EMERGENCY MEDICINE PRACTICE
EBMEDICINE.NET
AN EVIDENCE-BASED APPROACH TO EMERGENCY MEDICINE

The Acute Presentation Of Chronic Obstructive Pulmonary Disease In The Emergency Department: A Challenging Oxymoron

It's 10 pm and Patient 1, A 57-year-old male, is brought in by paramedics from home after he called 911 saying, "I can't breathe." He is thin, has weathered skin, and is visibly dyspneic. His pulse oximetry reading is 84% despite receiving home oxygen via nasal cannula. When you listen to his lungs, you hear almost nothing. Fifteen minutes ago, you sent a patient with septic shock to your hospital's last ICU bed. The patient doesn't look good and you contemplate the best strategy to stabilize his respiratory status and turn him around....

While the nurse is putting Patient 1 on a monitor, Patient 2, a 78-year-old female with a history of "heart problems" and "chronic bronchitis" is brought in by family members who report that she has been increasingly fatigued over the past day and complaining of "not breathing right." She reports that her inhalers are not helping her like they should. She has mild hypoxia, scattered wheezes, lower extremity edema, and cardiomegaly on chest x-ray. The differential of her presentation is long, time is short, and you begin to prioritize which tests will have the best return...

Few medical conditions rival chronic obstructive pulmonary disease (COPD) in prevalence, burden on medical resources, acuity, and frequency of presentation. Hardly a shift goes by in most emergency departments (EDs) without the opportunity to manage the dyspneic emphysematous or bronchitic patient, with hospital admission being a frequent outcome. Compared to the attention paid to cardiovascular disease, diabetes, cancer, and infectious diseases, COPD is virtually invisible. Although there have been efforts in

November 2008
Volume 10, Number 11

Authors

Phillip Gruber, MD
Chief Resident, Los Angeles County/University of Southern California Medical Center, Los Angeles, CA

Stuart Swadron, MD, FRCP(C), FACEP, FAAEM
Program Director, Los Angeles County/University of Southern California Medical Center, Los Angeles, CA

Peer Reviewers

Peter DeBlieux, MD
Professor of Clinical Medicine, LSU Health Science Center; Director of EM Services, University Hospital, New Orleans, LA

Bret Nelson, MD
Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY

CME Objectives

Upon completion of this article, you should be able to:

1. Describe the cardinal clinical and historical features of a patient presenting with a COPD exacerbation.
2. Apply a patient-based diagnostic strategy for determining the severity of an exacerbation and identifying comorbid conditions.
3. Aggressively treat an exacerbation with a combination of medical and other therapeutic interventions.
4. Prevent, identify, and treat the complications of intubation in this patient population.

Date of original release: September 1, 2008
Date of most recent review: July 10, 2008
Termination date: September 1, 2011
Time to complete activity: 4 hours
Medium: Print & online
Method of participation: Print or online answer form and evaluation
Prior to beginning this activity, see "Physician CME Information" on the back page.

Accreditation: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of EB Medicine. EB Medicine is accredited by the ACCME to provide continuing medical education for physicians. **Faculty Disclosure:** Dr. Swadron, Dr. Gruber, Dr. DeBlieux, and their related parties report no significant financial interest or other relationship with the manufacturer(s) of any commercial product(s) discussed in this educational presentation. Dr. Nelson has received grant support for a study of Continuous Positive Airway Pressure in acute asthma from Vitaid, Inc.
Commercial Support: *Emergency Medicine Practice* does not accept any commercial support.

recent years to refocus the medical community on early diagnosis and optimal treatment of COPD, this disease is still seen by both healthcare providers and the public as a largely untreatable, progressive, end-stage consequence of cigarette smoking.

Many patients with a diagnosis of COPD label themselves as having asthma, chronic bronchitis, or emphysema. This confusion in large part reflects a similar confusion among health care providers and in the medical literature. Although each of these terms has a specific clinical or pathological definition, in reality there is significant overlap among all of these entities. Clinical decision making should thus be guided by the specific presentation of each individual patient.

The presentation of COPD to the ED often results in a diagnostic dilemma, since patients with COPD frequently have comorbidities that make it difficult to pinpoint the underlying reason for their acute presentation. In addition, the serious prognostic implications of COPD exacerbations are underappreciated by emergency physicians, often because their ultimate morbidity and mortality are delayed by days or weeks.

This issue of *Emergency Medicine Practice* reviews the most recent evidence-based recommendations for the management of COPD exacerbations. In addition, some of the more challenging practical issues that surface when dealing with the chronic lung disease patient who presents with acute dyspnea are addressed, such as:

- How to best assess respiratory status: is an ABG necessary?
- When to order a BNP: is BNP helpful in differentiating COPD from CHF exacerbations?
- How to deliver oxygen therapy: how much is too much?
- How to administer bronchodilators: which ones, how often, and by which route?
- When to consider other underlying diagnoses: is a workup for pulmonary embolism (PE) or acute coronary syndrome (ACS) warranted?
- When to consider outpatient management: who is safe to send home?

Critical Appraisal Of The Literature

Ovid MEDLINE was searched for articles relating to exacerbations of COPD or chronic bronchitis, limited to those published within the last ten years; references were then searched for additional articles. The Cochrane database, the National Guideline Clearinghouse, and secondary references that were used in the formation of several consensus statements and guidelines were also reviewed.

There is a remarkable disconnect between the magnitude of the problem posed by COPD and the amount and quality of research that has been conducted, both for management of stable disease and acute exacerbations. This may be due to several factors: a historical lack of a consistent objective disease definition, the perception that COPD only strikes the elderly and/or smokers, and the perception that it is a disease for which medical science has no effective therapies. One of the single greatest challenges when reviewing the literature on COPD is understanding the dramatic heterogeneity of disease encompassed by COPD. Comparing chronic bronchitics to emphysematous patients to lifelong asthmatics is remarkably challenging, particularly when considering the vast differences in pathophysiology between these groups.

With respect to the management of exacerbations in the hospital setting, the state of the literature is a particular problem for emergency physicians: most original research relates to the management of chronic stable disease or to the outpatient management of mild exacerbations that are more likely to present to non-emergency department settings. Many studies have small numbers of patients at one or two centers. While a consensus definition of an exacerbation has been recently agreed upon, it is symptom based and no objective confirmatory test or biomarker has been developed. Accordingly, many studies have nonspecific definitions for patient inclusion criteria or large proportions of excluded patients. Additionally, outcome measures are notoriously difficult to define and measure and will vary from study to study with respect to physiologic measurements, symptom scales, length of stay, or rate of relapse. Fortunately, there is progress being made to correct these challenges. Large collaborative efforts to standardize the diagnosis and management of COPD have been undertaken, and research is ongoing in the area of biomarkers and outcome measures.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD), a combined effort of the World Health Organization and the U.S. National Heart, Lung, and Blood Institute, has produced a consensus statement; it was initially created in 2000 and was revised in 2006. This document, "Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease," contains a consensus definition of the disease, staging of disease severity based on objective spirometric criteria **(see Table 1)**, and evidence-based management guidelines.[1]

The American Thoracic Society (ATS) and European Respiratory Society (ERS) have together produced another consensus document, "Standards for the Diagnosis and Management of Patients with COPD,"

Table 1. Staging Of COPD Based On Post-Bronchodilator Spirometric Criteria

Stage	FEV1/FVC	FEV1
I: Mild	< 0.70	> 80% predicted
II: Moderate		50%–80% predicted
III: Severe		30%–50% predicted
IV: Very Severe		< 30% predicted or chronic respiratory failure

written in 2004 as an update to the initially separate recommendations from each society that were developed in the 1990s.[2]

The recent introduction of a consensus definition will hopefully serve to help facilitate a resurgence in COPD research as well as improvements in our understanding of its epidemiology, pathophysiology, and public health implications.

Epidemiology, Etiology, And Pathophysiology

Epidemiology

COPD is recognized to be a major cause of morbidity, mortality, and health care expenditure worldwide, and it is one of the few diseases increasing in prevalence. From 1990 to 2030, it is projected to climb from the sixth to the fourth leading cause of death worldwide.[3,4] In the U.S., COPD is a primary or contributing cause of nearly 10% of all hospitalizations, rising to nearly 20% in patients older than 65.[5] It is also a top-ten cause of disability, both in developed and developing nations.[6] The aging of the world's population and continued tobacco use are the major determinants of these trends. These two factors are also believed to account for the striking fact that in 2000 more women than men died of COPD in the U.S. The costs associated with COPD are also remarkable. In 1996, costs related to COPD in the U.S. were estimated to be $14.5 billion, with exacerbations, associated ED visits, and hospital admissions accounting for the majority of expenditures.[7-9]

The definition of a COPD exacerbation that has recently been agreed upon is clinical: "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD."[1] The fact that this definition is symptom-based and does not have a quantifiable biochemical marker is underscored by a relative lack of knowledge about the pathophysiology of COPD exacerbations. Nonetheless, from the practical perspective of an emergency physician, for whom uncertainty and imprecision in diagnosis is a reality of everyday practice, clinical definitions are valuable as a starting point for research into management strategies and outcomes.

Most COPD patients experience several exacerbations of their disease per year, with more frequent exacerbations associated with worsening airway obstruction. An analysis of data from the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial, a 3-year, randomized controlled trial evaluating inhaled steroids in the management of stable COPD, found that patients with moderate to severe COPD had an overall average of 1 exacerbation per year, rising to almost 2.5 exacerbations per year for patients with the most severe airway obstruction.[10,11]

Exacerbations are a dangerous event for a COPD patient. Although mortality estimates for patients admitted with exacerbations vary widely depending on the characteristics of the patient population considered, a retrospective analysis of 71,000 COPD admissions showed an overall mortality rate of 2.5%.[12] In the subset of patients requiring mechanical ventilatory assistance, this figure rose to 28%. Other studies have shown even higher mortality rates, with initial hospitalization mortality rates of 8%–11% and 23%–43% mortality rates at 1-year follow up.[13-16] There is also data to suggest that exacerbations permanently degrade lung function. Two prospective trials, each with approximately 100 patients, showed that patients with more frequent exacerbations have an accelerated decline in their FEV1,[17] and 7% of patients who experience an exacerbation never return completely to their pre-exacerbation state.[18]

Etiology

Currently, exacerbations are believed to result from an inciting stressor, such as infection or exposure to particulate pollution. This results in an acute worsening of airway inflammation and, when coupled with worsened lung physiology, conspires to overcome a patient's compensatory mechanisms and physiologic reserve.

Although exact numbers vary by source, it is believed that most exacerbations are caused by respiratory tract infection, with bacteria and viruses causing up to 50% and 40% of exacerbations, respectively.[19-21] *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are the most common bacterial pathogens[22,23] implicated in COPD exacerbations; rhinovirus, influenza, and RSV are the most common viruses.[21,23,24] Severe exacerbations are more likely to have microbiologic evidence of bacterial infection and a higher incidence of gram-negative infection.[25] Determining the causality of infections in COPD exacerbations is hindered by the fact that a significant proportion of stable COPD patients are colonized with respiratory pathogens at any given time. In addition, many of the data were obtained using microbiologic techniques that are now outdated. It is also not clear whether the appearance of new antigenic strains of a colonizing bacterial species is a casual factor in acute exacerbation.[26]

Air pollution has been associated with COPD exacerbations and admissions; although causality is difficult to prove, it is hypothesized to be responsible for up to 10% of acute exacerbations. A well-designed study analyzing 108,000 cases in 5 European cities over several years found an increase of 1%–4% in daily COPD admissions for every 50 microgram per cubic meter increase in 4 different pollutants.[27] Similar analyses have been conducted in the U.S.[28] and elsewhere in Europe, with similar conclusions.[29,30]

Pathophysiology

The current understanding of the pathophysiology of COPD is that a primary insult (usually chronic

particulate pollution exposure) combined with an abnormal host response results in the classic pathologic features of the disease: recurrent inflammation (bronchitis), alveolar destruction, and small airway remodeling (emphysema). The abnormal host response is a combination of imbalances in the protease-antiprotease and oxidant-antioxidant milieu of the lungs, and it may be due to genetic susceptibility in some individuals, as exemplified by alpha-1 antitrypsin deficiency. The resultant pathologic changes contribute over many years to impaired gas exchange, airway obstruction, and airflow limitation. As the disease progresses in severity, extrapulmonary pathophysiology becomes more important. Extrapulmonary features include:

- Vascular disease (cerebral, coronary, peripheral) due to chronic inflammation, in addition to shared etiologic risk factors
- Skeletal muscle dysfunction, likely due to a combination of chronic inflammation and disuse[31]
- Cachexia and wasting

Chronic hypoxia may cause polycythemia. Hypoxic pulmonary vasoconstriction and emphysematous destruction of parenchymal vasculature may cause increased pulmonary vascular resistance and eventually right heart failure (cor pulmonale).

Exacerbations of COPD are associated with small but measurable worsening of lung function parameters, in addition to worsening inflammation and bronchospasm. Together they produce the symptoms of an exacerbation (dyspnea, increased sputum volume and purulence) and worsen the patient's already compromised respiratory physiology. Although there is no established test to 'diagnose' an exacerbation, there is a possibility that measurement of certain inflammatory markers may one day be used for this purpose.

Dynamic hyperinflation seems to be the dominant physiologic parameter that correlates with subjective dyspnea.[32,33] At higher lung volumes, the respiratory musculature is working at an even greater mechanical disadvantage as it is faced with simultaneously overcoming increased airflow resistance and elevated end-expiratory pressures (auto-PEEP). This occurs in the face of increased metabolic demand, worsened hypoxia, and decreased thoracic venous return as a result of elevated intrathoracic pressures. Ventilation/perfusion mismatch and increased dead-space result in gas exchange abnormalities. As patients deteriorate, there is progressive hypoxia and hypercapnia resulting in respiratory acidemia, CO_2 narcosis, coma, and death. Successful treatment of an exacerbation involves interrupting and reversing this downward spiral.

Differential Diagnosis

The astute clinician can quickly narrow the very broad differential diagnosis of the acutely dyspneic patient based upon history, clinical impression, and a few selected data points. Nonetheless, there often remain several particularly difficult to distinguish diagnoses, especially in patients with multiple comorbidities. Life-threatening diagnoses that may either mimic or co-exist with an acute COPD exacerbation include:

- Decompensated heart failure
- Cardiac dysrhythmia
- Acute asthma
- Pneumonia
- Acute myocardial infarction
- Pulmonary embolism
- Pneumothorax
- Pericardial or pleural effusion

Less common diagnoses include the obesity-hypoventilation syndrome, bronchiectasis, and lung cancer.

Prehospital Care

Prehospital care for the COPD patient focuses on rapid assessment, supportive care, and transport to the hospital. Patients who present with respiratory distress or who are found to be hypoxic should receive supplemental oxygen. In severe cases of imminent respiratory failure or respiratory arrest, ventilatory assistance or advanced airway management may be required. Depending on local prehospital policies, providers may administer inhaled bronchodilators either by inhaler or nebulizer, and/or they may assist patients with the administration of their own bronchodilator medications.

There is ongoing concern in the prehospital community that supplemental oxygen may result in hypercapnic respiratory failure in COPD patients. Current EMT and paramedic teaching resources recommend that providers use oxygen with caution, starting with 1–3 liters per minute via nasal cannula or 24%–28% via Venturi mask, with upward titration as necessary.[34-36] However, these recommendations rely on a reliable determination that the patient is in fact suffering from a COPD exacerbation, one that can be difficult even after arrival at the hospital. Observational studies conducted in the U.K. have shown that, despite similar training recommendations, 49% of patients were given high flow oxygen in the prehospital setting.[37] These studies also found that few COPD patients correctly identify themselves as such, with up to 40% identifying themselves as having asthma.[38]

In EMS systems who utilize field pulse oximetry, an initial saturation goal for COPD patients between 88% and 92% may help prevent CO_2 narcosis.[39] In urban settings, where transport times are brief, these concerns may be less important. In rural settings, where the challenge is greater due to time constraints, appropriate therapy awaits evidence-based recommendations regarding oxygen administration, provider training, and patient education.

Non-invasive positive pressure ventilation (NPPV,

sometimes also referred to as CPAP or BiPAP) is gradually (and appropriately) being used for a wider range of indications in the ED. As ventilators become more portable and technologically advanced, they are increasingly suitable for use outside the hospital. Thus far, only small feasibility studies have been performed in patients with pulmonary edema,[40,41] with moderate success. If further research confirms that prehospital NPPV is as beneficial as NPPV in the ED, there may be a future role for this therapy modality in the prehospital setting.

ED Evaluation

During the primary survey, the patient's work of breathing, oxygenation, mental status, and vital signs should be simultaneously assessed and addressed by immediate interventions when life-threatening abnormalities are present. Occasionally, patients will present in obvious or imminent respiratory failure and require definitive airway management (e.g., endotracheal intubation), possibly in the absence of a provisional diagnosis. Special precautions must be taken in these cases to avoid, recognize, and treat the lung injury and cardiovascular collapse that are associated with intubation and mechanical ventilation.

History

In patients who do not present in extremis, history taking should be directed at establishing the diagnosis of a COPD exacerbation, assessing the presence of comorbidities, and identifying the possibility of alternative or co-existing life-threatening diagnoses.

Many patients with significant airway obstruction remain undiagnosed, especially those not receiving regular medical care. Therefore, a certain index of suspicion for the underlying chronic disease must be maintained when interviewing a patient with acute respiratory distress, especially when certain risk factors are present. The most important of these are:

- Decreased functional capacity
- A significant smoking history
- Advanced age
- Occupational exposure to dusts or chemicals
- Exposure to indoor air pollution (e.g., smoke from indoor cooking or heating—much more of a concern in developing nations)

Inquiring about the patient's exercise tolerance, functional limitations, frequency of exacerbations, and current treatment can help gauge the severity of the patient's chronic stable disease. Of the aforementioned factors, those that have been shown to be predictive of increased mortality in the year following an exacerbation are age and decreased functional status;[14] however, these factors are not sufficiently predictive to be used directly in guiding management in the acute care setting.

By definition, increased dyspnea, sputum production, cough, or changes in sputum quality are the presenting symptoms of an exacerbation. Other symptoms may include wheezing, nasal congestion, sore throat, and occasionally fever, generalized weakness, or altered mental status. A well-designed cohort study in the U.K. followed 101 COPD patients for 2.5 years and analyzed the symptoms and time course of their exacerbations.[18] Sixty-four percent of exacerbations were associated with increased dyspnea, 42% with increased sputum purulence, 35% with wheeze, 35% with cold symptoms (nasal congestion/ rhinorrhea), and 20% with cough.

The onset and duration of these presenting symptoms should be noted as well as their relationship to prior exacerbations. A study of 40 patients admitted for COPD exacerbation used bronchoscopy to verify that increased sputum purulence, as defined by a reported change in color from clear or white to yellow or green, is associated with bacterial infection in the lower airways.[42] Important historical factors include the presence of comorbid conditions (especially heart failure, cardiac disease, and malignancy), risk factors for pulmonary embolism, and a review of systems.

Physical Findings

Many physical examination findings by themselves are fairly nonspecific with regard to guiding management, but they are invaluable in producing an overall impression of the clinical status of a patient. Some findings are more important in suggesting alternative diagnoses.

Assessing the work of breathing is critical to gauge the severity of an exacerbation and guide the aggressiveness of therapy. Tachypnea, tachycardia, use of accessory muscles, diaphoresis, cyanosis, and agitation are all suggestive of increased physiologic load as a patient strives to overcome the work of breathing. Altered or depressed mental status is an especially ominous sign; it requires immediate and aggressive management.

Evidence from several prospective observational studies,[43-45] each with approximately 100 stable outpatients, showed that clinical findings predictive of significant airflow obstruction include wheezing, decreased breath sounds, hyperresonance on lung percussion, decreased cardiac dullness, and increased forced expiratory time. The finding of a "barrel chest" has a much poorer sensitivity. These findings may or may not be helpful in acute presentation, and it is important to remember that the absence of wheezing can be an ominous sign in patients presenting with COPD exacerbation or asthma.

Other physical findings to seek include jugular venous distension (suggestive of heart failure or increased intrathoracic pressure and decreased venous return), peripheral edema (heart failure or, if asymmetric, deep venous thrombosis), and asymmetry of lung findings (pneumothorax, pneumonia, and atelectasis). Cachexia or a low body mass index (< 20)

in patients presenting with an acute exacerbation is a poor prognostic sign.[14,46]

Diagnostic Studies

Patients with a history of COPD who present with shortness of breath require a tailored approach to diagnostic testing. **Table 2** provides a summary of diagnostic modalities that may be helpful in the evaluation of these patients.

Pulse Oximetry

Pulse oximetry has become an indispensable tool in the ED, owing to its noninvasive and rapid assessment of arterial oxygenation. It could be argued that every patient who presents to an ED with any complaint attributable to the cardiac or respiratory systems should undergo an urgent pulse oximetry measurement. Pulse oximetry is potentially unreliable in patients with very dark skin, cold extremities, peripheral vascular constriction, or opaque nail polish (which can be removed).

For patients with the lowest level of severity, the American Thoracic Society/European Respiratory Society guidelines suggest that no further diagnostic testing is required beyond pulse oximetry to ensure oxygenation. These are patients who have a mild exacerbation, mild to moderate underlying COPD, few comorbidities, and/or immediate response to initial therapy.

Arterial Blood Gas (ABG) Sampling

Co-oximetry of arterial blood has long been considered the gold standard for assessment of respiratory and metabolic status in patients with COPD exacerbation; however, its use has become less common in modern management. Although the information obtained from an ABG can be useful for the diagnosis of respiratory failure (defined as a $PaO_2 < 60$ mm Hg and/or $PaCO_2 > 50$ mm Hg) and acidemia (pH < 7.36), clinical criteria and evaluation are much more important than blood gas values in making management decisions.

Caution must be exercised when interpreting blood gas values in COPD patients, as their "normal" or expected values change over time as their underlying COPD progresses. In the early stages of disease, ABG values may show only a mild hypoxia due to ventilation/perfusion mismatch. As the disease progresses, worsening hypoxia stimulates respiratory drive, resulting in hyperventilation and respiratory alkalosis. Finally, airflow obstruction and alveolar hypoventilation become severe enough to result in chronic CO_2 retention and respiratory acidosis. In the stable state, renal compensation provides a metabolic alkalosis to normalize arterial pH. With acute exacerbation, worsened respiratory acidosis results in acidemia despite chronically elevated serum bicarbonate levels.

It is partly because of this variation that clinical evaluation is much more important than blood gas values in making management decisions, especially in the absence of a given patient's baseline or stable-state values. Blood gas measurements may be considered in patients whose clinical status suggests a severe exacerbation with need for admission or in the post-intubation management of intubated patients. Drawbacks of arterial blood sampling include patient discomfort and vascular complications. Although the frequency that ABGs may be performed inures many physicians to the pain and discomfort caused, it is important to consider the use of topical or injected local anesthetics before arterial puncture.

Chest X-Ray

Chest x-rays are routinely performed on patients in the ED with respiratory complaints. Consensus guidelines routinely recommend chest radiography for COPD patients who present to EDs or outpatient facilities with radiology capability.[1,2] Typical and expected "baseline" x-ray findings in COPD patients include hyperinflation and flattening of the diaphragms, but neither of these is reliably present nor diagnostic. Although there have been attempts to identify a subpopulation of patients for whom a chest x-ray can be safely omitted,[47] these efforts have not proved successful. Depending on study population and methodology, 5%–21% of patients will have an abnormality that will change management, most commonly a pneumonic infiltrate or pulmonary edema.[48,49] In addition, chest x-rays may identify important complications of COPD, such as pneumothoracies and lobar atelectasis.

Caution must be exercised when interpreting x-ray findings in COPD patients with advanced emphysema

Table 2. Summary Of Diagnostic Modalities In COPD Exacerbations

- Tests to perform in all patients:
  - Pulse oximetry to assess for presence and degree of hypoxia
- Tests to perform in most patients:
  - Chest x-ray to assess for pneumonia, pulmonary edema, and structural lung disease
  - ECG to identify silent ischemia or arrhythmia as a cause for decompensation
  - Basic blood tests (blood count and chemistries) to identify comorbid conditions such as anemia, electrolyte derangements, or renal impairment
- Tests to consider performing in certain patients:
  - Cardiac biomarkers—if clinical or ECG findings are concerning for coronary disease
  - D-dimer, lower extremity ultrasound, CT angiography—if clinical or historical factors suggest venous thromboembolism
  - Arterial blood gas measurement—in intubated patients
- Testing whose value is questioned or controversial:
  - B-type natriuretic peptide—may help identify the presence of comorbid decompensated heart failure
  - Spirometry/peak flow measurement—may be useful as a crude marker of disease progression and risk stratification but is not useful as a marker of acute change
  - Sputum testing—not generally useful in guiding clinical management except when tuberculosis is a concern

and the resultant distortions of anatomy. For example, peripheral or apical bullae may be mistaken for a pneumothorax. Also, infection by typical respiratory pathogens with clinical pneumonia and lobar consolidation may have a very atypical appearance on chest x-ray and may be mistaken for interstitial edema or fibrosis.[50] Uniform densities in a lobar distribution representing lobar atelectasis may be mistaken for lobar pneumonia. Lobar atelectasis may be differentiated from pneumonic consolidation by the presence of volume loss (raised hemidiaphragm, shifting of fissures or other landmarks) and the absence of air bronchograms.

Electrocardiograms (ECG)

Electrocardiograms are also routinely obtained on patients presenting with presumed COPD exacerbation and are recommended by consensus guidelines.[1,2] As with chest x-ray, this is largely to identify comorbid or confounding illness that may be the underlying cause of the patient's decompensation, especially acute coronary syndromes.

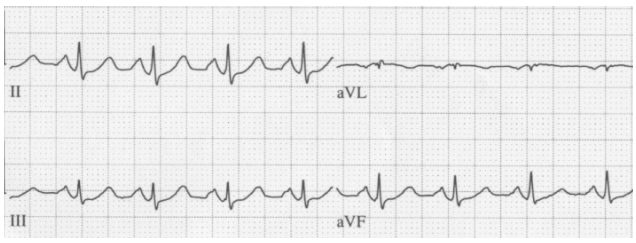
Morphological abnormalities associated with COPD include signs of right atrial enlargement (P pulmonale, a P wave with height > 2.5 mm in leads II, III, aVF, shown in **Figure 1**), and right ventricular hypertrophy (right axis deviation, prominent R in V1 and V2, right precordial ST depression and T wave inversion, rS pattern in V5-V6). The lung hyperinflation associated with COPD can cause rightward rotation of the heart (associated with poor R wave progression) as well as low voltages.[51]

The most common dysrhythmias associated with COPD are supraventricular, such as sinus tachycardia, multifocal atrial tachycardia, supraventricular tachycardia, atrial fibrillation, and atrial flutter. These may be managed in the usual fashion and in some cases may require nothing beyond treatment of the underlying pulmonary pathology. *For a complete discussion on the management of ST, MAT, SVT, AF, and atrial flutter, see the April 2008 Emergency Medicine Practice issue, "An Evidence-Based Approach To Supraventricular Tachycardia."*

Spirometry/Peak Flow Measurement

Spirometry is essential to the diagnosis and monitoring of patients with COPD, but not in the setting of acute decompensation. Unlike asthma, the peak expiratory flow rate (PEFR) and one-second forced expiratory volume (FEV1) are relatively unchanged during COPD exacerbations. In two prospective observational studies that measured symptomatic and physiologic variables over time in a cohort of COPD patients, the PEFR fell by only 2.8%–4.5%, and the FEV1 fell by only 2.2% during acute exacerbation.[18,52] Spirometric measurements also correlate poorly with arterial blood gas values, and they are not predictive of the need for admission, likelihood of recidivism, or response to therapy in COPD exacerbations.[53] Current consensus guidelines discourage the routine use of spirometric assessment for patients presenting with COPD exacerbation.[1]

Figure 1. P Pulmonale



Note the large P waves in the inferior leads II, III, aVF.

Sputum Testing

Although once common, gram stain and culture of sputum samples has fallen out of favor. There is a low yield of useful information that rarely changes clinical management in a meaningful way.[54] Even when organisms are isolated, it is difficult to be sure of their etiologic role, as many COPD patients are colonized with pathogenic organisms in the stable state. Collection of sputum for testing may be considered in a patient who is severely ill and producing sputum that is noticeably purulent; it should be considered more strongly in a patient who has risk factors for tuberculosis or who has already failed a course of antibiotic therapy. A recent observational study found that sputum testing of 118 patients hospitalized with COPD exacerbation and purulent sputum changed antibiotic therapy in 29% of cases,[55] although this has not been shown to affect clinical outcomes.

Laboratory Tests

Consensus guidelines recommend "routine blood tests" including cell count, electrolytes, and renal function measurements.[1,2] Although classically associated with polycythemia, one observational study has shown that a significant proportion of patients with severe COPD are anemic (8%–12%), at least as many as those that are polycythemic (8%).[56] The same study found an inverse association between hemoglobin concentration and mortality. Another study identified an association between hyperglycemia and poor outcomes in acute exacerbation.[57] However, the main value of "routine" blood tests, like many of the other diagnostic tests discussed here, is to identify comorbid conditions that may change management—especially in those patients who are likely to require admission and aggressive treatment.

Consensus guidelines do not address the measurement of cardiac markers in the evaluation of an exacerbation. Two recent observational studies have shown a relatively high (18%–25%) incidence of elevated troponin levels in patients admitted with a primary diagnosis of acute exacerbation of COPD and without ECG changes suggestive of acute myocardial infarction.[58,59] Acute hypoxemia and right ventricular strain associated with COPD exacerbation may result in

troponin elevation, even in the absence of other clinical evidence of acute coronary syndrome. However, the methodology of these studies does not consider that patients who have chest pain as part of their presenting complaints or have elevated troponin values discovered in the ED may not be coded as primary COPD admissions.

This data is not sufficient to guide the emergency physician as to when cardiac markers should be obtained in this setting. It is also difficult to make management recommendations for those patients with mild troponin elevations, for whom treatment of the underlying pulmonary process may be sufficient. At this point, only an individualized approach based on clinical judgment can be recommended.

B-Type Natriuretic Peptide

B-type natriuretic peptide (BNP), which is released from the ventricles in response to stretch, may be a useful diagnostic adjunct in some patients presenting with acute dyspnea, especially since symptoms of heart failure may be mistakenly attributed to pulmonary disease in patients with known COPD. An observational study of 46,000 patients in northern California found COPD patients 7 times more likely than patients without COPD to have a concomitant diagnosis of CHF.[60] A Dutch study of 400 COPD patients older than 65 showed that a large proportion of these patients have undiagnosed CHF.[61]

Increases in BNP above 500 pg/mL are suggestive of decompensated heart failure, and levels below 100 pg/mL suggest the absence of heart failure.[31] Amino-terminal pro-BNP has also been shown to have similar testing characteristics, with values above 2500 pg/mL indicating left ventricular dysfunction and values below 1000 pg/mL indicating the absence of heart failure.[62]

Some authors have suggested that BNP measurement reduces time spent in the emergency department, reduces total costs,[63] and improves diagnostic accuracy.[64,65] However, sensitivity and specificity of BNP values vary depending on the cut-offs used in the test and the characteristics of a given assay. Because data on the clinical utility of BNP are derived from studies that include patients with clear clinical features of either pulmonary or cardiac disease, its usefulness in the subset of patients in whom a true diagnostic dilemma exists is much less clear.[66,67]

Elevations in BNP may arise from either the left or right ventricle. Thus, cor pulmonale and pulmonary embolism may also cause elevated BNP as a result of right ventricular strain. BNP also may be falsely elevated in the setting of renal failure. Therefore, BNP levels cannot be relied upon to either "rule in" a diagnosis of congestive heart failure nor to "rule out" significant pulmonary pathology. These important pitfalls of BNP measurement must be understood to prevent an over reliance on this test, which can help inform clinical decision making but must not supplant clinical judgment.

Venous Thromboembolism Evaluation

Determining when and how to pursue the diagnosis of PE in COPD patients who present with acute dyspnea remains a real challenge for emergency physicians. There is little scientific data to guide us in this area. Risk factors and presenting signs and symptoms are similar for both COPD exacerbation and pulmonary embolism. Fortunately, with the exception of ventilation perfusion scanning, the performance of clinical decision rules, d-dimer testing, CT angiography, and pulmonary angiography are not significantly affected by the presence of COPD.[68,69]

Treatment: Medical Management

The treatment of a COPD exacerbation should occur concurrently with its diagnosis and evaluation. Although there are several effective therapies, the evidence in support of these therapies is not as strong as in other common diseases, such as acute coronary syndromes. Most studies have small numbers of patients and many use physiologic markers (e.g., FEV1) as surrogates for the more important clinical outcomes (e.g., death, survival to discharge). Nonetheless, there is enough data to provide some clinical guidance in most cases. See **Table 3** for a summary of medical therapies.

Oxygen

Supplemental oxygen should be administered to prevent hypoxemia, with a goal SpO_2 of 88%–92% or PaO_2 > 60 mm Hg.[39] The method of administration should be determined individually by patient tolerability and reliability of delivery. Nasal cannula or prongs are usually tolerated well, and they appear to have a low risk of inducing hypercapnia. However, because of the low flow delivered, the amount of supplemental oxygen varies depending on the patient's minute ventilation. High-flow devices such as Venturi masks are capable of delivering a more reliable concentration of supplemental oxygen regardless of minute ventilation, but they are not as well tolerated. Simple face masks or non-rebreather masks may be used to deliver higher concentrations of oxygen when hypoxemia does not respond to a lower

Table 3. Summary Of Medical Therapies For COPD Exacerbations

- Oxygen: administer to a goal SpO_2 of 88%–92%
- Bronchodilators: use inhaled beta-agonists and anticholinergics liberally
- Steroids: low dose (30–40 mg) oral prednisone or equivalent for patients with mild to moderate exacerbations; high dose (125 mg) intravenous methylprednisolone or equivalent in patients with severe exacerbations
- Antibiotics: in patients with increased sputum volume and purulence and in those with severe exacerbations **(Table 4)**
- Magnesium: often used in severe exacerbations, although benefit has not been conclusively demonstrated

FiO_2; however, these patients appear to be at higher risk for oxygen-induced hypercapnia and thus require closer monitoring.

Consensus guidelines recommend reevaluation of a patient's blood gases approximately 30–60 minutes after institution of therapy in order to verify successful treatment of hypoxemia and to identify patients who develop respiratory acidosis.[1] However, clinical indicators, such as the patient's level of alertness and mental status, are more important and relevant in guiding emergency department management. In fact, reliance on numbers obtained from ABGs to the exclusion of these clinical indicators may result in unnecessary or inappropriate management decisions. Additionally, end-tidal carbon dioxide monitoring can be used to monitor hypoventilation.

Bronchodilators

Administration of bronchodilators is a first line strategy for improving the symptoms and lung physiology of the patient with COPD exacerbation. The most frequently used agents are beta-agonists and anticholinergics.

Beta-agonists, such as albuterol, induce relaxation of airway smooth muscle via increased cyclic adenosine monophosphate. They act within minutes, with peak effect at approximately 30 minutes and duration of several hours. Anticholinergics, such as ipratropium bromide, also cause bronchodilation and decreased mucosal secretion via competitive inhibition of muscarinic pulmonary acetylcholine receptors. Their onset of action is slower than beta-agonists, approximately 10–15 minutes, with peak effect at 60–90 minutes and duration of 4–6 hours.[70]

Although most studies examine the effects of these medications on airflow obstruction (e.g., FEV1), the more modern view of the pathophysiology of COPD exacerbations is that improvements in airflow obstruction are less important than reductions in dynamic lung hyperinflation, which are more closely related to symptomatic and clinical improvement.[32] Several studies have evaluated the use of beta-agonists versus anticholinergics, finding no clinically significant advantage for either class.[71,72] Systematic reviews have come to the same conclusion.[73,74] Similarly, data suggest clinical equivalence among the modes of administration of bronchodilator agents, either nebulized or inhaled via metered dose inhaler (with spacer).[75-80] The decision to use nebulizers or inhalers should be guided by local needs and practical considerations: cost, ease of administration, and available resources.

Current consensus guidelines recommend increasing the dose and/or frequency of a patient's short-acting bronchodilator regimen when treating an exacerbation, although the optimal dosing is not known. One study showed a non-statistically significant trend towards benefit with every 20 minute dosing of nebulized albuterol compared with hourly albuterol.[81] Given the pharmacokinetics of these agents, their favorable side-effect profile, and a lack of rigorous data, an empiric symptom-based approach is the best that can be currently recommended.[82]

There is conflicting data regarding the benefit of combination therapy. Some studies show additional benefit with the addition of anticholinergics to beta-agonist therapy[83,84] while others show no additional benefit.[85,86] Consensus guidelines recommend the addition of a second class of bronchodilator if there is inadequate response with one class. However, many practitioners simply give both classes simultaneously, given the low cost and excellent safety profiles of these drugs.

Side effects of these bronchodilators are usually mild and well tolerated. Beta-agonists may cause hypokalemia, tachycardia, tremor, and a transient decrease in oxygenation, believed to be due to worsened ventilation-perfusion mismatch.[71] Although the sinus tachycardia and occasionally other tachydysrhythmias that may be induced by inhaled beta-agonists can be unnerving, these effects must be weighed against their clinical benefit, especially if a patient appears to be responding to the beta-agonist. Anticholinergics may cause dry mouth, tremor, or urinary retention. Anticholinergics are poorly absorbed into the systemic circulation from the lungs and gastrointestinal tract, so they tend to have fewer side effects than the beta-agonists. One important adverse effect of inhaled anticholinergics is their mydriatic effects that can occur if there is inadvertent exposure of the eye (e.g., exposure to the vapor from the nebulizer or inhaler or handling of the used medication capsule followed by eye rubbing). Theoretically, this may precipitate acute angle closure glaucoma in susceptible persons or mislead the clinician into suspecting uncal herniation in the unconscious patient.[70]

Methylxanthines

Once used as a mainstay for the treatment of airflow obstruction in both COPD and asthma, methylxanthines have fallen out of favor due to their adverse effects. One randomized controlled trial from 1991 showed a trend toward reduced hospitalization in patients treated in the emergency department with intravenous aminophylline (loading dose of 5.6 mg/kg followed by 0.9 mg/kg/hr infusion), although the results did not meet the threshold for statistical significance.[87] Other randomized controlled trials[88-90] and a systematic review[91] found increased side effects and no significant benefits. Despite the lack of evidence for their efficacy, methylxanthines such as theophylline and aminophylline continue to appear on current consensus guidelines as second line agents for use in patients who do not respond to other bronchodilators.

Magnesium

Anecdotally, intravenous magnesium administration is a therapeutic strategy used by many emergency

physicians for treatment of bronchospastic conditions. Consensus guidelines for asthma recommend intravenous magnesium as a second-line therapy in patients with severe exacerbations that are unresponsive to conventional measures.[92] Magnesium is not even mentioned in COPD guidelines. There is only one randomized controlled trial performed on a small number of COPD patients[93] that showed that 1.5 grams of intravenous magnesium did not provide any direct bronchodilatory effect (as measured by the FEV1), but they did improve response to inhaled beta-agonists. Although the evidence is lacking, as a practical matter, magnesium has few side effects and a large therapeutic index, so it is not unreasonable to administer it in patients who have moderate to severe exacerbations, especially if they have suboptimal response to conventional therapy.

Steroids

Administration of systemic steroids to patients presenting with COPD exacerbation has been shown to improve FEV1,[94-96] shorten hospital stay,[97] and reduce short-term treatment failure[98-100] by helping to reverse some of the inflammatory response that contributes to airway hypersensitivity, bronchial obstruction, and worsened lung physiology. Unfortunately, there is wide variability in the dose, route, and duration of therapy in the various studies.

The most frequent adverse effect of steroids is hyperglycemia.[101] Other adverse effects are possible, including psychiatric events, skin changes, myopathy, decreased bone density, hypertension, and immune suppression leading to serious infections. Although these more uncommon side effects have not yet been shown to be increased with short courses of therapy for exacerbation, few studies are designed to evaluate this.

In light of the fact that steroid-induced side effects are believed to be dose-dependent,[102] consensus guidelines recommend systemic steroid therapy at the lower end of the spectrum used in the above-cited trials: 30–40 mg of prednisone (or its equivalent) daily for 1–2 weeks, either orally or intravenously. However, the largest trial to date of systemic steroids in COPD exacerbation[99] used a much higher dose, methylprednisolone 125 mg IV every 6 hours (equivalent to approximately 150 mg prednisone daily); as a result, practice patterns vary widely.[103]

Two studies performed on patients hospitalized with "non-acidotic" exacerbations[96,104] suggest that nebulized budesonide has effects on airflow obstruction that are similar to oral or intravenous steroids but with a trend toward fewer adverse events. However, the clinical outcomes associated with the use of inhaled steroids for acute exacerbations have not yet been evaluated.

In light of the current data, it can be recommended that systemic steroids be used to treat COPD exacerbations, with oral therapy in lower doses used for outpatients and intravenous therapy in higher doses for more critically ill patients. However, exact dosing and duration of regimens should be individualized, with consideration given to cost, local resources, patient comorbidities, and tolerance of adverse effects.

Antibiotics

Many COPD exacerbations are believed to be caused by bacterial infection of the lower respiratory tract. The most commonly implicated community-acquired pathogens are *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*; in severely ill patients (mechanically ventilated in the ICU), gram-negative *enterics*, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Acinetobacter baumannii* are not uncommon.[25,105] Although one might surmise that antibiotics would be of unquestioned benefit in the treatment of exacerbations, surprisingly, their role is not clearly delineated.

As with many aspects of COPD research, there is tremendous heterogeneity in the quality of data and the subsets of patients studied, with many of the studies done on small numbers of patients with uncertain diagnoses. A meta-analysis[106] and systematic review[107] have concluded that treatment with antibiotics, regardless of the specific agents used, decreases recurrence and short-term mortality and increases peak expiratory flow rates. The data also suggest that the benefit is proportional to the severity of the exacerbation, with patients needing mechanical ventilation deriving the most benefit.[108]

A seminal study by Anthonisen et al[109] found that the outpatients most likely to benefit from antibiotic therapy are those that present with 2 or more of 3 cardinal symptoms: increased dyspnea, sputum volume, or purulence. More recent data suggest that increased sputum purulence alone is evidence of lower airway bacterial infection, although an associated response to antibiotics has not yet been studied.[42] Current consensus guidelines[1] suggest that patients meeting the above criteria be given antibiotics as shown in **(see Table 4)**.

In patients who are severely ill or who have risk factors for pseudomonal infection, consideration should be given to high dose fluoroquinolones and/or

Table 4. Antibiotics For COPD Exacerbations

For patients who will be discharged from the ED:
- Aminopenicillins (in communities with low local prevalence of beta-lactamase producing organisms and penicillin-resistant *S. pneumoniae*)
- Second- or third-generation cephalosporins
- Trimethoprim/sulfamethoxazole
- Doxycycline
- Macrolides

For admitted patients or in discharged patients who have recently failed a course of antibiotics:
- Beta-lactam/beta-lactamase inhibitor combinations (e.g., amoxicillin/clavulanate)
- Respiratory fluoroquinolones
- Second- or third-generation cephalosporins

combination therapy for pseudomonal coverage. A recent observational study found that recent antibiotic use (within 2 weeks) and a prior history of intubation were significant risk factors for infection with a variety of multi-drug resistant bacteria.[105] As always, local antibiotic resistance patterns should be kept in mind, including the possibility of the increasingly frequent methicillin-resistant *S. aureus* in both its community- and hospital-acquired strains as well as increasing levels of cephalosporin and macrolide-resistant strains of *S. pneumoniae*.[22] In severe presentations where concomitant pneumonia is suspected, addition of vancomycin may be considered to include coverage for these multi-drug resistant pathogens.

There is little data to guide the duration of antibiotic therapy, although recent data from outpatient trials suggests that courses as short as 3–5 days may be as effective as the more traditional 7–14 day courses.[110-116]

Treatment: Ventilatory Support

In patients whose acute exacerbation begins to overwhelm their physiologic reserves, hypercapnic respiratory acidosis ensues, impairing respiratory muscle function and initiating a downward cycle of respiratory failure. In order to interrupt this cycle, ventilatory support may be necessary. In patients who are appropriate candidates, non-invasive positive pressure ventilation (NPPV) may be employed, while some patients may require invasive positive pressure ventilation (endotracheal intubation).

NPPV

Since the 1980s, non-invasive positive-pressure ventilation has emerged as a primary therapy for respiratory distress in appropriate COPD patients to reduce symptoms, avoid intubation, and decrease morbidity and mortality. GOLD consensus guidelines list the following as indications for NPPV:

- Significant respiratory distress, with dyspnea, tachypnea, accessory muscle use, or respiratory fatigue
- Hypercapnia (pCO_2 > 45 mm Hg or > 6 kPa), with or without acidemia (pH < 7.35)

Table 5. NPPV Exclusion Criteria

- Inability to tolerate the mask or use it effectively:
  - Patient discomfort
  - Craniofacial abnormalities or trauma
  - Facial hair, burns, extreme obesity, other skin abnormalities
- Inability to protect the airway or coordinate breaths with the ventilator:
  - Significant alterations in mental status/obtundation
  - Hemodynamic instability (hypotension, dysrhythmias, hemorrhage)
  - Respiratory arrest/apnea
  - Inability to clear secretions
- Inability to tolerate possible aerophagia (e.g., recent gastrointestinal surgery)

Although blood gas values are included in the suggested indications, it is important to reiterate the primacy of the patient's clinical status over specific blood gas values.

Typically, a cushioned face or nasal mask is applied to the patient's face, through which a small portable ventilator provides inspiratory pressure support (IPAP) triggered by the patient's inspiration, with or without end-expiratory positive pressure (EPAP or PEEP), similar to pressure-support ventilatory mode on a conventional ventilator. The pressure support reduces the work of breathing and helps to improve gas exchange, presumably by splinting open distal airways.[117,118]

The main advantages of NPPV are the avoidance of endotracheal intubation (and its consequent complications) as well as its improved resource utilization. Side effects (damage to facial skin from the pressure of the mask used and insufflation of the stomach) of NPPV are usually minor and well tolerated. Due to the use of the nasal/facial mask and patient-triggered support, certain common-sense exclusion criteria must be kept in mind **(see Table 5)**.[119]

Randomized controlled trials[120-126] and several systematic reviews and meta-analyses[127-129] have found noninvasive ventilation to improve gas exchange and reduce intubation, treatment failure, costs, and mortality. Some have questioned whether NPPV may simply delay the inevitable in patients with severe exacerbations; however, recent data suggests that NPPV is effective and worth attempting even in patients with pH < 7.25.[130] Although there is some variability in the mask type and the ventilatory support modes available with NPPV, these variables do not appear to change its efficacy significantly.[131,132]

NPPV should be instituted early in the patient's ED course, not only after other modalities have failed. It has been found to be most effective at preventing intubation when used early in the management of patients with moderate to severe presentations. Patients who are placed on NPPV should be considered at high risk and should continue to be closely monitored and receive aggressive medical therapy. A significant proportion of patients will fail NPPV and require intubation. A recent observational study of patients being treated for respiratory failure with NPPV found that a GCS < 13 on presentation to the emergency department and/or persistent acidemia or tachypnea after a 1-hour trial of NPPV were predictive of the need for intubation.[133]

Invasive Ventilation

As with severe asthma, intubation and mechanical ventilation should be avoided if at all possible because mortality increases dramatically once a patient is intubated (from 1.7% to 28% in 1 large study).[12] However, in cases where patients do not respond to initial management or are in frank respiratory failure, it can be lifesaving. Although clinical judgment should

always be the overriding consideration when deciding to intubate, consensus guidelines have been developed **(Table 6)**.

Although it is preferable to avoid intubation if possible, it is even less desirable to intubate a patient in an uncontrolled manner. If a patient is clearly on a path to respiratory failure, they should be intubated before they progress to respiratory or cardiorespiratory arrest. The precise timing of endotracheal intubation in patients with asthma or COPD is complex and continues to remain more in the realm of art than science. The decision to intubate and its timing should ideally be made by the clinician with the most experience in these cases. Once the decision has been made, the clinician must proceed rapidly without delay. In addition to airway management devices, needle and tube thoracostomy equipment should be easily accessible. If time permits, preoxygenation with high flow oxygen is recommended. If conscious and cooperative, the patient should be allowed to remain in a position of comfort as long as possible.

Most of the literature addressing airway management of patients in acute respiratory distress focuses on asthma, not COPD. Rapid sequence intubation (RSI) is generally recommended. However, in some cases, awake intubation with or without pharmacologic adjuncts may be considered. For example, if a patient has features suggesting a difficult intubation (e.g., short neck, extreme obesity, craniofacial abnormalities), it may be safer to avoid paralyzing the patient and secure an airway using endoscopic guidance. The choice of induction and paralytic agents is dictated by the individual clinical scenario and practitioner experience and preference. Ketamine is preferred by many practitioners in this setting because of its ability to sedate the patient while maintaining protective airway reflexes and ventilation. To help minimize the added airway resistance caused by the endotracheal tube, the largest tube size that can be accommodated by the airway should be used.

Post-Intubation Management

Although placement of a definitive airway can be a relief for both the patient in severe distress and the treatment team, it is critical to maintain a high level of vigilance and care after intubation, as serious post-intubation complications may occur. Chief among these complications is dynamic hyperinflation that results in elevated end-expiratory pressures, sometimes called intrinsic PEEP or auto-PEEP. This is essentially a worsening of the same process that characterizes the COPD exacerbation itself: severe expiratory flow limitation results in incomplete exhalation, increased lung volumes, and increased airway and intrathoracic pressures. All of these pathophysiologic factors create an increased work of breathing for the patient's respiratory system. In the immediate post-intubation scenario, this may be exacerbated by over-zealous bag-valve mask ventilation. Thus, it is critical to remember to ventilate the patient slowly and allow sufficient time for exhalation, despite the anxiety and excitement that may accompany the intubation of a critically ill patient.

Table 6. Indications For Intubation[1,2]

- Respiratory arrest
- Failure or contraindication to NPPV
- Hemodynamic instability
- Decreased level of consciousness
- Severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Respiratory rate greater than 35 breaths per minute
- Life-threatening hypoxemia (PaO_2 < 40 mm Hg or PaO_2/FiO_2 < 200 mm Hg)
- Severe acidosis (pH < 7.25) and/or hypercapnia ($PaCO_2$ > 60 mm Hg)

The increased airway and intrathoracic pressures may also cause decreased venous return and subsequent hypotension and frank shock. Ventilator-induced lung injury (VILI) may also occur: pneumomediastinum, pneumothorax, and tension pneumothorax. Pneumothorax should be treated with tube thoracostomy for any patient on positive pressure ventilation. Hypotension should be addressed by allowing increased expiratory time to relieve the elevated intrathoracic pressure and intravenous fluid boluses to address relative and absolute hypovolemia, which often develops in patients with decreased intake and increased insensible losses from prolonged respiratory distress. In extreme cases (e.g., PEA arrest immediately following intubation) it is necessary to disconnect the ET tube from the bag-valve-mask or ventilator and gently apply manual pressure to the patient's chest, allowing extended decompression while simultaneously performing bilateral needle and/or tube thoracostomy.

Previously, the goals of mechanical ventilation for respiratory failure included normalization of blood gas levels and pH. However, this would often require inordinately high pressures and volumes, resulting in VILI and cardiovascular collapse. Mechanical ventilation strategies aim to improve gas exchange and increase alveolar ventilation while minimizing hyperinflation. To achieve those goals, it is often necessary to hypoventilate the patient with lower tidal volumes and respiratory rates that maximize expiratory time while minimizing hyperinflation. This involves permissive hypercapnia that allows for more manageable ventilator settings and fewer complications.[134] Although it is not known what degree of respiratory acidosis is acceptable, most authors use an initial goal for pH of 7 if it reduces the risk of lung overdistention injury.[20] Initial ventilator settings should be geared towards low respiratory rates (8–10), low inspiratory:expiratory (I:E) ratios, high inspiratory flow rates (80–100 L/min), low tidal volumes (6–8 mL/kg ideal body weight), and little to no added PEEP.[135] Further adjustment should be guided by blood gases and measurements of airway physiology, as summarized in **Tables 7 and 8**.

Modern ventilators are capable of providing a confusing array of physiologic measurements. Peak

airway pressures are not a reliable indicator of risk of VILI, since high pressures may be required to overcome resistance in communicating airways. Since direct measurement of intrinsic PEEP with an end-expiratory hold does not reflect the pressure in alveoli behind obstructed or collapsed airways during expiration, it may not adequately reflect alveolar pressure. Plateau pressure, although measured at end inspiration, is believed to better reflect mean alveolar pressure and the degree of dynamic hyperinflation. Plateau pressures correlate with the risk of VILI, with fewer complications occurring when plateau pressures are maintained below 30 cm H_2O.[135]

Although it would seem that PEEP should be minimized in order to reduce intra-alveolar pressures and the risk of VILI, data suggest that, in some patients, splinting open airways with PEEP helps reduce expiratory airway resistance and reduces dynamic hyperinflation in a counter-intuitive fashion.[136] One study examining this phenomenon found no patient characteristics to predict responders and suggested that a trial of PEEP be used to observe its effect in patients with high plateau pressures.[137] A reasonable strategy may be to start with little to no PEEP, then gradually increase the PEEP and observe the resultant response in plateau pressure.

Achieving the above physiologic goals may be difficult and may require very low tidal volumes, respiratory rates, and/or additional patient sedation or paralysis. Although it may be necessary to paralyze a patient to ventilate them, long-acting paralytics should be used with extreme caution as they may, in conjunction with steroid-induced myopathy, cause long-term respiratory muscle dysfunction and ventilator dependence.[138]

Additionally, aggressive medical therapy should be continued after intubation, with the use of in-line bronchodilator therapy, intravenous antibiotics, and steroids.

Special Circumstances

Are Patients With COPD Exacerbation At Especially High Risk Of Thromboembolic Disease?

As with many of the other relevant clinical questions, the data available on this question is often of questionable validity for the ED patient. Pulmonary embolism (PE) prevalence estimates vary by study population and methodology, ranging from 3% in unselected patients admitted to the floor for acute exacerbation[139] to 25% in patients for whom no apparent etiology for their exacerbation could be found.[140] One large study of ICU patients found a prevalence of deep venous thrombosis of 11%.[141] Other smaller studies have also found similar rates.[142,143]

A recent Swiss study prospectively examined the incidence of PE in patients requiring admission for COPD exacerbation.[139] From an initial group of 521 patients, 385 patients were excluded for having an obvious cause of dyspnea such as pneumonia or pulmonary edema, already being on anticoagulation therapy, renal insufficiency, or a requirement for assisted ventilation. Of the 123 patients remaining, all received a standardized evaluation including chest x-ray, ECG, and ABG. After this preliminary evaluation, the treating clinician was asked to decide whether or not they believed that further evaluation for PE was warranted. All patients were then further tested with a d-dimer assay, lower extremity ultrasound, and CT pulmonary angiogram. In those patients where the attending physician believed that further evaluation was indicated, 6.2% (95% confidence interval, 2.3%–17%) received a final diagnosis of PE after this standardized work-up. In patients for whom the clinician felt further workup was not necessary, 1.3% (95% confidence interval, 0.3%–7.1%) were diagnosed with PE. The authors interpreted these data as supporting a more selective strategy for PE evaluation in patients presenting with COPD exacerbation. Although this study has many advantages, such as its "real-life" approach looking at an undifferentiated population presenting to an ED, the large number of patients excluded from the analysis, the use of non-patient oriented outcomes, and the large overlap in the confidence intervals of patients eventually diagnosed with PE limit its applicability to clinical practice.

The GOLD consensus guidelines state that "a low systolic blood pressure and an inability to increase the

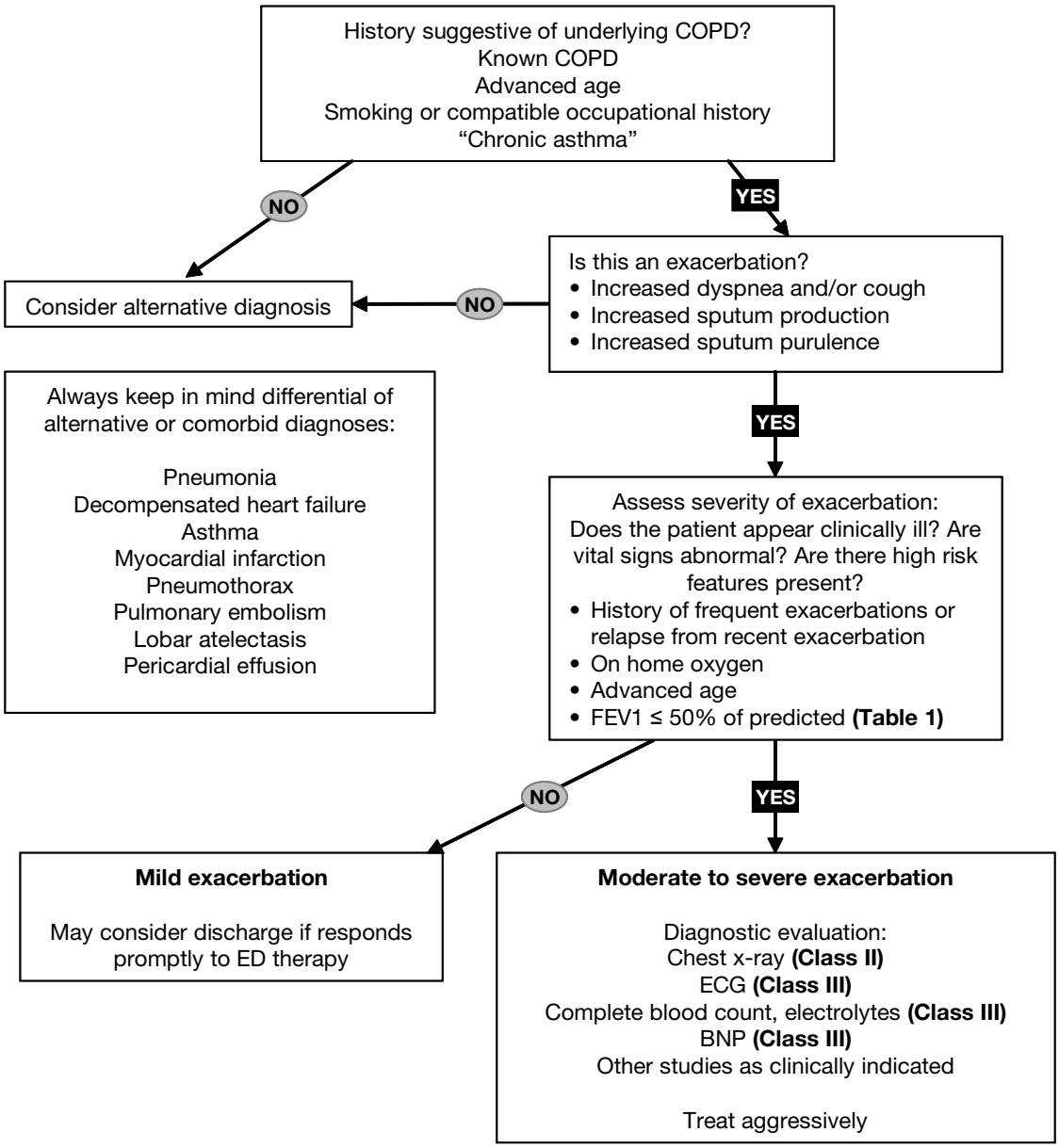
Table 7. Initial Ventilator Settings For The Intubated COPD Patient

Mode: Assist control
Respiratory rate: 10/min
Tidal volume: 6–8 mL/kg ideal body weight
PEEP: 5 mm Hg
FiO_2: 1.0
ABG in 15–20 minutes
Allow hypoventilation/permissive hypercapnia to a pH as low as 7.20
Continue aggressive medical management
Avoid air trapping: high flows between 80 and 100 L/min

Table 8. Post-Intubation Troubleshooting

Problem	Interventions To Consider
High plateau pressure?	• Consider pneumothorax • Increase inspiratory flow rate • Decrease I:E ratio • Perform trial of gradually increasing PEEP • Sedate patient as needed to facilitate ventilation
Persistent hypoxia?	• Aggressive suctioning • Ensure proper tube placement • Consider pneumothorax
Hypotension?	• Decrease I:E ratio • Provide fluid resuscitation • Consider pneumothorax
PEA arrest?	• General ACLS measures • Disconnect ET tube and apply manual pressure to chest • Place bilateral chest tubes • Provide fluid resuscitation

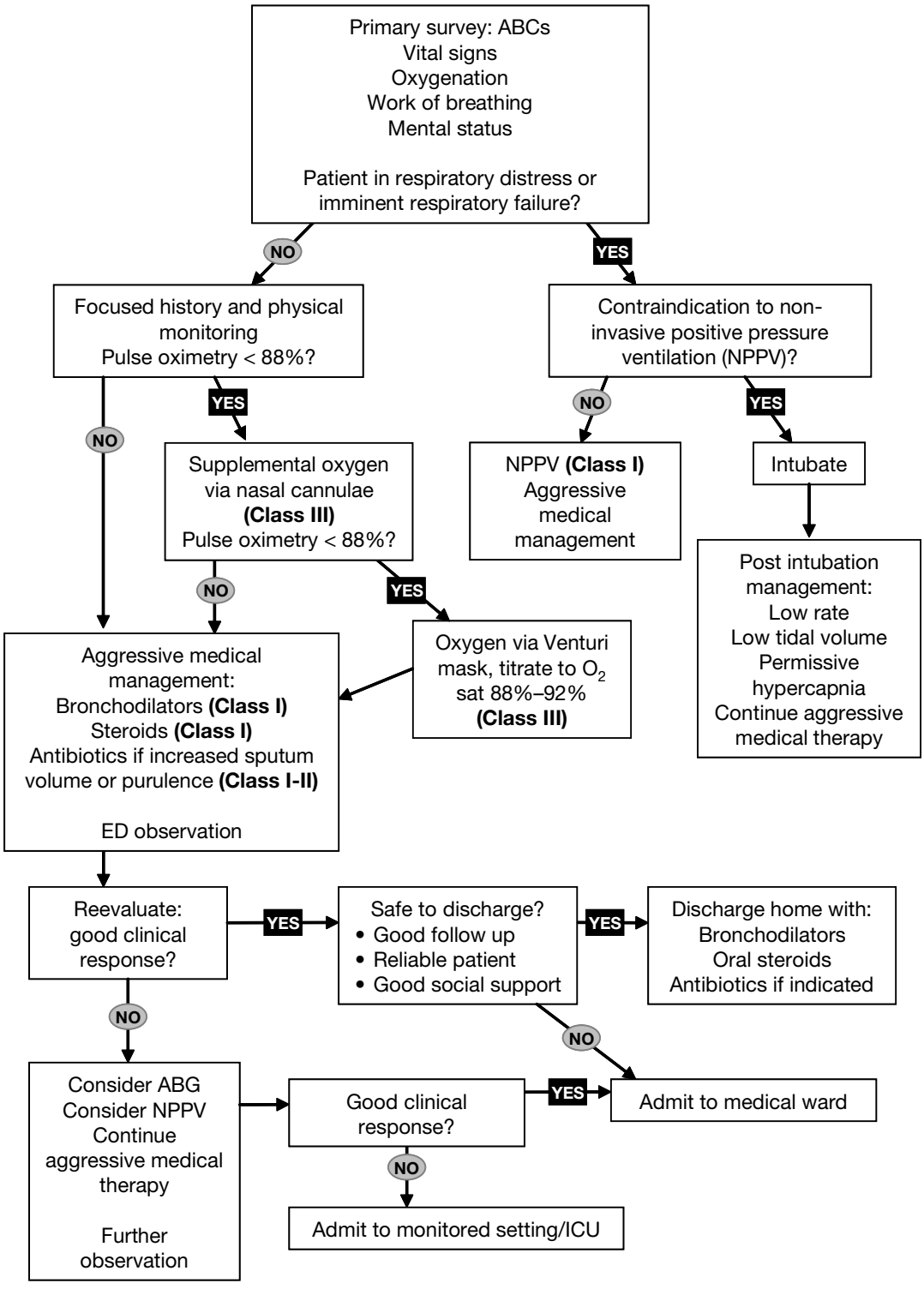
Clinical Pathway: Diagnostic Evaluation Of COPD Exacerbation



The **evidence for recommendations** is graded using the following scale. For complete definitions, see back page. **Class I:** Definitely recommended. Definitive, excellent evidence provides support. **Class II:** Acceptable and useful. Good evidence provides support. **Class III:** May be acceptable, possibly useful. Fair-to-good evidence provides support. **Class Indeterminate:** Continuing area of research.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Clinical Pathway: Therapeutic Management Of COPD Exacerbation



The **evidence for recommendations** is graded using the following scale. For complete definitions, see back page. **Class I:** Definitely recommended. Definitive, excellent evidence provides support. **Class II:** Acceptable and useful. Good evidence provides support. **Class III:** May be acceptable, possibly useful. Fair-to-good evidence provides support. **Class Indeterminate:** Continuing area of research.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

PaO_2 above 8.0 kPa (60 mm Hg) despite high-flow oxygen also suggest pulmonary embolism. If there are strong indications that PE has occurred, it is best to treat for this along with the exacerbation."[1] Although empiric treatment for PE may be appropriate in patients who meet these criteria, we could not find data to directly support this approach. Moreover, the use of readily available bedside diagnostic modalities (such as transthoracic echocardiography) may help to confirm the diagnosis of a hemodynamically significant PE, reducing the risk of potentially dangerous empiric therapy if it is not truly indicated, especially when fibrinolytic agents are being considered.

In summary, the diagnosis of thromboembolic disease in the setting of COPD remains difficult and further research is needed to guide decision making. Because of its significant incidence and specific treatment, it remains an important consideration. In the absence of a validated diagnostic methodology specific to patients with COPD, using one of the many published evaluation strategies for PE in the undifferentiated patient with dyspnea is appropriate.

Theophylline

Although becoming increasingly uncommon, there are still some patients who use oral theophylline for maintenance therapy of their COPD. Theophylline is a methylxanthine, in the same class as caffeine. It is highly protein-bound, has a small volume of distribution, and is extensively metabolized by the cytochrome P450 system. Serum levels correlate poorly with the dosing history[144] and can vary widely due to drug interactions or concomitant liver disease. Therapeutic levels are generally regarded as being between 10 mcg/mL and 20 mcg/mL; however, theophylline has a narrow therapeutic index. Toxic effects begin even within the traditional therapeutic range, and the incidence of serious toxic effects correlates poorly with serum levels.[145]

The most common toxic effects are nausea and vomiting, and the most serious are electrolyte abnormalities, seizures, and dysrhythmias. Theophylline predisposes to a wide range of atrial and ventricular dysrhythmias, ranging from sinus tachycardia or occasional PVCs to atrial fibrillation, multifocal atrial tachycardia, and life-threatening ventricular arrhthmias.[146-150] Treatment includes correction of electrolyte abnormalities, supportive care, and hemodialysis or hemoperfusion for life-threatening toxicity. Due to the lack of evidence for benefit and the potential toxicities, it is not recommended that methylxanthines be initiated in patients presenting to the emergency department.

Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin (AAT) is a protein synthesized by the liver and respiratory epithelium. It inhibits human neutrophil elastase, a serine protease that normally degrades elastin and other connective tissue elements. Patients with a genetic lack of alpha-1 antitrypsin have unopposed neutrophil elastase activity, resulting in destruction of the connective tissue architecture of the lung and emphysema. The most common clinically significant mutation is the Z allele. This mutation is most common in patients of northern European descent, but it is found worldwide. Patients homozygous for the Z allele account for 95% of clinically significant disease, and these patients are at risk for development of emphysema and COPD at an unusually young age: in the fourth or fifth decade and even earlier in smokers. Because the mutation prevents hepatic secretion of the defective protein into the blood, intracellular buildup can also cause liver disease and cirrhosis.

Current estimates are that 2%–3% of patients with COPD have alpha-1 antitrypsin deficiency as an underlying or contributory cause. Although attempts have been made to slow lung function decline in AAT patients by replacing the deficient enzyme with intravenous infusions of purified human alpha-1 antitrypsin, these efforts have been met with only modest success at a high cost.[151] Due to these difficulties, screening for the presence of the mutation has questionable benefit, and it is currently recommended only for patients who develop emphysema at a young age.[1]

End Of Life Concerns

End-stage COPD can pose special challenges. As with other terminal illnesses, patient autonomy is of utmost importance, and patients' wishes must be respected. However, it is difficult to determine when "very severe" COPD transitions into "end-stage" COPD— patients may live for years with chronic respiratory failure, and a large proportion of patients die of related comorbidities rather than respiratory failure.

Decisions regarding goals of care are best made collaboratively with patients, their families, and all of the members of the health care team. Such decisions should take into account the risks and discomforts of aggressive supportive care, such as prolonged invasive ventilation and/or tracheostomy. Ideally these decisions should be made during a time of stability. Unfortunately, these issues are often first considered in the setting of impending respiratory failure in the emergency department. Under such circumstances, the above considerations still apply: when patient wishes have been clearly expressed and documented, every effort should be made to honor them. However, in the absence of clear directives, the clinician must err on the side of aggressive treatment until further information is available.

As with any discussion of patient treatment preferences, it is important to make a distinction between Do Not Resuscitate (DNR) orders and end of life care preferences. Patients and providers alike frequently confuse these very different concepts. DNR orders specifically refer to what interventions a patient

wishes to be undertaken to interrupt or reverse death in the event of a deterioration of condition that may be sudden or unexpected. End of life care preferences determine the acceptability of therapies and the goals of care in the context of terminal illness or severely reduced quality of life.

When it is determined that symptom palliation is the primary goal of care, it is important to remember the usefulness of opiates in reducing the tremendous discomfort of dyspnea. Although most studies that have examined opioid treatment for dyspnea have employed small numbers of patients, a meta-analysis showed benefit as compared with placebo, with only minor effects on gas exchange and respiratory drive.[152] The analysis showed that both oral and parenteral opiates were effective, but nebulized opiates were not. The precise dosing is unknown, but the relatively rapid onset of most opiates makes a strategy of starting with a modest dose and titrating up as necessary most practical. Benzodiazepines may also be used to treat anxiety.[153] It is also important to remember to prevent or treat the nausea and constipation caused by opiates.

Controversies/Cutting Edge

Oxygen Therapy

Although there is no doubt that prevention of hypoxia is of paramount importance, it has long been recognized that administration of high oxygen concentrations to COPD patients sometimes induces or worsens hypercapnia and may result in respiratory acidosis, CO_2 narcosis, and clinical deterioration. However, the pathophysiologic mechanisms underlying this phenomenon and its clinical significance remain contentious. Suppression of hypoxic respiratory drive and release of hypoxic mediators of vasoconstriction (leading to worsened ventilation/perfusion mismatch) are the two main mechanisms believed to account for this phenomenon, although others have been postulated. Studies trying to determine which is the dominant factor are conflicting,[154-157] and they have used varying methods and patient populations, making it difficult to draw firm conclusions. Additionally, only a subset of COPD patients are at risk of developing oxygen-induced hypercapnia, but no reliable method of identifying these patients has been uncovered. Conversely, some patients will progress to hypercapnic respiratory failure regardless of oxygen administration.[158]

Currently, the solution to this dilemma is to use just enough oxygen therapy to avoid critical hypoxia, while also avoiding delivery of higher oxygen concentrations than are absolutely necessary. Observational data suggests that a target oxygen saturation level in the range of 88%–92% may help avoid inducing further respiratory acidosis.[39] This target is also near the "flat" part of the oxygen/hemoglobin dissociation curve, where increased partial pressures of oxygen result in marginally smaller benefits.

The most common methods to achieve this goal are through the use of low-flow devices (such as nasal cannulae) or through high-flow devices that allow for tighter regulatory of FiO_2 (such as Venturi masks). Oxygen delivery by low-flow devices is dependent on a patient's minute volume, with hyperventilating patients receiving a lower fraction of inspired oxygen. In theory, high-flow devices achieve a more reliable FiO_2 in the face of patient hyperventilation. There is some data to support this concept,[159] although it is unknown whether there are associated clinical benefits. More specific recommendations, especially for identifying those patients who are most at risk of suffering harm from oxygen therapy, await further research and controlled trials.

Alternatives To Arterial Blood Gases

Although arterial blood gas analysis is performed less frequently in the ED, there are still situations where the information provided is useful. Because of the discomfort and complications associated with the procedure, there has been a search for alternative methods of making these measurements, with incomplete success.

The relationship between venous blood gas (VBG) measurements and their arterial counterparts has been studied. Although studies in mechanically-ventilated ICU patients[160] and in COPD-exacerbation patients[161] have derived equations for predicting ABG values from VBG values, these results are single center specific, and most have not been validated. A well-designed Australian study found that venous samples could be used to reliably estimate arterial values of pH but not pCO_2.[162] In a later validation study at the same center, it was estimated that approximately 30% of ABGs could be avoided by using a venous pCO_2 of 45 mm Hg as a cut-off value for ruling out hypercarbia (defined as $pCO_2 > 50$ mm Hg).[163]

Other methods of measuring blood gases have also been studied. Sampling of capillary blood from the earlobe has been shown to have satisfactory correlation with blood gas values in patients presenting with COPD exacerbation,[164] although this method requires placement of a vasodilatory paste on the earlobe for 10 minutes prior to sampling, and there is some question whether earlobe puncture is significantly less painful than radial artery sampling. Transcutaneous monitoring of pCO_2 has also been shown to correlate well with ABG values in a study of hospitalized patients over age 65[165] and in patients undergoing non-invasive ventilation for COPD exacerbation.[166]

These alternative methods of blood-gas measurement are subject to the same limitations as traditional measurements from arterial puncture; they cannot be interpreted separately from the other clinical data available.

Capnography

Continuous monitoring of exhaled carbon dioxide (capnography), long a standard of care during operating room anesthesia, is becoming more commonplace in the emergency department for a variety of uses. Most commonly, it is used to confirm tracheal intubation and to guide cardiopulmonary resuscitation. Emerging uses include monitoring during procedural sedation as well as for diagnostic purposes. Aside from the obvious implications for airway management in patients who require intubation, capnography has potential for diagnostic utility in COPD patients.[167]

Bronchospasm and airway obstruction cause a delay in the exhalation of CO_2 rich alveolar air that changes the capnography tracing in characteristic ways **(Figure 2)**. Unfortunately, at the moment, this diagnostic potential is limited to qualitative pattern recognition by the emergency physician, since a quantitative system to analyze the capnographic tracing (analogous to ECG definitions such as waves and intervals) has not been developed.

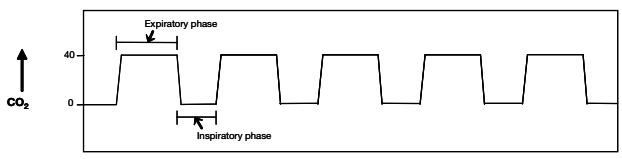
While it may seem that end-tidal CO_2 may also have application as a non-invasive proxy for the measurement of arterial carbon dioxide tension, the gradient between $PaCO_2$ and end-tidal CO_2, which is very small in normal subjects, may be increased in patients with lung disease. Thus, the measured end-tidal CO_2 may be falsely reassuring in precisely those patients whose gas exchange is the most impaired.

Transtracheal Open Ventilation

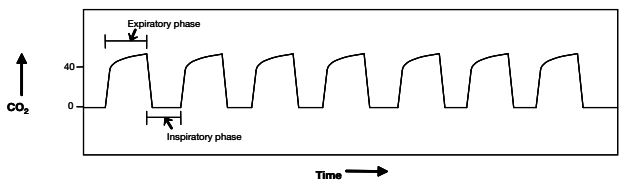
Due to its associated complications, such as ventilator-associated pneumonia and paralysis-associated neuromuscular dysfunction, alternatives to endotracheal intubation have been investigated. One promising method is transtracheal open ventilation, where a small cuffless tracheostomy tube is placed within the trachea and the patient is ventilated using high pressure-support settings. This allows the patient to remain awake and preserve their airway protective reflexes. A recent randomized controlled trial evaluated this technique; 39 patients with COPD exacerbation who had failed non-invasive ventilation were randomized to traditional endotracheal intubation or transtracheal open ventilation.[168] The transtracheal ventilation group had similar blood gas values after randomization, but they had significantly decreased complication rates and lengths of stay in the ICU.

Figure 2. End Tidal Capnography Tracings

Normal capnography tracing:



Capnography tracing in bronchospasm and obstruction—note the blunted upslope at the beginning of exhalation due to expiratory airflow limitation



Ultrasound

Bedside ultrasound in the emergency department has been increasingly used to diagnose pneumothorax in patients with both medical and traumatic presentations. Ultrasound in this setting has excellent test characteristics, with very high sensitivity and specificity. However, until recently, the possible effect that structural lung disease and emphysema may have on diagnosis of pneumothorax had not been studied. A 2006 study of 41 patients, 9 of whom had pneumothorax and 18 of whom had COPD, found that the presence of COPD increased the false-positive rate.[169] Although this study involved a relatively small number of patients, it suggests that ultrasound continues to be an effective tool for ruling out pneumothorax in COPD patients, but positive results should be confirmed by other diagnostic modalities before therapy is instituted.

Biomarker-Guided Therapy

Several biomarkers are being investigated as tools to aid in the diagnosis and management of COPD exacerbations.

Procalcitonin is a precursor of calcitonin, a hormone released by neuroendocrine cells in the thyroid gland.[170] Serum levels of procalcitonin have been found to increase in response to systemic inflammation, but they are suppressed by cytokines that are released during viral infection. Because of these properties, it has been investigated as a marker of bacterial infection. A recent partially-blinded controlled trial randomized 208 patients presenting with COPD exacerbation to either standard care or to procalcitonin testing, with high or low serum levels "encouraging" or "discouraging" antibiotic therapy. The patients in the intervention group were prescribed antibiotics 44% less frequently than the control group, with no rebound effect at 6-month follow up and no significant difference in clinical outcomes.[171]

Other studies have looked at the diagnostic and prognostic value of other sputum and serum markers. Measurement of inflammatory cytokines in sputum samples during an exacerbation has been found to be predictive of the etiology as being either due to viruses, *Pseudomonas aeruginosa*, or non-pseudomonas bacteria.[172] Persistent elevations of serum inflammatory markers has been associated with risk of recurrent exacerbation.[173] Another study suggests that copeptin, a precursor to vasopressin, may be useful as a prognostic marker during COPD exacerbations.[174] Although these results have yet to be validated, and many of these

assays are not widely available, these are promising areas for future research.

Glycemic Control

Previous work has shown an association between hyperglycemia and poor outcomes in critically ill patients with a variety of medical and surgical conditions, and a recent observational study has found a similar association among COPD patients, independent of prior diagnoses of diabetes mellitus.[57] Prospective studies evaluating the clinical benefit of tight glycemic control have yet to be conducted in COPD exacerbations.

Hospital At Home

"Hospital at home" is an emerging management strategy for COPD exacerbations; it is intended to provide care at home via specially trained visiting nurses. Ideally, this provides the advantages of allowing the patient to remain in a familiar and comfortable environment, while avoiding the high costs of inpatient hospital stays.

Several studies, including a 2003 Cochrane systematic review, have found that well-designed hospital-at-home programs do not increase the hospital readmission rate or mortality, and most patients who are treated at home express a preference for such care.[175-180] Data suggest that approximately 25%–30% of patients evaluated meet inclusion criteria for these programs.[175,181] Two studies found that overall costs were lower for patients in the hospital-at-home group.[177]

A key component to any system of providing care at home for COPD exacerbations is patient selection. Most studies employed strict selection criteria designed to limit patients to those with fairly mild, uncomplicated exacerbations. Common criteria include:

- Normal mental status
- Absence of acidemia
- Absence of significant comorbid conditions
- Absence of chest x-ray changes
- No need for additional supplemental oxygen (beyond what the patient normally employs at home)
- Stable social support at home

It is important to note that, although the relapse/readmission rate is not increased by the use of hospital-at-home services, up to 10% of patients sent home for treatment of an exacerbation will require readmission before the resolution of the exacerbation. Thus, although hospital at home programs will reduce the number of admissions for carefully selected patients, it is important for both care providers and patients to understand that there is still a significant chance that they may require admission in the near term.

Although the concept of "hospital at home" is specifically intended to avoid admission, it shares many of the same components and selection issues that apply to "early discharge" programs that are intended to shorten inpatient stays for COPD exacerbation patients by providing structured early discharge criteria and appropriate home care. Some authors do not make a distinction between hospital at home and early discharge programs, making it difficult to make recommendations that specifically apply to emergency department decision making.

Naturally, these programs are very dependent on local resources and conditions, and they require certain financial and social support structures to be in place. Nearly all of the relevant research has been conducted in countries with socialized medical care and universal coverage; therefore, the results may not be entirely applicable to other systems.

Disposition

Outpatient Versus Inpatient Care

Over the years, many studies have attempted to identify prognostic factors in acute exacerbations of COPD. Interpretation of this data is made difficult by the variety of populations (unselected, medical ward, specialty ward, ICU, or some combination of these) and outcomes (short-term or long-term) studied as well as varying methodological quality. COPD research still awaits a robust decision rule to help risk stratify patients and guide disposition and management, similar to the tools available for pneumonia patients. One such rule was developed for COPD exacerbations in the 1990s, but it was only able to identify 57% of patients who would relapse in 48 hours.[182]

Among studies examining short term outcomes such as mortality or relapse, the most consistently identified prognostic factor is age.[12,183-187] Other studies have identified a wide variety of additional prognostic factors, including markers of respiratory dysfunction or severity of underlying COPD,[46,185,186,188-191] severity of exacerbation,[184,192-194] history of frequent exacerbations or relapse after exacerbation,[182,195,196] presence or severity of comorbidities,[12,185-187,192] or poor general health or functional status.[194] However, many of these measurements are inconsistent from study to study, and none have been prospectively validated for use in risk stratification.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) and ATS/ERS guidelines for disposition are shown in **Table 9**. Of note, one recent study has found that there is a high level of concordance between the consensus guidelines and clinical practice in EDs in the U.S. and Canada.[197]

Patients Who Are Going Home

Patients discharged home should receive a short course of oral steroids and antibiotics (for those with an in-

crease in sputum volume or purulence) in addition to their maintenance medications **(Table 10)**. If a patient has not had pneumococcal or influenza vaccination, these should be administered as well. Although they have not been shown to have any effect on mortality, there is some evidence that they may reduce the incidence of pneumonia and infective exacerbations, and they have minimal side effects.[198-201]

Patients who smoke should be informed that quitting is one of the most effective things they can do to improve the course of their disease, and they should be offered smoking cessation resources upon discharge. Although emergency department interventions have not been shown to have a high efficacy, the American College of Emergency Physicians has developed a guideline recommending universal screening and brief interventions to help patients quit.[202]

Additional Disposition Considerations

A recent large, well-designed trial in patients with moderate to severe COPD (FEV1 < 60% of predicted) has shown that combination therapy consisting of an inhaled long-acting bronchodilator and inhaled steroid reduces exacerbation frequency and improves symptoms, although it does not reduce mortality.[203] Another large study also found that treatment with inhaled steroids reduces exacerbation frequency in patients with severe COPD.[204] This data supports current consensus guidelines, which recommend long acting inhaled bronchodilators for patients with moderate to severe disease (FEV1 < 80% of predicted) and inhaled steroids for patients with severe disease (FEV1 < 50% of predicted).[1] Additionally, all patients should have a short-acting inhaled bronchodilator to use as needed (analogous to a rescue inhaler for asthma patients).

One recent retrospective study suggested that statins may reduce mortality in COPD patients.[205] Whether this is due to reduced mortality from concomitant coronary artery disease or due to anti-inflammatory effects (or a combination of both) is unknown, and these results have yet to be prospectively validated. However, it makes sense that, given the common risk factors and high rates of comorbidity, aggressive cardiac risk-factor modification should be undertaken for COPD patients just the same as is done for patients being evaluated for chest pain or active coronary disease.

Table 9. Indications For Hospital Admission

- Older age
- Significantly worsened symptoms (e.g., dyspnea)
- Significantly worsened signs: respiratory distress, tachypnea, cyanosis, peripheral edema
- Severe underlying COPD, which may be assessed by
  - — Recent spirometry or pack-years smoked as a surrogate marker
  - — Use of home oxygen
- Failure to respond to initial therapy
- Failure to respond to recent outpatient intervention or history of relapse after exacerbation
- Presence of significant comorbidities (e.g., new onset dysrhythmia, heart failure, diabetes)
- Uncertain diagnosis
- Lack of home support, inability to care for self, and poor functional status

Indications for ICU/monitored setting admission:

- Intubation
- Severe dyspnea that does not improve with initial therapy
- Altered level of consciousness
- Refractory respiratory failure (PaO_2 < 40 mm Hg or $PaCO_2$ > 60 mm Hg) or acidemia (pH < 7.25)

Discharge Checklist

- Ensure that there is a stable home environment/ support or good independent functional status
- Ensure availability of close primary physician follow up—within several days
- Provide antibiotics, short-course oral steroids, and short-acting bronchodilators as indicated for current exacerbation
- Ensure that patients with moderate to severe diseases have an inhaled long-acting bronchodilator and inhaled steroids
- Provide influenza and pneumococcal vaccines as indicated
- Provide brief smoking-cessation intervention

Summary

Compared to other major cardiopulmonary illnesses of similar prevalence and morbidity, our understanding of chronic obstructive pulmonary disease is in relative infancy. With the current renaissance of investigation into its pathophysiology and management, we can expect and hope for continued advances that will help our patients live longer and more full lives. As this article has shown, there is already much we can do for these patients to help them feel better, to help them live longer, and to dispel the notion that COPD is an untreatable illness.

Case Conclusions

Patient 1: While simultaneously starting nebulized bronchodilators and steroids for the 57-year-old male, you call for chest x-ray and BiPAP. Although it takes a few minutes for respiratory therapy to set things up, the patient responds well to therapy and begins to turn around. An hour after arrival, he is tolerating BiPAP well and appears much more comfortable. His venous blood gas shows only mild acidosis and hyponatremia. His chest x-ray is unremarkable, but he describes a marked change in the quality of his sputum over the past several days, so you start antibiotics. After several hours of observation, you feel comfortable admitting him to the medicine ward.

Patient 2: Given her age, comorbidities, and the unclear clinical circumstances, you treat the 78-year-old female aggressively for both decompensated COPD and heart failure. You forgo the BNP, since it would be unlikely to change your clinical management. You give her aspirin,

Risk Management Pitfalls For COPD

1. **"His history didn't include COPD."**

   Aside from patients who may not know their medical history or who do not receive regular medical care, the confusing array of terminology associated with COPD may result in patients not knowing their diagnosis. COPD should be suspected in patients with a history of smoking or other particulate exposure in middle-aged or elderly patients, chronic poorly controlled "asthma," and clinical findings such as wheezing or responsiveness to bronchodilators.

2. **"I didn't hear any wheeze."**

   Even though it seems obvious and is considered a novice mistake, the paradox of decreased breath sounds in patients who have such severe obstruction that they are unable to move air may trip up even experienced clinicians when coupled with diagnostic uncertainty or clinical complexity.

3. **"I didn't give inhaled bronchodilators because he was so tachycardic."**

   Although tachycardia may be a side effect of inhaled bronchodilators, it is rarely if ever hemodynamically significant, and hemodynamic compromise is of secondary concern if respiratory failure is untreated ("B comes before C").

4. **"I thought the rule about giving too much oxygen is just for internists on the ward."**

   For reasons that remain contentious and poorly understood, some patients will develop worsened hypercapnic respiratory failure in the face of hyperoxia. We currently have no way of identifying which patients will develop this response. In the absence of a compelling argument in favor of hyperoxia, the prudent approach is to give no more oxygen than is necessary to achieve an SaO_2 in the range of 88%–92%.

5. **"His ABG didn't indicate that he required intubation," or the closely related "His pulse-ox was just fine until…"**

   Numeric values may be deceptive, especially in the COPD patient, who may have striking and unpredictable abnormalities at baseline and even more so when acutely decompensated. Therefore, it is of paramount importance that decisions regarding airway management and aggressive management be based on integration of the overall clinical picture rather than one or two laboratory or monitoring values.

6. **"I adjusted the ventilator to weight-appropriate settings."**

   Permissive hypercapnia is an effective strategy to maintain oxygenation while avoiding iatrogenic VILI. While it can be very uncomfortable to leave a patient at a pH of 7.20, carbon dioxide narcosis is no longer of concern once a patient is intubated, and the mild acidemia does not appear to be of clinical consequence.

7. **"I needled the chest after the breath sounds decreased, but he coded anyway."**

   Needle thoracostomy is insufficient therapy for pneumothorax in the setting of positive pressure ventilation—chest tube placement is mandatory.

8. **"Even intubation didn't help."**

   While adjusting ventilator settings, finding an ICU bed, and managing a busy ED, it is easy to forget to continue aggressive medical management even after securing an airway. In-line nebulized bronchodilators, antibiotics, steroids, and management of comorbid conditions must continue post-intubation.

9. **"But it looked like a pneumothorax on CXR!"**

   Underlying structural lung disease can confound radiographic diagnosis of pneumothorax, especially in a patient who is already at risk for the same and may have hypoxic respiratory failure and/or decreased breath sounds. If the suspected pneumothorax does not have the classical contour on chest x-ray or if obviously severe bullous abnormalities are visible, it may be necessary to obtain a CT to confirm that it is not a bleb to avoid unnecessary and possibly dangerous interventions.

10. **"The nurses kept asking for more paralytics to keep the vent from alarming and to keep the patient still."**

    Although paralytics may be necessary to ventilate a patient initially after intubation, there are many pitfalls to their use, including the possibility of paralysis without adequate sedation and analgesia as well as long-term neuromuscular dysfunction and ventilator dependence. Analgesia and sedation (e.g., benzodiazepines and opioids) are preferred whenever possible to keep the patient comfortable and in-sync with the ventilator.

nitrates, bronchodilators, steroids, and antibiotics. She has been largely sedentary and has normal renal function, so you order a CT angiogram of her chest. Meanwhile, she reports that the bronchodilators and nitrates have made her breathing feel better. After confirming that the CT shows no pulmonary emboli, you admit the patient to a telemetry-monitored bed where she can continue to have serial troponins drawn.

Key Points

- Although it is a frequently encountered entity, COPD should not be underestimated in its complexity and clinical impact.
- The differential diagnosis of COPD exacerbation includes some serious diagnoses and no easy exclusions. Keep these in mind!
- A, B, and C: Antibiotics, Bronchodilators, and Corticosteroids are the mainstays of medical therapy.
- Since there is no clinical difference between routes of administration for bronchodilators, use what is most practical (cost, ease of use).
- Think early institution of NPPV and be liberal with its use—it is one of our most effective therapies for avoiding intubation and bad outcomes.
- Don't let numbers—ABG, BNP, pulse-ox, troponin, etc.—supplant your clinical judgment.
- Watch out for blebs mimicking pneumothorax—consider CT of the chest in those patients that are hemodynamically stable without respiratory distress.
- Avoid intubation when possible—and when it is necessary, be aggressive with continued monitoring and therapy.

Cost-Effective Strategies

1. **Use clinical judgment rather than extensive (and expensive) testing.**

   Avoid excessive or protocol-driven ABGs, sputum cultures, spirometry, or BNP testing. These and other tests should be performed only when clinically needed, not routinely. Airway management decisions should be driven by clinical, not laboratory, data.

   Risk Management Caveat: In patients who have failed initial management (whether outpatient or in the ED), there may be a role for sputum collection and testing. In more severe exacerbations where ABGs may be performed, consider the use of local anesthetics to reduce patient discomfort associated with a painful procedure.

2. **Use non-invasive ventilation.**

   Having been proven to reduce the incidence of intubation, this may be the most cost-effective intervention in our arsenal, since intubation and ICU admission are so expensive. Be aggressive with the use of non-invasive positive pressure ventilation—use early and often.

   Risk Management Caveat: Remember the contraindications to NPPV: it is not for patients who are not breathing spontaneously or protecting their airway or who are hemodynamically unstable.

3. **Vaccinate.**

   Although the supporting data for routine vaccination in COPD patients is not as robust as for vaccination of elderly patients in general, there is some evidence that influenza and pneumococcal vaccines reduces the frequency of exacerbations. Given the low cost of this intervention, even a modest reduction in the number of exacerbations would make vaccination cost effective.

4. **Help patients quit smoking.**

   The cost-saving benefits of COPD prevention are simultaneously the most difficult to measure and possibly the most effective. Although smoking-cessation interventions in the ED by themselves have a low success rate, they are low cost and are recommended by several leading emergency medicine organizations.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

*1. Rabe K, Hurd S, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary. *Am J Respir Crit Care Med*. 2007;176(6):532-555. **(Systematic review; consensus guidelines)**

2. Celli B, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*. 2004;23(6):932-946. **(Systematic review; consensus guidelines)**

3. Mathers C, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3(11):e442. **(Retrospective; epidemiologic study)**

4. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet*. 1997;349(9064):1498-1504. **(Retrospective; epidemiologic study)**

5. Mannino D, Watt G, Hole D, et al. The natural history of chronic obstructive pulmonary disease. *Eur Respir J*. 2006;27(3):627-643. **(Review)**

6. Lopez A, Mathers C, Ezzati M, Jamison D, Murray C. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006;367(9524):1747-1757. **(Retrospective; epidemiologic study)**

7. Wilson L, Devine E, So K. Direct medical costs of chronic obstructive pulmonary disease: chronic bronchitis and emphysema. *Respir Med*. 2000;94(3):204-213. **(Retrospective; epidemiologic study)**

8. Chapman K, Mannino D, Soriano J, et al. Epidemiology and costs of

chronic obstructive pulmonary disease. *Eur Respir J*. 2006;27(1):188-207. **(Review)**
9. Miravitlles M, Murio C, Guerrero T, Gisbert R. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. *Chest*. 2002;121(5):1449-1455. **(Prospective; epidemiologic study; 2414 patients)**
10. Burge S, Wedzicha J. COPD exacerbations: definitions and classifications. *Eur Respir J Suppl*. 2003;41:46s-53s. **(Consensus committee report)**
11. Burge P, Calverley P, Jones P, Spencer S, Anderson J. Prednisolone response in patients with chronic obstructive pulmonary disease: results from the ISOLDE study. *Thorax*. 2003;58(8):654-658. **(Randomized; controlled trial; 751 patients)**
12. Patil S, Krishnan J, Lechtzin N, Diette G. In-hospital mortality following acute exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med*. 2003;163(10):1180-1186. **(Retrospective; epidemiologic study; 71,130 patients)**
13. Chang C, Sullivan G, Karalus N, Hancox R, McLachlan J, Mills G. Audit of acute admissions of chronic obstructive pulmonary disease: inpatient management and outcome. *Intern Med J*. 2007;37(4):236-241. **(Retrospective; observational study; 94 patients)**
14. Connors AJ, Dawson N, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med*. 1996;154(4 Pt 1):959-967. **(Prospective; epidemiologic study; 1016 patients)**
15. Groenewegen K, Schols A, Wouters E. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest*. 2003;124(2):459-467. **(Prospective; epidemiologic study; 171 patients)**
16. Kinnunen T, Säynäjäkangas O, Keistinen T. The COPD-induced hospitalization burden from first admission to death. *Respir Med*. 2007;101(2):294-299. **(Retrospective; epidemiologic study; 8325 patients)**
17. Donaldson G, Seemungal T, Bhowmik A, Wedzicha J. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax*.;57(10):847-852. **(Prospective; observational study; 109 patients)**
18. Seemungal T, Donaldson G, Bhowmik A, Jeffries D, Wedzicha J. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161(5):1608-1613. **(Prospective; observational study; 101 patients)**
19. Papi A, Bellettato C, Braccioni F, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med*. 2006;173(10):1114-1121. **(Prospective; observational study; 64 patients)**
20. Ball P. Epidemiology and treatment of chronic bronchitis and its exacerbations. *Chest*. 1995;108(2 Suppl):43S-52S. **(Review article)**
21. Seemungal T, Harper-Owen R, Bhowmik A, et al. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001;164(9):1618-1623. **(Prospective; observational study; 83 patients)**
22. Querol-Ribelles J, Molina J, Naberan K, Esteban E, Herreras A, Garcia-de-Lomas J. Discrepancy between antibiotics administered in acute exacerbations of chronic bronchitis and susceptibility of isolated pathogens in respiratory samples: multicentre study in the primary care setting. *Int J Antimicrob Agents*. 2006;28(5):472-476. **(Prospective; observational study; 1537 patients)**
23. Ko F, Ip M, Chan P, et al. A 1-year prospective study of the infectious etiology in patients hospitalized with acute exacerbations of COPD. *Chest*. 2007;131(1):44-52. **(Prospective; observational study; 373 patients)**
24. Monsó E, Ruiz J, Rosell A, et al. Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med*. 1995;152(4 Pt 1):1316-1320. **(Case control; observational study; 69 patients)**
25. Soler N, Torres A, Ewig S, et al. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med*. 1998;157(5 Pt 1):1498-1505. **(Prospective; observational study; 50 patients)**
26. Sapey E, Stockley R. COPD exacerbations . 2: aetiology. *Thorax*. 2006;61(3):250-258. **(Review article)**
27. Anderson H, Spix C, Medina S, et al. Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. *Eur Respir J*. 1997;10(5):1064-1071. (**Epidemiologic study)**
28. Medina-Ramón M, Zanobetti A, Schwartz J. The effect of ozone and PM10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study. *Am J Epidemiol*. 2006;163(6):579-588. **(Case control; epidemiologic study; 578,006 cases)**
29. Sunyer J, Schwartz J, Tobías A, Macfarlane D, Garcia J, Antó J. Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particle air pollution: a case-crossover analysis. *Am J Epidemiol*. 2000;151(1):50-56. **(Epidemiologic study**)
30. Sunyer J, Sáez M, Murillo C, Castellsague J, Martínez F, Antó J. Air pollution and emergency room admissions for chronic obstructive pulmonary disease: a 5-year study. *Am J Epidemiol*. 1993;137(7):701-705. **(Epidemiologic study)**
31. Le Jemtel T, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol*. 2007;49(2):171-180. **(Review article)**
32. Stevenson N, Walker P, Costello R, Calverley P. Lung mechanics and dyspnea during exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;172(12):1510-1516. (**Prospective; observational study; 22 patients)**
33. O'Donnell D, Parker C. COPD exacerbations . 3: Pathophysiology. *Thorax*. 2006;61(4):354-361. **(Review article)**
34. MJ S. Mosby's Paramedic Textbook. 2nd ed. ed: Mosby; 2001. **(Textbook)**
35. Browner BD PA, et al. Emergency care and transportation of the sick and injured: Jones and Bartlett; 2002. **(Textbook)**
36. Bledsoe BE CR. Brady Intermediate Emergency Care. 2nd ed. ed: Prentice Hall; 1998. **(Textbook)**
37. Durrington H, Flubacher M, Ramsay C, Howard L, Harrison B. Initial oxygen management in patients with an exacerbation of chronic obstructive pulmonary disease. *QJM*. 2005;98(7):499-504. **(Observational study; 108 patients)**
38. Denniston A, O'Brien C, Stableforth D. The use of oxygen in acute exacerbations of chronic obstructive pulmonary disease: a prospective audit of pre-hospital and hospital emergency management. *Clin Med*. 2002;2(5):449-451. **(Observational study; 97 patients)**
39. Plant P, Owen J, Elliott M. One year period prevalence study of respiratory acidosis in acute exacerbations of COPD: implications for the provision of non-invasive ventilation and oxygen administration. *Thorax*. 2000;55(7):550-554. **(Observational study; 199 patients)**
40. Weitz G, Struck J, Zonak A, Balnus S, Perras B, Dodt C. Prehospital noninvasive pressure support ventilation for acute cardiogenic pulmonary edema. *Eur J Emerg Med*. 2007;14(5):276-279. **(Randomized trial; 23 patients)**
41. Kosowsky J, Stephanides S, Branson R, Sayre M. Prehospital use of continuous positive airway pressure (CPAP) for presumed pulmonary edema: a preliminary case series. *Prehosp Emerg Care*. 2001;5(2):190-196. **(Prospective; observational study; 19 patients)**
42. Soler N, Agustí C, Angrill J, Puig De la Bellacasa J, Torres A. Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease. *Thorax*. 2007;62(1):29-35. **(Prospective; observational study; 40 patients)**
43. Marini J, Pierson D, Hudson L, Lakshminarayan S. The significance of wheezing in chronic airflow obstruction. *Am Rev Respir Dis*. 1979;120(5):1069-1072. **(Prosptective; observational study; 83 patients)**
44. Badgett R, Tanaka D, Hunt D, et al. Can moderate chronic obstructive pulmonary disease be diagnosed by historical and physical findings alone? *Am J Med*. 1993;94(2):188-196. **(Prospective; observational study; 92 patients)**
45. Holleman DJ, Simel D, Goldberg J. Diagnosis of obstructive airways disease from the clinical examination. *J Gen Intern Med*. 1993;8(2):63-68. **(Prosptective; observational study; 164 patients)**
46. Gunen H, Hacievliyagil S, Kosar F, et al. Factors affecting survival of hospitalised patients with COPD. *Eur Respir J*. 2005;26(2):234-241. **(Observational study; 205 patients)**
47. Sherman S, Skoney J, Ravikrishnan K. Routine chest radiographs in exacerbations of chronic obstructive pulmonary disease. Diagnostic value. *Arch Intern Med*. 1989;149(11):2493-2496. **(Retrospective; observational study; 242 patients)**
48. Emerman C, Cydulka R. Evaluation of high-yield criteria for chest radiography in acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med*. 1993;22(4):680-684. **(Retrospective; observational study; 685 patients)**
49. Tsai T, Gallagher E, Lombardi G, Gennis P, Carter W. Guidelines for the selective ordering of admission chest radiography in adult obstructive airway disease. *Ann Emerg Med*. 1993;22(12):1854-1858. **(Prospective; observational study; 128 patients)**
50. Takasugi J, Godwin J. Radiology of chronic obstructive pulmonary disease. *Radiol Clin North Am*. 1998;36(1):29-55. **(Review article)**
51. Harrigan R, Jones K. ABC of clinical electrocardiography. Conditions affecting the right side of the heart. *BMJ*. 2002;324(7347):1201-1204. **(Review article)**
52. Seemungal T, Donaldson G, Paul E, Bestall J, Jeffries D, Wedzicha J. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157(5 Pt 1):1418-1422. **(Prospective; observational study; 70 patients)**
53. Emerman C, Connors A, Lukens T, Effron D, May M. Relationship between arterial blood gases and spirometry in acute exacerbations of chronic obstructive pulmonary disease. *Ann Emerg Med*. 1989;18(5):523-527. **(Prospective; observational study; 70 patients)**
54. Minocha A, Moravec CJ. Gram's stain and culture of sputum in the routine management of pulmonary infection. *South Med J*. 1993;86(11):1225-1228. **(Prospective; observational study; 171 patients)**
55. Roche N, Kouassi B, Rabbat A, Mounedji A, Lorut C, Huchon G. Yield of sputum microbiological examination in patients hospitalized for exacerbations of chronic obstructive pulmonary disease with purulent sputum. *Respiration*. 2007;74(1):19-25. **(Observational study; 118 patients)**
56. Chambellan A, Chailleux E, Similowski T. Prognostic value of the hematocrit in patients with severe COPD receiving long-term oxygen therapy. Chest. 2005;128(3):1201-1208. **(Retrospective; observational study; 2524 patients)**
57. Baker E, Janaway C, Philips B, et al. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax*. 2006;61(4):284-289. **(Retrospective; observational study; 348 patients)**
58. Harvey M, Hancox R. Elevation of cardiac troponins in exacerbation

of chronic obstructive pulmonary disease. *Emerg Med Australas*. 2004;16(3):212-215. **(Retrospective; observational study; 235 patients)**
59. Baillard C, Boussarsar M, Fosse J, et al. Cardiac troponin I in patients with severe exacerbation of chronic obstructive pulmonary disease. *Intensive Care Med*. 2003;29(4):584-589. **(Prospective; observational study; 71 patients)**
60. Sidney S, Sorel M, Quesenberry CJ, DeLuise C, Lanes S, Eisner M. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest*. 2005;128(4):2068-2075. **(Retrospective; observational study; 45,966 cases)**
61. Rutten F, Cramer M, Grobbee D, et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J*. 2005;26(18):1887-1894. **(Prospective; observational study; 405 patients)**
62. Abroug F, Ouanes-Besbes L, Nciri N, et al. Association of left-heart dysfunction with severe exacerbation of chronic obstructive pulmonary disease: diagnostic performance of cardiac biomarkers. *Am J Respir Crit Care Med*. 2006;174(9):990-996. **(Prospective; observational study; 148 patients)**
63. Mueller C, Laule-Kilian K, Frana B, et al. Use of B-type natriuretic peptide in the management of acute dyspnea in patients with pulmonary disease. *Am Heart J*. 2006;151(2):471-477. **(Subgroup analysis of randomized; controlled trial; 226 patients)**
64. Steg P, Joubin L, McCord J, et al. B-type natriuretic peptide and echocardiographic determination of ejection fraction in the diagnosis of congestive heart failure in patients with acute dyspnea. *Chest*. 2005;128(1):21-29. **(Prospective; observational study; 1586 patients)**
65. McCullough P, Hollander J, Nowak R, et al. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med*. 2003;10(3):198-204. **(Subgroup analysis of prospective observational trial, 417 patients)**
66. Hohl C, Mitelman B, Wyer P, Lang E. Should emergency physicians use B-type natriuretic peptide testing in patients with unexplained dyspnea? *CJEM*. 2003;5(3):162-165. **(Editorial)**
67. Hohl C. Should natriuretic peptide testing be incorporated into emergency medicine practice? *CJEM*. 2006;8(4):259-261. **(Editorial)**
68. Hartmann I, Hagen P, Melissant C, Postmus P, Prins M. Diagnosing acute pulmonary embolism: effect of chronic obstructive pulmonary disease on the performance of D-dimer testing, ventilation/perfusion scintigraphy, spiral computed tomographic angiography, and conventional angiography. ANTELOPE Study Group. Advances in New Technologies Evaluating the Localization of Pulmonary Embolism. *Am J Respir Crit Care Med*. 2000;162(6):2232-2237. **(Subgroup analysis of prospective; observational study; 91 patients)**
69. Sohne M, Kruip M, Nijkeuter M, et al. Accuracy of clinical decision rule, D-dimer and spiral computed tomography in patients with malignancy, previous venous thromboembolism, COPD or heart failure and in older patients with suspected pulmonary embolism. *J Thromb Haemost*. 2006;4(5):1042-1046. **(Subgroup analysis of prospective; observational study; 341 patients)**
70. Gross N. Anticholinergic agents in asthma and COPD. *Eur J Pharmacol*. 2006;533(1-3):36-39. **(Review article)**
71. Karpel J, Pesin J, Greenberg D, Gentry E. A comparison of the effects of ipratropium bromide and metaproterenol sulfate in acute exacerbations of COPD. *Chest*. 1990;98(4):835-839. **(Randomized; controlled trial; 32 patients)**
72. Rebuck A, Chapman K, Abboud R, et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. *Am J Med*. 1987;82(1):59-64. **(Randomized; controlled trial; 51 patients)**
73. McCrory D, Brown C. Inhaled short-acting beta2-agonists versus ipratropium for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2001(2):CD002984. **(Systematic review and meta-analysis)**
74. McCrory D, Brown C. Anti-cholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2002(4):CD003900. **(Systematic review and meta-analysis)**
75. Zehner WJ, Scott J, Iannolo P, Ungaro A, Terndrup T. Terbutaline vs albuterol for out-of-hospital respiratory distress: randomized, double-blind trial. *Acad Emerg Med*. 1995;2(8):686-691. **(Randomized; controlled trial; 83 patients)**
76. Summer W, Elston R, Tharpe L, Nelson S, Haponik E. Aerosol bronchodilator delivery methods. Relative impact on pulmonary function and cost of respiratory care. Arch Intern Med. 1989;149(3):618-623. **(Randomized; controlled trial; 36 patients)**
77. Turner J, Corkery K, Eckman D, Gelb A, Lipavsky A, Sheppard D. Equivalence of continuous flow nebulizer and metered-dose inhaler with reservoir bag for treatment of acute airflow obstruction. *Chest*. 1988;93(3):476-481. **(Randomized; controlled trial; 75 patients)**
78. Turner M, Patel A, Ginsburg S, FitzGerald J. Bronchodilator delivery in acute airflow obstruction. A meta-analysis. *Arch Intern Med*. 1997;157(15):1736-1744. **(Meta-analysis)**
79. Jasper A, Mohsenifar Z, Kahan S, Goldberg H, Koerner S. Cost-benefit comparison of aerosol bronchodilator delivery methods in hospitalized patients. *Chest*. 1987;91(4):614-618. **(Randomized; controlled trial; 34 patients)**
80. Berry R, Shinto R, Wong F, Despars J, Light R. Nebulizer vs spacer for bronchodilator delivery in patients hospitalized for acute exacerbations of COPD. *Chest*. 1989;96(6):1241-1246. **(Prospective; crossover study; 20 patients)**
81. Emerman C, Cydulka R. Effect of different albuterol dosing regimens in the treatment of acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med*. 1997;29(4):474-478. **(Randomized; controlled trial; 86 patients)**
82. Rodríguez-Roisin R. COPD exacerbations.5: management. *Thorax*. 2006;61(6):535-544. **(Review article)**
83. Cydulka R, Emerman C. Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med*. 1995;25(4):470-473. **(Randomized; controlled trial; 57 patients)**
84. Shrestha M, O'Brien T, Haddox R, Gourlay H, Reed G. Decreased duration of emergency department treatment of chronic obstructive pulmonary disease exacerbations with the addition of ipratropium bromide to beta-agonist therapy. *Ann Emerg Med*. 1991;20(11):1206-1209. **(Randomized; controlled trial; 76 patients)**
85. Moayyedi P, Congleton J, Page R, Pearson S, Muers M. Comparison of nebulised salbutamol and ipratropium bromide with salbutamol alone in the treatment of chronic obstructive pulmonary disease. *Thorax*. 1995;50(8):834-837. **(Randomized; controlled trial; 70 patients)**
86. Patrick D, Dales R, Stark R, Laliberte G, Dickinson G. Severe exacerbations of COPD and asthma. Incremental benefit of adding ipratropium to usual therapy. *Chest*. 1990;98(2):295-297. **(Randomized; controlled trial; 50 patients)**
87. Wrenn K, Slovis C, Murphy F, Greenberg R. Aminophylline therapy for acute bronchospastic disease in the emergency room. *Ann Intern Med*. 1991;115(4):241-247. **(Randomized; controlled trial; 133 patients)**
88. Duffy N, Walker P, Diamantea F, Calverley P, Davies L. Intravenous aminophylline in patients admitted to hospital with non-acidotic exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Thorax*. 2005;60(9):713-717. **(Randomized; controlled trial; 80 patients)**
89. Rice K, Leatherman J, Duane P, et al. Aminophylline for acute exacerbations of chronic obstructive pulmonary disease. A controlled trial. *Ann Intern Med*. 1987;107(3):305-309. **(Randomized; controlled trial; 28 patients)**
90. Seidenfeld J, Jones W, Moss R, Tremper J. Intravenous aminophylline in the treatment of acute bronchospastic exacerbations of chronic obstructive pulmonary disease. *Ann Emerg Med*. 1984;13(4):248-252. **(Randomized; controlled trial; 52 patients)**
91. Barr R, Rowe B, Camargo C. Methylxanthines for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2003(2):CD002168. **(Systematic review)**
92. Bateman E, Hurd S, Barnes P, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;31(1):143-178. **(Systematic review; consensus guidelines)**
93. Abreu González J, Hernández García C, Abreu González P, Martín García C, Jiménez A. [Effect of intravenous magnesium sulfate on chronic obstructive pulmonary disease exacerbations requiring hospitalization: a randomized placebo-controlled trial]. *Arch Bronconeumol*. 2006;42(8):384-387. **(Randomized; controlled trial; 24 patients)**
94. Albert R, Martin T, Lewis S. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med*. 1980;92(6):753-758. **(Randomized; controlled trial; 44 patients)**
95. Bullard M, Liaw S, Tsai Y, Min H. Early corticosteroid use in acute exacerbations of chronic airflow obstruction. *Am J Emerg Med*. 1996;14(2):139-143. **(Randomized; controlled trial; 113 patients)**
96. Maltais F, Ostinelli J, Bourbeau J, et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Crit Care Med*. 2002;165(5):698-703. **(Randomized; controlled trial; 199 patients)**
97. Davies L, Angus R, Calverley P. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet*. 1999;354(9177):456-460. **(Randomized; controlled trial; 56 patients)**
98. Thompson W, Nielson C, Carvalho P, Charan N, Crowley J. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med*. 1996;154**(2 Pt 1):407-412. (Randomized; controlled trial; 27 patients)**
99. Niewoehner D, Erbland M, Deupree R, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med*. 1999;340(25):1941-1947. **(Randomized; controlled trial; 271 patients)**
100. Aaron S, Vandemheen K, Hebert P, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med*. 2003;348(26):2618-2625. **(Randomized; controlled trial; 147 patients)**
101. Singh J, Palda V, Stanbrook M, Chapman K. Corticosteroid therapy for patients with acute exacerbations of chronic obstructive pulmonary disease: a systematic review. *Arch Intern Med*. 2002;162(22):2527-2536. **(Systematic review)**
102. McEvoy C, Niewoehner D. Adverse effects of corticosteroid therapy for COPD. A critical review. *Chest*. 1997;111(3):732-743. **(Review article)**
103. Vondracek S, Hemstreet B. Retrospective evaluation of systemic corticosteroids for the management of acute exacerbations of chronic

obstructive pulmonary disease. *Am J Health Syst Pharm*. 2006;63(7):645-652. **(Retrospective; observational study; 123 patients)**

104. Gunen H, Hacievliyagil S, Yetkin O, Gulbas G, Mutlu L, In E. The role of nebulised budesonide in the treatment of exacerbations of COPD. *Eur Respir J*. 2007;29(4):660-667. **(Randomized; controlled trial; 159 patients)**
105. Nseir S, Di Pompeo C, Cavestri B, et al. Multiple-drug-resistant bacteria in patients with severe acute exacerbation of chronic obstructive pulmonary disease: Prevalence, risk factors, and outcome. *Crit Care Med*. 2006;34(12):2959-2966. **(Prospective; observational study; 857 patients)**
106. Saint S, Bent S, Vittinghoff E, Grady D. Antibiotics in chronic obstructive pulmonary disease exacerbations. A meta-analysis. *JAMA*. 1995;273(12):957-960. **(Meta-analysis)**
107. Ram F, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes N. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006(2):CD004403. **(Systematic review; meta-analysis)**
108. Nouira S, Marghli S, Belghith M, Besbes L, Elatrous S, Abroug F. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. *Lancet*. 2001;358(9298):2020-2025. **(Randomized; controlled trial; 93 patients)**

*109. Anthonisen N, Manfreda J, Warren C, Hershfield E, Harding G, Nelson N. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106(2):196-204. **(Randomized; controlled trial; 173 patients)**

110. Zervos M, Martinez F, Amsden G, Rothermel C, Treadway G. Efficacy and safety of 3-day azithromycin versus 5-day moxifloxacin for the treatment of acute bacterial exacerbations of chronic bronchitis. *Int J Antimicrob Agents*. 2007;29(1):56-61. **(Randomized; controlled trial; 342 patients)**
111. Gotfried M, Busman T, Norris S, Notario G. Role for 5-day, once-daily extended-release clarithromycin in acute bacterial exacerbation of chronic bronchitis. *Curr Med Res Opin*. 2007;23(2):459-466. **(Randomized; controlled trial; 818 patients)**
112. Roede B, Bresser P, El Moussaoui R, et al. Three vs. 10 days of amoxycillin-clavulanic acid for type 1 acute exacerbations of chronic obstructive pulmonary disease: a randomised, double-blind study. *Clin Microbiol Infect*. 2007;13(3):284-290. **(Randomized ; controlled trial ; 46 patients)**
113. Fogarty C, de Wet R, Mandell L, Chang J, Rangaraju M, Nusrat R. Five-day telithromycin once daily is as effective as 10-day clarithromycin twice daily for the treatment of acute exacerbations of chronic bronchitis and is associated with reduced health-care resource utilization. *Chest*. 2005;128(4):1980-1988. **(Randomized; controlled trial; 552 patients)**
114. Wilson R, Allegra L, Huchon G, et al. Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis. *Chest*. 2004;125(3):953-964. **(Randomized; controlled trial; 354 patients)**
115. Urueta-Robledo J, Ariza H, Jardim J, et al. Moxifloxacin versus levofloxacin against acute exacerbations of chronic bronchitis: the Latin American Cohort. *Respir Med*.;100(9):1504-1511. **(Randomized; controlled trial; 563 patients)**
116. Alvarez-Sala J, Kardos P, Martínez-Beltrán J, Coronel P, Aguilar L. Clinical and bacteriological efficacy in treatment of acute exacerbations of chronic bronchitis with cefditoren-pivoxil versus cefuroxime-axetil. Antimicrob Agents Chemother. 2006;50(5):1762-1767. **(Randomized; controlled trial; 541 patients)**
117. Girault C, Chevron V, Richard J, et al. Physiological effects and optimisation of nasal assist-control ventilation for patients with chronic obstructive pulmonary disease in respiratory failure. *Thorax*. 1997;52(8):690-696. **(Prospective; observational study; 15 patients)**
118. Diaz O, Iglesia R, Ferrer M, et al. Effects of noninvasive ventilation on pulmonary gas exchange and hemodynamics during acute hypercapnic exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1997;156(6):1840-1845. **(Prospective; observational study; 10 patients)**
119. Meyer T, Hill N. Noninvasive positive pressure ventilation to treat respiratory failure. *Ann Intern Med*. 1994;120(9):760-770. **(Review article)**
120. Kramer N, Meyer T, Meharg J, Cece R, Hill N. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med*. 1995;151(6):1799-1806. **(Randomized; controlled trial; 31 patients)**
121. Bott J, Carroll M, Conway J, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet*. 1993;341(8860):1555-1557. **(Randomized; controlled trial; 60 patients)**
122. Angus R, Ahmed A, Fenwick L, Peacock A. Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chronic obstructive pulmonary disease. *Thorax*. 1996;51(10):1048-1050. **(Randomized; controlled trial; 17 patients)**
123. Avdeev S, Tret'iakov A, Grigor'iants R, Kutsenko M, Chuchalin A. [Study of the use of noninvasive ventilation of the lungs in acute respiratory insufficiency due exacerbation of chronic obstructive pulmonary disease]. Anesteziol Reanimatol. 1998(3):45-51. **(Randomized; controlled trial; 58 patients)**
124. Celikel T, Sungur M, Ceyhan B, Karakurt S. Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. *Chest*. 1998;114(6):1636-1642. **(Randomized; controlled trial; 30 patients)**
125. Dikensoy O, Ikidag B, Filiz A, Bayram N. Comparison of non-invasive ventilation and standard medical therapy in acute hypercapnic respiratory failure: a randomised controlled study at a tertiary health centre in SE Turkey. *Int J Clin Pract*. 2002;56(2):85-88. **(Randomized; controlled trial; 34 patients)**

*126. Plant P, Owen J, Elliott M. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. *Thorax*. 2001;56(9):708-712. **(Randomized; controlled trial; 236 patients)**

127. Ram F, Picot J, Lightowler J, Wedzicha J. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2004(3):CD004104. **(Systematic review; meta-analysis)**
128. Keenan S, Kernerman P, Cook D, Martin C, McCormack D, Sibbald W. Effect of noninvasive positive pressure ventilation on mortality in patients admitted with acute respiratory failure: a meta-analysis. *Crit Care Med*. 1997;25(10):1685-1692. **(Meta-analysis)**
129. Keenan S, Sinuff T, Cook D, Hill N. Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. *Ann Intern Med*. 2003;138(11):861-870. **(Systematic review)**
130. Crummy F, Buchan C, Miller B, Toghill J, Naughton M. The use of noninvasive mechanical ventilation in COPD with severe hypercapnic acidosis. *Respir Med*. 2007;101(1):53-61. **(Prospective; observational study; 29 patients)**
131. Vitacca M, Rubini F, Foglio K, Scalvini S, Nava S, Ambrosino N. Non-invasive modalities of positive pressure ventilation improve the outcome of acute exacerbations in COLD patients. *Intensive Care Med*. 1993;19(8):450-455. **(Randomized; controlled trial; 29 patients)**
132. Meecham Jones D, Paul E, Grahame-Clarke C, Wedzicha J. Nasal ventilation in acute exacerbations of chronic obstructive pulmonary disease: effect of ventilator mode on arterial blood gas tensions. *Thorax*. 1994;49(12):1222-1224. **(Prospective; observational study; 12 patients)**
133. Merlani P, Pasquina P, Granier J, Treggiari M, Rutschmann O, Ricou B. Factors associated with failure of noninvasive positive pressure ventilation in the emergency department. *Acad Emerg Med*. 2005;12(12):1206-1215. **(Observational study; 104 patients)**
134. Bidani A, Tzouanakis A, Cardenas VJ, Zwischenberger J. Permissive hypercapnia in acute respiratory failure. *JAMA*. 1994;272(12):957-962. **(Review article)**
135. Jain S, Hanania N, Guntupalli K. Ventilation of patients with asthma and obstructive lung disease. *Crit Care Clin*. 1998;14(4):685-705. **(Review article)**
136. Kondili E, Alexopoulou C, Prinianakis G, Xirouchaki N, Georgopoulos D. Pattern of lung emptying and expiratory resistance in mechanically ventilated patients with chronic obstructive pulmonary disease. *Intensive Care Med*. 2004;30(7):1311-1318. **(Observational study; 10 patients)**
137. Caramez M, Borges J, Tucci M, et al. Paradoxical responses to positive end-expiratory pressure in patients with airway obstruction during controlled ventilation. *Crit Care Med*. 2005;33(7):1519-1528. **(Observational study; 8 patients)**
138. Segredo V, Caldwell J, Matthay M, Sharma M, Gruenke L, Miller R. Persistent paralysis in critically ill patients after long-term administration of vecuronium. *N Engl J Med*. 1992;327(8):524-528. **(Observational study; 16 patients)**

*139. Rutschmann O, Cornuz J, Poletti P, et al. Should pulmonary embolism be suspected in exacerbation of chronic obstructive pulmonary disease? *Thorax*. 2007;62(2):121-125. **(Prospective; observational study; 123 patients)**

140. Tillie-Leblond I, Marquette C, Perez T, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med*. 2006;144(6):390-396. **(Prospective; observational study; 211 patients)**
141. Schönhofer B, Köhler D. Prevalence of deep-vein thrombosis of the leg in patients with acute exacerbation of chronic obstructive pulmonary disease. *Respiration*. 1998;65(3):173-177. **(Prospective; observational study; 196 patients)**
142. Erelel M, Cuhadaroğlu C, Ece T, Arseven O. The frequency of deep venous thrombosis and pulmonary embolus in acute exacerbation of chronic obstructive pulmonary disease. *Respir Med*. 2002;96(7):515-518. **(Prospective; observational study; 56 patients)**
143. Akgun M, Meral M, Onbas O, et al. Comparison of clinical characteristics and outcomes of patients with COPD exacerbation with or without venous thromboembolism. *Respiration*. 2006;73(4):428-433. **(Prospective; observational study; 120 patients)**
144. Emerman C, Connors A, Lukens T, May M, Effron D. Theophylline concentrations in patients with acute exacerbation of COPD. *Am J Emerg Med*. 1990;8(4):289-292. **(Prospective; observational study; 79 patients)**
145. Aitken M, Martin T. Life-threatening theophylline toxicity is not predictable by serum levels. *Chest*. 1987;91(1):10-14. **(Retrospective; observational study; 54 patients)**
146. Patel A, Skatrud J, Thomsen J. Cardiac arrhythmias due to oral aminophylline in patients with chronic obstructive pulmonary disease. *Chest*. 1981;80(6):661-665. **(Prospective; observational study; 15 patients)**
147. Conradson T, Eklundh G, Olofsson B, Pahlm O, Persson G. Cardiac arrhythmias in patients with mild-to-moderate obstructive lung disease. Comparison of beta-agonist therapy alone and in combination with a xanthine derivative, enprofylline or theophylline. *Chest*. 1985;88(4):537-542. **(Prospective; observational study; 20 patients)**

148. Coleman J, Vollmer W, Barker A, Schultz G, Buist A. Cardiac arrhythmias during the combined use of beta-adrenergic agonist drugs and theophylline. *Chest*. 1986;90(1):45-51. **(Prospective; observational study; 15 patients)**
149. Sessler C, Cohen M. Cardiac arrhythmias during theophylline toxicity. A prospective continuous electrocardiographic study. *Chest*. 1990;98(3):672-678. **(Prospective; observational study; 16 patients)**
150. Bittar G, Friedman H. The arrhythmogenicity of theophylline. A multivariate analysis of clinical determinants. *Chest*. 1991;99(6):1415-1420. **(Prospective; observational study; 100 patients)**
151. Ioachimescu O, Stoller J. A review of alpha-1 antitrypsin deficiency. *COPD*. 2005;2(2):263-275. **(Review article)**
152. Jennings A, Davies A, Higgins J, Gibbs J, Broadley K. A systematic review of the use of opioids in the management of dyspnoea. *Thorax*. 2002;57(11):939-944. **(Systematic review)**
153. Seamark D, Seamark C, Halpin D. Palliative care in chronic obstructive pulmonary disease: a review for clinicians. *J R Soc Med*. 2007;100(5):225-233. **(Review article)**
154. Aubier M, Murciano D, Milic-Emili J, et al. Effects of the administration of O_2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis*. 1980;122(5):747-754. **(Observational study; 22 patients)**
155. Sassoon C, Hassell K, Mahutte C. Hyperoxic-induced hypercapnia in stable chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1987;135(4):907-911. **(Observational study; 17 patients)**
156. Dick C, Liu Z, Sassoon C, Berry R, Mahutte C. O_2-induced change in ventilation and ventilatory drive in COPD. Am J *Respir Crit Care Med*. 1997;155(2):609-614. (**Observational study; 11 patients)**
157. Robinson T, Freiberg D, Regnis J, Young I. The role of hypoventilation and ventilation-perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161(5):1524-1529. **(Observational study; 22 patients)**
158. Murphy R, Driscoll P, O'Driscoll R. Emergency oxygen therapy for the COPD patient. *Emerg Med J*. 2001;18(5):333-339. **(Review article)**
159. Agustí A, Carrera M, Barbé F, Muñoz A, Togores B. Oxygen therapy during exacerbations of chronic obstructive pulmonary disease. *Eur Respir J*. 1999;14(4):934-939. **(Randomized; controlled trial; 18 patients)**
160. Chu Y, Chen C, Lee C, Chen C, Chang H, Hsiue T. Prediction of arterial blood gas values from venous blood gas values in patients with acute respiratory failure receiving mechanical ventilation. *J Formos Med Assoc*. 2003;102(8):539-543. **(Observational study; 46 patients)**
161. Ak A, Ogun C, Bayir A, Kayis S, Koylu R. Prediction of arterial blood gas values from venous blood gas values in patients with acute exacerbation of chronic obstructive pulmonary disease. *Tohoku J Exp Med*. 2006;210(4):285-290. **(Observational study; 132 patients)**
162. Kelly A, Kyle E, McAlpine R. Venous pCO(2) and pH can be used to screen for significant hypercarbia in emergency patients with acute respiratory disease. *J Emerg Med*. 2002;22(1):15-19. **(Prospective; observational study; 196 patients)**
163. Kelly A, Kerr D, Middleton P. Validation of venous pCO_2 to screen for arterial hypercarbia in patients with chronic obstructive airways disease. *J Emerg Med*. 2005;28(4):377-379. **(Prospective; observational study; 107 patients)**
164. Murphy R, Thethy S, Raby S, et al. Capillary blood gases in acute exacerbations of COPD. *Respir Med*. 2006;100(4):682-686. **(Observational study; 55 patients)**
165. Janssens J, Laszlo A, Uldry C, Titelion V, Picaud C, Michel J. Non-invasive (transcutaneous) monitoring of PCO_2 ($TcPCO_2$) in older adults. *Gerontology*. 2005;51(3):174-178. **(Observational study; 40 patients)**
166. Cox M, Kemp R, Anwar S, Athey V, Aung T, Moloney E. Non-invasive monitoring of CO_2 levels in patients using NIV for AECOPD. *Thorax*. 2006;61(4):363-364. **(Observational study; 22 patients)**
*167. Krauss B, Hess D. Capnography for procedural sedation and analgesia in the emergency department. *Ann Emerg Med*. 2007;50(2):172-181. **(Review article)**
168. Gregoretti C, Squadrone V, Fogliati C, Olivieri C, Navalesi P. Transtracheal open ventilation in acute respiratory failure secondary to severe chronic obstructive pulmonary disease exacerbation. *Am J Respir Crit Care Med*. 2006;173(8):877-881. **(Randomized; controlled trial; 39 patients)**
169. Slater A, Goodwin M, Anderson K, Gleeson F. COPD can mimic the appearance of pneumothorax on thoracic ultrasound. *Chest*. 2006;129(3):545-550. **(Prospective; observational study; 41 patients)**
170. Becker K, Nylén E, White J, Müller B, Snider RJ. Clinical review 167: Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. *J Clin Endocrinol Metab*. 2004;89(4):1512-1525. **(Review article)**
171. Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest*. 2007;131(1):9-19. **(Randomized; controlled trial; 208 patients)**
172. Dal Negro R, Micheletto C, Tognella S, Visconti M, Guerriero M, Sandri M. A two-stage logistic model based on the measurement of pro-inflammatory cytokines in bronchial secretions for assessing bacterial, viral, and non-infectious origin of COPD exacerbations. *COPD*. 2005;2(1):7-16. **(Prospective; observational study; 124 patients)**
173. Perera W, Hurst J, Wilkinson T, et al. Inflammatory changes, recovery and recurrence at COPD exacerbation. *Eur Respir J*. 2007;29(3):527-534. **(Prospective; observational study; 73 patients)**
174. Stolz D, Christ-Crain M, Morgenthaler N, et al. Copeptin, C-reactive protein, and procalcitonin as prognostic biomarkers in acute exacerbation of COPD. *Chest*. 2007;131(4):1058-1067. **(Prospective; observational study; 167 patients)**
175. Ram F, Wedzicha J, Wright J, Greenstone M. Hospital at home for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2003(4):CD003573. **(Systematic review; meta-analysis)**
176. Davies L, Wilkinson M, Bonner S, Calverley P, Angus R. "Hospital at home" versus hospital care in patients with exacerbations of chronic obstructive pulmonary disease: prospective randomised controlled trial. *BMJ*. 2000;321(7271):1265-1268. **(Randomized; controlled trial; 150 patients)**
177. Hernandez C, Casas A, Escarrabill J, et al. Home hospitalisation of exacerbated chronic obstructive pulmonary disease patients. *Eur Respir J*. 2003;21(1):58-67. **(Randomized; controlled trial; 222 patients)**
178. Ojoo J, Moon T, McGlone S, et al. Patients' and carers' preferences in two models of care for acute exacerbations of COPD: results of a randomised controlled trial. *Thorax*. 2002;57(2):167-169. **(Randomized; controlled trial; 60 patients)**
179. Skwarska E, Cohen G, Skwarski K, et al. Randomized controlled trial of supported discharge in patients with exacerbations of chronic obstructive pulmonary disease. *Thorax*. 55(11):907-912. **(Randomized; controlled trial; 184 patients)**
180. Nicholson C, Bowler S, Jackson C, Schollay D, Tweeddale M, O'Rourke P. Cost comparison of hospital- and home-based treatment models for acute chronic obstructive pulmonary disease. *Aust Health Rev*. 2001;24(4):181-187. **(Randomized; controlled trial; 25 patients)**
181. Quantrill S, Lowe D, Hosker H, Anstey K, Pearson M, Michael Roberts C. Survey of early discharge schemes from the 2003 UK National COPD Audit. *Respir Med*. 2007;101(5):1026-1031. **(Observational study; 7529 patients)**
182. Murata G, Gorby M, Kapsner C, Chick T, Halperin A. A multivariate model for the prediction of relapse after outpatient treatment of decompensated chronic obstructive pulmonary disease. *Arch Intern Med*. 1992;152(1):73-77. **(Prospective; observational study; 289 patients)**
183. Heuser M, Case L, Ettinger W. Mortality in intensive care patients with respiratory disease. Is age important? *Arch Intern Med*. 1992;152(8):1683-1688. **(Prospective; observational study; 3050 patients)**
184. Warren P, Flenley D, Millar J, Avery A. Respiratory failure revisited: acute exacerbations of chronic bronchitis between 1961-68 and 1970-76. *Lancet*. 1980;1(8166):467-470. **(Retrospective; observational study; 135 patients)**
185. Fuso L, Incalzi R, Pistelli R, et al. Predicting mortality of patients hospitalized for acutely exacerbated chronic obstructive pulmonary disease. *Am J Med*. 1995;98(3):272-277. **(Retrospective; observational study; 590 patients)**
186. Kim S, Clark S, Camargo CJ. Mortality after an emergency department visit for exacerbation of chronic obstructive pulmonary disease. *COPD*. 2006;3(2):75-81. **(Retrospective; observational study; 482 patients)**
187. Seneff M, Wagner D, Wagner R, Zimmerman J, Knaus W. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *JAMA*. 1995;274(23):1852-1857. **(Prospective; observational study; 362 patients)**
188. Emerman C, Effron D, Lukens T. Spirometric criteria for hospital admission of patients with acute exacerbation of COPD. *Chest*. 1991;99(3):595-599. **(Observational study; 83 patients)**
189. Murata G, Gorby M, Chick T, Halperin A. Treatment of decompensated chronic obstructive pulmonary disease in the emergency department--correlation between clinical features and prognosis. *Ann Emerg Med*. 1991;20(2):125-129. **(Observational study; 352 patients)**
190. de la Iglesia F, Díaz J, Pita S, et al. Peak expiratory flow rate as predictor of inpatient death in patients with chronic obstructive pulmonary disease. *South Med J*. 2005;98(3):266-272. **(Prospective; observational study; 284 patients)**
191. Cao Z, Ong K, Eng P, Tan W, Ng T. Frequent hospital readmissions for acute exacerbation of COPD and their associated factors. *Respirology*. 2006;11(2):188-195. **(Observational study; 186 patients)**
192. Jeffrey A, Warren P, Flenley D. Acute hypercapnic respiratory failure in patients with chronic obstructive lung disease: risk factors and use of guidelines for management. *Thorax*. 1992;47(1):34-40. **(Prospective; observational study; 95 patients)**
193. Dewan N, Rafique S, Kanwar B, et al. Acute exacerbation of COPD: factors associated with poor treatment outcome. *Chest*. 2000;117(3):662-671. **(Retrospective; observational study; 107 patients)**
194. Portier F, Defouilloy C, Muir J. Determinants of immediate survival among chronic respiratory insufficiency patients admitted to an intensive care unit for acute respiratory failure. A prospective multicenter study. The French Task Group for Acute Respiratory Failure in Chronic Respiratory insufficiency. *Chest*. 1992;101(1):204-210. **(Prospective; observational study; 322 patients)**
195. Ball P, Harris J, Lowson D, Tillotson G, Wilson R. Acute infective exacerbations of chronic bronchitis. *QJM*. 1995;88(1):61-68. **(Observational study; 471 patients)**
196. Almagro P, Barreiro B, Ochoa de Echaguen A, et al. Risk factors for hospital readmission in patients with chronic obstructive pulmonary disease. *Respiration*. 2006;73(3):311-317. **(Prospective; observational study; 129 patients)**
197. Tsai C, Clark S, Cydulka R, Rowe B, Camargo CJ. Factors associated

with hospital admission among emergency department patients with chronic obstructive pulmonary disease exacerbation. *Acad Emerg Med*. 2007;14(1):6-14. **(Prospective; observational study; 384 patients)**
198. Alfageme I, Vazquez R, Reyes N, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. *Thorax*. 2006;61(3):189-195. **(Randomized; controlled trial; 596 patients)**
199. Granger R, Walters J, Poole P, et al. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006(4):CD001390. **(Systematic review; meta-analysis)**
200. Poole P, Chacko E, Wood-Baker R, Cates C. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006(1):CD002733. **(Systematic review; meta-analysis)**
201. Lee T, Weaver F, Weiss K. Impact of pneumococcal vaccination on pneumonia rates in patients with COPD and asthma. *J Gen Intern Med*. 2007;22(1):62-67. **(Retrospective; case-control study; 30,102 patients)**
202. Bernstein S, Boudreaux E, Cydulka R, et al. Tobacco control interventions in the emergency department: a joint statement of emergency medicine organizations. *Ann Emerg Med*. 2006;48(4):e417-426. **(Review article; consensus statement)**
203. Calverley P, Anderson J, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356(8):775-789. **(Randomized; controlled trial; 6112 patients)**
204. Kardos P, Wencker M, Glaab T, Vogelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;175(2):144-149. **(Randomized; controlled trial; 994 patients)**
205. Søyseth V, Brekke P, Smith P, Omland T. Statin use is associated with reduced mortality in COPD. *Eur Respir J*. 2007;29(2):279-283. **(Retrospective; cohort study; 854 patients)**

CME Questions

1. **Which of the following is a risk factor for development of COPD?**
   a. Exposure to airborne particulate matter
   b. Low fiber diet
   c. Obesity
   d. Family history
2. **What is believed to cause most COPD exacerbations?**
   a. Relative adrenal insufficiency
   b. Myocardial ischemia
   c. Surfactant depletion
   d. Respiratory tract infection
3. **Which of the following is associated with poor prognosis in the patient presenting with COPD exacerbation?**
   a. Smoking history
   b. Decreased body mass index
   c. Female gender
   d. Caucasian race
4. **The dominant physiologic abnormality believed to correlate with worsened dyspnea during an exacerbation is:**
   a. FEV1
   b. Dynamic hyperinflation
   c. Increased vital capacity
   d. Increased FEV1/FVC
5. **What is the approximate target oxygen saturation level for a COPD patient?**
   a. 75%–80%
   b. 80%–85%
   c. 88%–92%
   d. 98%–100%
6. **Which of the following tests is indicated in most patients who present to the emergency department for COPD exacerbation?**
   a. Blood cultures
   b. Arterial blood gas sampling
   c. Sputum gram stain and culture
   d. Chest x-ray
7. **Which of the following DVT/pulmonary embolism testing modalities has significantly degraded performance in COPD patients?**
   a. Ventilation perfusion scanning
   b. D-dimer
   c. CT angiography
   d. Angiography
8. **Which of the following therapies is considered second-line for COPD exacerbation?**
   a. Inhaled beta-agonists
   b. Intravenous methylxanthines
   c. Oral steroids
   d. Inhaled anticholinergics
9. **What is the most common adverse effect of corticosteroid administration?**
   a. Psychosis
   b. Urinary retention
   c. Hyperglycemia
   d. Tachycardia
10. **Antibiotics should be administered in a patient who presents with:**
    a. Increased fatigue
    b. Dehydration
    c. Wheezing
    d. Increased sputum purulence
11. **Which of the following is a contraindication to the use of non-invasive positive pressure ventilation?**
    a. Significant respiratory distress
    b. Obtundation
    c. Pulmonary edema
    d. $PaCO_2 > 45$
12. **When should non-invasive positive pressure ventilation be initiated in an awake patient with moderate to severe COPD exacerbation?**
    a. After unsatisfactory response to medical therapy
    b. Just prior to intubation
    c. As soon as possible
    d. After pneumonia has been ruled out
13. **Which of the following is a likely cause of hypotension immediately after intubation?**
    a. Overzealous bag-valve-mask ventilation
    b. Gastric distention
    c. Pulmonary embolism
    d. Septic shock
14. **What is the appropriate response to PEA arrest following intubation of a COPD patient?**
    a. Defibrillation
    b. Pericardiocentesis
    c. Intravenous tPA
    d. Disconnection of the ET tube, bilateral tube thoracostomy

Coming In Future Issues

Hypothermia

Severe TBI

Cervical Spine Injuries

STDs

Errata: Volume 10, Number 7

In the August 2008 article, "Ventilator Management: Maximizing Outcomes In Caring For Asthma, COPD, and Pulmonary Edema," the information below was incorrect. We regret any confusion this may have caused.

- Page 8, Figure 10: "I-time too short" should be "E-time too short."
- Page 15, Figure 12: "Low compliance and decreased change in volume/pressure" should be at the very top of the curve.

Class Of Evidence Definitions:

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case-control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Class Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. JAMA1992;268(16):2289-2295.

Physician CME Information

Date of Original Release: November 1, 2008. Date of most recent review: July 10, 2008. Termination date: November 1, 2011.

Accreditation: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of EB Medicine. EB Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation: EB Medicine designates this educational activity for a maximum of *48 AMA PRA Category 1 Credit(s)*™ per year. Physicians should only claim credit commensurate with the extent of their participation in the activity.

ACEP Accreditation: *Emergency Medicine Practice* is approved by the American College of Emergency Physicians for 48 hours of ACEP Category 1 credit per annual subscription.

AAFP Accreditation: *Emergency Medicine Practice* has been reviewed and is acceptable for up to 48 Prescribed credits per year by the American Academy of Family Physicians. AAFP Accreditation begins August 1, 2008. Term of approval is for two years from this date. Each issue is approved for 4 Prescribed credits. Credits may be claimed for two years from the date of this issue.

AOA Accreditation: *Emergency Medicine Practice* has been approved for 48 Category 2B credit hours per year by the American Osteopathic Association.

Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals & Objectives: Upon completion of this article, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for the topic covered.

Discussion of Investigational Information: As part of the newsletter, faculty may be presenting investigational information about pharmaceutical products that is outside Food and Drug Administration-approved labeling. Information presented as part of this activity is intended solely as continuing medical education and is not intended to promote off-label use of any pharmaceutical product. **Disclosure of Off-Label Usage:** Despite its frequent use for acutely exacerbated patients, ipratropium bromide is FDA approved only for the maintenance treatment of chronic bronchitis. Intravenous magnesium sulfate is not approved for treatment of bronchospasm. Corticosteroids in general are not FDA-approved for treatment of COPD exacerbations. Doxycycline and beta-lactam/beta-lactamase inhibitor combinations are not specifically approved for the treatment of COPD exacerbations.

Faculty Disclosure: It is the policy of Mount Sinai School of Medicine to ensure objectivity, balance, independence, transparency, and scientific rigor in all CME-sponsored educational activities. All faculty participating in the planning or implementation of a sponsored activity are expected to disclose to the audience any relevant financial relationships and to assist in resolving any conflict of interest that may arise from the relationship. Presenters must also make a meaningful disclosure to the audience of their discussions of unlabeled or unapproved drugs or devices.

In compliance with all ACCME Essentials, Standards, and Guidelines, all faculty for this CME activity were asked to complete a full disclosure statement. **The information received is as follows: Dr. Gruber, Dr. Swadron, Dr. Deblieux, and their related parties report no significant financial interest or other relationship with the manufacturer(s) of any commercial product(s) discussed in this educational presentation. Dr. Nelson has received grant support for a study of Continuous Positive Airway Pressure in acute asthma from Vitaid, Inc.**

Method of Participation:
- **Print Semester Program:** Paid subscribers who read all CME articles during each *Emergency Medicine Practice* six-month testing period, complete the post-test and the CME Evaluation Form distributed with the June and December issues, and return it according to the published instructions are eligible for up to 4 hours of CME credit for each issue. You must complete both the post test and CME Evaluation Form to receive credit. Results will be kept confidential. CME certificates will be delivered to each participant scoring higher than 70%.
- **Online Single-Issue Program:** Current paid subscribers who read this *Emergency Medicine Practice* CME article and complete the online post-test and CME Evaluation Form at ebmedicine.net are eligible for up to 4 hours of Category 1 credit toward the AMA Physician's Recognition Award (PRA). You must complete both the post-test and CME Evaluation Form to receive credit. Results will be kept confidential. CME certificates may be printed directly from the website to each participant scoring higher than 70%.

Hardware/Software Requirements: You will need a Macintosh or PC to access the online archived articles and CME testing. Adobe Reader is required to view the PDFs of the archived articles. Adobe Reader is available as a free download at www.adobe.com.

Emergency Medicine Practice is not affiliated with any pharmaceutical firm or medical device manufacturer.

CEO: Robert Williford
President and Publisher: Stephanie W. Ivy
Associate Editor & CME Director: Jennifer Pai
Director of Member Services: Liz Alvarez

Direct all questions to:
EB Medicine
1-800-249-5770
Outside the U.S.: 1-678-366-7933
Fax: 1-770-500-1316
5550 Triangle Parkway, Suite 150
Norcross, GA 30092
E-mail: **ebm@ebmedicine.net**
Web Site: **ebmedicine.net**

Subscription Information:
1 year (12 issues) including evidence-based print issues, 48 AMA/ACEP Category 1, AAFP Prescribed, or AOA Category 2B CME credits, and full online access to searchable archives and additional CME: $329
1 year institutional/hospital/library rate: $899
Individual issues, including 4 CME credits: $30
(Call 1-800-249-5770 or go to www.empractice.com to order)