitions of acute exacerbations of chronic obstructive pulmonary disease need to be assessed. The utility and performance characteristics of diagnostic testing need to be determined for this difficult

patient population. Specific diagnostic tests include measures of dyspnea, spirometry and exercise tolerance, measures of gas exchange, airway inflammation, and chest imaging. It remains unclear which patient-specific therapies (oxygen, bronchodilators, corticosteroids, antibiotics, non-invasive positive pressure ventilation, and methylxanthines) should be used and monitored. Finally, the utility of education of both health care providers and patients and how it may be applied to the acute setting need to be addressed. **Key words:** chronic obstructive pulmonary disease; acute exacerbation; emergency department. *ACADEMIC EMERGENCY MEDICINE* 2005; 12:742-750.

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) continues to be a serious problem, according to data from the National Hospital Ambulatory Medical Care Survey.¹ In 1992, there were 1.1 million emergency department (ED) visits with chronic obstructive pulmonary disease (COPD) listed

as the primary diagnosis. The absolute numbers of patients with COPD, as well as the morbidity and mortality, have been steadily increasing and are projected to continue to increase for the foreseeable future.²⁻⁴

In June 2002, a group of emergency physicians and researchers with a special interest in respiratory emergencies met to discuss the optimal management of patients presenting to the ED with AECOPD. The meeting was chaired by Dr. Carlos A. Camargo Jr., principal investigator of the Emergency Medicine Network, a research collaboration with more than 160 participating hospitals (<http://www.emnet-usa.org>). The meeting was supported through an unrestricted educational grant from Boehringer-Ingelheim (Ridgefield, CT). The primary goals of the meeting were to 1) discuss current guidelines for the management of AECOPD and how they might apply to the ED setting and 2) identify areas where insufficient research currently exists. The evidence base for acute care was believed to be inadequate, and there was agreement to continue discussion via conference calls and e-mail. The continued paucity of emergency medicine research on AECOPD provided the motivation for the authors to review the literature again and identify opportunities in the management of AECOPD. This report is a summary of those research opportunities (see Table 1).

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TABLE 1. Summary of Research Opportunities in Acute Exacerbation of COPD

Diagnosis
Definition of COPD exacerbation
Differential diagnosis (vs. comorbidity)
Diagnostic testing
Dyspnea
Spirometry
Exercise tolerance
Gas exchange
Airway inflammation
Chest imaging
Therapy
Oxygen
Bronchodilators
Corticosteroids
Antibiotics
Noninvasive positive pressure ventilation
Methylxanthines
Education
Treatment
Prevention
Special considerations
Gender differences
Comorbid conditions

DIAGNOSIS

The definitions of AECOPD, as used by researchers and by general emergency medicine providers, have not been adequately assessed in terms of their reliability and validity and remain controversial.⁵ The Anthonisen criteria are widely recognized as one method to grade exacerbations and are based on subjective patient complaints about increased dyspnea, sputum, and/or sputum purulence (sputum thickness and color).⁶ Type 1 AECOPD is defined as having all three of these key symptoms, type 2 has any two of the symptoms, and type 3 has any one of the symptoms. These criteria have been used to predict outcome when antibiotic therapy is provided during acute exacerbations,⁶ but their role in other aspects of AECOPD management is not clear. Gompertz et al. defined AECOPD as “any combination of worsening respiratory symptoms including one or more of: increased sputum volume, purulence or breathlessness, with or without other minor symptoms, including increased sputum viscosity, cough, wheeze, chest pain, malaise, fever or rigors.”⁷ In addition to difficulties with diagnosing an acute exacerbation, just defining COPD using clinical and/or spirometric criteria is somewhat controversial and problematic.^{8–10}

Difficulty also exists regarding the differentiation of AECOPD from other acute illnesses. Recent research on the use of B-type natriuretic peptide assays to differentiate congestive heart failure from AECOPD is promising; however, this approach is costly and remains controversial.^{11,12} An excellent review of this complex topic was recently published.¹³ Differentiat-

ing AECOPD from other diseases, such as pulmonary embolism and community-acquired pneumonia, is less well studied.

There is also considerable heterogeneity in the etiology of acute exacerbations that may need to be considered when reviewing studies of AECOPD. Bacteria, viruses, and air quality parameters interact with various host factors to lead to an acute exacerbation.¹⁴ All of these are potentially confounding variables when interpreting and performing research on AECOPD diagnostic testing, therapy, and education.

DIAGNOSTIC TESTING

Measures of dyspnea, spirometry, exercise tolerance, gas exchange, airway inflammation, and chest imaging are areas of diagnostic testing that require further research in the acute care setting. Concerning all diagnostic tests, it is unknown 1) if they can be performed and interpreted reliably, 2) if they are clinically relevant in terms of diagnosis of disease or in terms of predicting short-term adverse events, and 3) how physicians incorporate the results of these tests into clinical decision making, which would affect their overall utility.

Measures of Dyspnea. Dyspnea, a major component of AECOPD, is frequently measured using an ordinal Borg score or a continuous 10-cm visual analog scale, although other multidimensional scales exist.¹⁵ These scales have been primarily used in healthy subjects and those with stable COPD undergoing exercise testing. In these populations, they have been shown to have good test characteristics.^{16–22}

Dyspnea correlates somewhat with pulmonary function but is distinct from it.¹⁵ While dyspnea correlates with long-term survival in patients with stable COPD, dyspnea can improve without an improvement in spirometry.²³ Recent research on blunted perception of dyspnea may explain the poor correlation between dyspnea and pulmonary function testing.²⁴

Questions that remain unanswered include the following. What is the reliability and validity of different dyspnea scales when used to assess acute exacerbations? Which scales perform better: serial scales that measure static dyspnea or those that measure change in dyspnea? Is blunted perception of dyspnea prevalent in this population? Is dyspnea an independent predictor of poor outcome?

Spirometry and Exercise Tolerance. Spirometry has long been considered the criterion standard for assessment of the severity of COPD.⁸ However, obtaining adequate and reproducible measures in patients with obstructive airway disease is difficult, especially those patients experiencing an exacerbation.^{25,26} The utility of spirometry in assessing patient outcomes has

recently been called into question. In an outpatient rehabilitation setting, improvement in 6-minute walking distance, maximal exercise performance, peripheral and respiratory muscle strength, and quality of life were not associated with improvement in forced expiration volume in one second (FEV₁).²⁷ These outcomes, however, have little application in the emergency setting.

Spirometric measures other than FEV₁ may perform better. For example, peak expiratory flow and slow vital capacity have been shown to correlate with survival and symptom improvement, respectively.^{28–30} The plateau-phase slope of the exhaled capnogram has also been suggested as a noninvasive and continuous measure of airway obstruction but has not been assessed for reliability or validity.^{31–33} Additionally, research results have been mixed as to whether peak expiratory flow can be used to differentiate between acute exacerbations of congestive heart failure and COPD.^{34,35}

While spirometry is generally accepted as the criterion standard for diagnosing COPD, there is little evidence of its utility as a measure during an exacerbation. Indeed, recent literature suggests that patients may improve in terms of dyspnea with no significant improvement in FEV₁.²³ End-expiratory lung volume, inspiratory capacity, and negative expiratory pressure measurements during tidal breathing to detect tidal airflow limitation have been suggested as better measures of respiratory function.³⁶ While end-expiratory lung volume and negative expiratory pressure correlate well with degree of breathlessness, only inspiratory capacity showed greater change with treatment than FEV₁. O'Donnell et al. found that inspiratory capacity, and not FEV₁ or peak expiratory flow, was the only measure that correlated with a change in the Borg Dyspnea Index measured after exercise, before and after administration of ipratropium bromide.³⁷ Measures such as the noninvasive pressure-time index may provide unique information concerning respiratory load and inspiratory muscle force.³⁸

Exercise testing, such as the 6-minute walk test, is recommended by the American Thoracic Society but has not been studied in the ED setting.³⁹ This test, or a modification of it, potentially could be used to replace informal “walk tests” used by ED practitioners to assess if the patient is safe for discharge. Indeed, the utility of the informal “walk test” has not been studied. Clearly, more evidence is needed for the assessment of these measurements in the acute setting.

Multidimensional scales, such as the BODE index, predict mortality better than single-dimensional scores.⁴⁰ The BODE index combines body mass index, airflow obstruction, dyspnea, and exercise capacity. Unfortunately, it has been validated only in stable COPD patients. Other composite measures may need to be constructed for AECOPD.

Questions that remain unanswered include the following. Which of the above measures best predict short-term adverse outcomes? How do the different measures perform in patients with acute exacerbations? Do these measures provide unique clinically useful information to guide treatment decisions?

Measures of Gas Exchange. Current guidelines recommend that arterial blood gases be drawn in patients with AECOPD.^{41–43} However, arterial blood gases is not the only way to get information on gas exchange; oxygenation and ventilation can be assessed by pulse oximetry and venous pCO₂.⁴⁴ In addition, noninvasive capnography may potentially be used as a surrogate for assessing for changes in ventilation; this has not been adequately studied in this population.^{45–47} Questions that remain unanswered include the following. What is the role of capnography in diagnosing and monitoring AECOPD? Should hypercarbia change management for patients who appear clinically stable?

Measures of Airway Inflammation. The degree to which inflammation plays a role in AECOPD is unclear. Exhaled nitric oxide measurements have been shown to differentiate asthmatic subjects from healthy subjects.⁴⁸ However, patients with frequent exacerbations of COPD were compared with those with infrequent exacerbations on a variety of inflammatory mediators and no difference was found.⁷ Additionally, exhaled NO but not H₂O₂ from breath condensation has been shown to improve after treating COPD patients with corticosteroids.⁴⁹ Factor analysis suggests that airway inflammation and spirometry are independent factors in the pathophysiology of COPD.⁵⁰ The use of exhaled NO as well as sputum markers of inflammation are currently restricted to specialized research sites.^{51–54} However, with advancements in the technical aspects of their collection and analysis, they may eventually be useful bedside tools to aid clinicians in management decisions.

Chest Imaging. Chest imaging studies are often ordered during the assessment of patients with AECOPD. For example, in a recent study of 572 ED patients with wheezing who were 55 years of age and older, 81% received at least a chest radiograph, and only 24% of these were normal.⁵⁵ Imaging options include simple chest radiography, ventilation/perfusion scanning, computed tomography, and magnetic resonance imaging. These imaging studies are performed to evaluate the patient for acute illness (e.g., heart failure, pneumonia, pulmonary embolism, pneumothorax) either alone or in combination with AECOPD. Despite its importance, research data on imaging for AECOPD are sparse. Retrospective studies have suggested that a new infiltrate or findings suggestive of heart failure are the most common

findings on simple chest radiographs that may change management^{56,57}; however, some researchers have speculated that an infiltrate on the chest radiograph, by itself, should not alter the choice of antibiotics.^{58,59} Issues that should be addressed in this area include the following. Do all patients with AECOPD benefit from imaging studies regardless of their response to ED treatment or their need for hospitalization? Can factors of the medical history and physical examination predict radiographic findings that may change management?

THERAPY

The usefulness of all of the major treatment options for AECOPD (e.g., oxygen, bronchodilators, corticosteroids, antibiotics, noninvasive ventilation) requires further research. Moreover, information is almost completely lacking on COPD-related out-of-hospital care and on the implementation of ED-based guidelines for the management of AECOPD.

Oxygen. Oxygen is routinely administered in the treatment of patients with AECOPD. Current treatment recommendations suggest careful titration of low-dose oxygen to avoid respiratory drive suppression.⁶⁰ Mortality and quality-of-life measures have been evaluated only for long-term oxygen supplementation for hypoxic patients.^{61–63} The prevalence and significance of hypercarbia are controversial, and little is known of the benefits and risks associated with oxygen therapy.^{64–66} Two small studies suggest that the risk of developing clinically significant hypercarbia should not deter the use of oxygen during AECOPD.^{67,68} Questions that remain unanswered include the following. What oxygen saturation level provides the optimum risk-to-benefit ratio in patients with AECOPD? How should response to oxygen therapy be monitored? Can oxygen therapy-related hypercarbia be monitored clinically?

Heliox would potentially be beneficial in AECOPD because it has a significantly lower density than air; however, it also has a slightly higher viscosity. These properties affect the amount of force required to move laminar and turbulent gas flow. Unfortunately, heliox studies have generally been of poor methodological quality.^{69,70} Questions that remain include the following. Does heliox decrease adverse outcomes? In which subpopulations should it be used?

Bronchodilators. The options available to emergency physicians for the treatment of bronchospasm in AECOPD are beta-agonists, anticholinergics, or a combination of these two agents. Unfortunately, few studies of these agents have been performed on patients with AECOPD, and the studies that do explore this issue have many limitations.^{71,72} There is no clear benefit to anticholinergics combined with beta-agonists;

however, anticholinergics are believed to be a first-line agent in the treatment of AECOPD because of the possible deleterious effects of beta-agonists in elders.^{72,73} This remains controversial, and side effect profiles for these agents are largely unknown for patients with AECOPD. Questions that remain include the following. How much and how frequently should bronchodilator agents be given? How should response to treatment be measured? How should newer, longer-acting beta-agonists and anticholinergics be used in the ED and after discharge?

Systemic Corticosteroids. Most current recommendations suggest that patients with severe disease receive systemic corticosteroids while in the ED and during hospitalization.^{41–43} The evidence supporting these recommendations is based on ten randomized controlled trials summarized in a systematic review.⁷⁴ Systemic corticosteroids have been shown to improve FEV₁ over the first 72 hours of AECOPD but at a cost of increased side effects, including potentially life-threatening infections, impaired diabetic control, and other typical corticosteroid side effects. Improvement in spirometry after 72 hours or improvement in other outcome measures is less clear.^{74,75} Questions that remain include the following. What role should inhaled corticosteroids, or systemic corticosteroids other than methylprednisolone, play in the treatment of patients with AECOPD? For patients being discharged home from the ED, do the benefits of oral prednisone outweigh its potential side effects when used in conjunction with antibiotics and inhaled bronchodilators?^{74,76} Is the risk–benefit ratio more favorable for specific subgroups, such as those whose COPD is exacerbated by specific inflammatory mediators?

Recent studies have suggested that inflammatory mediator antagonists and anti-inflammatory agents other than corticosteroids may be necessary to adequately inhibit neutrophilic inflammation and the inhibitory effects of cigarette smoking on corticosteroids. Target molecules for these agents would include leukotriene B₄, chemokines, tumor necrosis factor α , inducible NO synthase, phosphodiesterase 4, nuclear factor κ B inhibitors, adhesion molecules, interleukin 10, mitogen-activated protein kinase, and phosphoinositide-3 kinase.⁷⁷ The utility of these novel drugs in AECOPD (or even stable COPD) is currently unknown.

Antibiotics. Antibiotics have been shown to have a small but statistically significant beneficial effect in the treatment of patients with AECOPD.⁷⁸ Additionally, the benefit of antibiotics may be greatest in sicker patients with dyspnea and increased sputum or those with a change in sputum purulence, but the evidence for this assertion is limited.^{6,78} The evidence supporting antibiotics is based on older trials using agents such as amoxicillin, trimethoprim-sulfamethoxazole,

and tetracycline. Nonrandomized controlled trial evidence, however, suggests that macrolides and fluoroquinolones may be appropriate treatments, particularly for those patients with recent antibiotic use, frequent corticosteroid use, and lack of response to therapy. There are a number of important questions with regard to antibiotic use in AECOPD that need to be answered for emergency physicians. For example, should antibiotics only be given to a particular subset of patients? How long should patients be treated with antibiotics? What is the effectiveness of the newer macrolides and fluoroquinolones compared with first-line agents? Should antibiotic selection be based on radiographic evidence of pneumonia, severity of illness, or other factors?

Noninvasive Positive Pressure Ventilation. Noninvasive positive pressure ventilation (NPPV) should be used as the first-line intervention, coupled with usual medical care, in all AECOPD patients with respiratory failure without a contraindication to NPPV. Studies have demonstrated that NPPV is a nonpharmacologic means of avoiding endotracheal intubation and reducing mortality in patients with severe AECOPD.^{79,80} In these studies, severe exacerbations were defined by the following: severe distress, increased pCO₂, (>38 mm Hg), increased respiratory rate (>25 breaths/min), acidosis (pH < 7.38), and possibly a past history of NPPV success.^{81,82}

Remaining questions include the following. Do patients with less severe exacerbations of COPD benefit from NPPV? For how long should patients be treated? Can patients unlikely to tolerate or benefit from NPPV be identified prospectively? What types of ventilator settings will maximize both tolerance and benefit?

Methylxanthines. Currently, there is no evidence supporting the routine use of methylxanthines in the treatment of patients with acute COPD.⁸³ It is possible, however, that certain subgroups of patients may benefit or that more selective agents would have a better risk/benefit ratio.

EDUCATION

In addition to diagnostic and therapeutic considerations, there are research opportunities in the general field of education. Few educational programs have been directed toward improving the knowledge of health care workers about AECOPD and, to our knowledge, none have included emergency physicians, nurses, or respiratory therapists.^{84,85} A question that remains unanswered is the following: what is the impact of these efforts on the practices of health care workers?

Although educational programs are presumed to play a role in the treatment of patients with AECOPD,

few studies have actually documented their impact on patient satisfaction with care, improved pulmonary function, walking distance, quality of life, number of exacerbations, ED visits, and hospital admissions.^{86–91} Furthermore, all the studies to date have been conducted in patients with stable COPD. The ED visit is a time of crisis during which the patients, caregivers, and family members are a captive audience and thus may be receptive to such an educational intervention. A question that remains is the following: what is the appropriate content and delivery method in this setting?

Education can also extend to the general field of secondary prevention. There are many opportunities to deliver preventive interventions for patients with AECOPD, especially those who are discharged from the ED. For example, influenza vaccination, nutritional support, and smoking cessation interventions have all proven to be important for patients with COPD.^{92–100} The ED may have an important role to play in delivering these educationally intensive interventions, thus preventing future relapses. Unfortunately, little research has been performed in the ED setting, and evidence is clearly required before embarking on such an ambitious effort.

SPECIAL CONSIDERATIONS

Gender Differences. Studies indicate that there are many gender differences in the characteristics and the treatment of COPD. These differences include a bias against diagnosing COPD in women, despite an increased susceptibility to its development in female cigarette smokers, higher prevalence of hyperresponsive airways among women, better technique with metered-dose inhaler use among men, fewer benefits from exercise training in women, better prognosis of women when using long-term home oxygen therapy, differences in functional performance, and differences in quality-of-life measures.^{101–108} Questions that remain include the following. Does gender influence symptom perception during exacerbations? Are outcomes of ED visits and home support systems different? Is the cost of treatment affected by the patient's gender?

Patients with Comorbid Conditions. Although emergency physicians recognize that many patients with AECOPD also have coexisting medical illnesses, there is little evidence to help direct the emergency management of such patients. For example, do coexisting conditions alter symptom perception and outcomes of treatment? Are these patients more likely to be hospitalized because of physician concern over multiple conditions or because they are indeed sicker than patients with a single condition? Can patients who have coexisting conditions, such as congestive heart failure, be directed to manage their care at home

when faced with increasing shortness of breath? Do emergency physicians recognize the numerous patients in whom depression and COPD coexist and how should these patients be treated?^{109–112}

CONCLUSIONS

AECOPD is a common problem in the ED; despite considerable research involving the management of this disease over the past decade, much remains unclear from an emergency medicine perspective. Increased research would better guide the management of these complex patients from the perspectives of the patient, the caregiver, and society. Overall, researchers in this field must pay close attention to the conduct of their studies. For example, studies should be focused on clinically meaningful questions, designed to reduce bias (randomized, concealed allocation, multiple levels of blinding, blinded outcome assessment, and so on), and conducted using clinically meaningful outcomes (e.g., quality of life, symptoms, relapse rate, and hospitalization).

The major areas of research on AECOPD can be divided into diagnosis, therapy, and education. The reliability and validity of different definitions of AECOPD need to be assessed. The utility and performance characteristics of diagnostic testing need to be determined for this difficult patient population. Specific diagnostic tests include measures of dyspnea, spirometry and exercise tolerance, measures of gas exchange, airway inflammation, and chest imaging. It remains unclear which patient-specific therapies (oxygen, bronchodilators, corticosteroids, antibiotics, NPPV, and methylxanthines) should be used and monitored. Finally, the utility of education of both health care providers and patients and how it may be applied to the acute setting need to be addressed.

Once such endeavors are undertaken and completed, the findings can be integrated into evidence-based guidelines on the emergency management of AECOPD. The application of these new clinical practice guidelines will in turn require research to determine the most appropriate approach to improve the treatment of patients with AECOPD.

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• APPENDIX A

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