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RELIAS MEDIA

Chronic Obstructive Pulmonary Disease Exacerbations

Scope of the Problem

Chronic obstructive pulmonary disease (COPD) is a significant global health problem. People with COPD frequently seek emergency care for acute exacerbations, which are associated with significant morbidity and mortality. Therefore, it is crucial for emergency physicians to understand how to assess and treat these patients appropriately.

Epidemiology

COPD is a widespread illness, affecting approximately 16 million people in the United States and 328 million people around the world.[1,2] The disease also is associated with significant mortality, contributing to 156,637 deaths in the United States in 2017 and about 2.9 million globally.[2,3] COPD not only takes a toll on health, but it also imposes enormous economic costs. In 2010, COPD resulted in a total medical cost of about $32.1 billion in the United States, with the cost projected to rise substantially to $49 billion by 2020.[4]

In the United States, COPD is most prevalent among women ages 65 to 74 years and men ages 75 to 84 years.[5] Symptoms such as chronic dyspnea and cough should prompt the clinician to consider a diagnosis of COPD. The diagnosis then is made definitively by spirometry demonstrating an airflow obstruction that does not fully respond to inhaled bronchodilators.[6]

Comorbidities are common among patients with COPD. Cardiovascular comorbidities are particularly common and are associated with poorer outcomes. Specifically, the prevalence of coronary artery disease among those with COPD is estimated to be as high as 33%, and approximately 24% have concomitant heart failure.[6,7]

COPD was responsible for an estimated 923,000 emergency department (ED) visits in 2017, the most recent year for which data are available.[8] Emergency visits relating to COPD are commonly due to acute exacerbations, characterized by a sudden worsening of symptoms. These are significant events in the progression of disease. A history of exacerbations predicts future exacerbations, with exacerbation frequency increasing in patients with more severe disease.[9,10] Patients with a history of myocardial infarction and heart failure tend to have more frequent exacerbations.[11] Even one exacerbation is associated with some deterioration in a patient's respiratory status.[12] Exacerbations also are associated with higher mortality.[11]

EXECUTIVE SUMMARY

- The most common cause of chronic obstructive pulmonary disease exacerbations is respiratory infections.
- Initial ancillary test evaluation should include pulse oximetry, complete blood count and chemistry panel, chest X-ray, and electrocardiogram.
- Initial treatment should include nasal cannula or mask oxygen to maintain oxygen saturation between 88% and 92%.
- If adequate oxygenation and ventilation cannot be maintained with supplemental oxygen, use in-sequence noninvasive ventilation, high-flow nasal cannula, and endotracheal intubation and mechanical ventilation.
- Initial treatment should include short-acting beta-2 agonists via nebulization or aerosol and systemic corticosteroids by mouth or intravenously.
- Disposition from the emergency department is determined by the severity of the exacerbation, the response to treatment, and the presence of comorbidities that increase short-term mortality.

Pathophysiology

COPD, as its name suggests, is defined by a chronic impediment to airflow through the bronchial tree. This impediment is primarily the product of two processes. The first is obstruction of the small airways by fibrosis and mucus. The second is emphysema, which describes the destruction of the lung's elastic structure by proteolytic enzymes. When the lung loses its supportive structure, the airways are prone to collapse with expiration. Both processes are triggered by chronic inflammation in the lungs that is most commonly the result of cigarette smoke but also can be influenced by environmental and occupational exposures.[6,13,14]

One notable complication of COPD is cor pulmonale. Because of the ventilation-perfusion (V/Q) mismatch that exists in the lungs, the pulmonary blood vessels undergo hypoxic vasoconstriction and remodeling over time. A decrease in nitric oxide production by endothelial cells also is theorized to contribute. Together, these processes increase the pressure in the pulmonary artery. This increased afterload induces the development of right ventricular hypertrophy, which can lead to right heart failure.[15]

Acute COPD exacerbations represent a sudden worsening of the chronic airway inflammation that defines this disease.[16] Greater bronchial edema and bronchoconstriction worsen the obstruction that exists at baseline, trapping oxygen-depleted air in the lungs and resulting in impaired ventilation of gas-exchanging lung segments. Concurrently, an increase in resistance to blood flow through the pulmonary arteries limits the amount of blood that reaches the alveoli to participate in gas exchange. Together, these changes aggravate the existing V/Q mismatch and lead to worsening hypoxemia and hypercapnia.[17]

Etiology

There are many causes of COPD exacerbations, with respiratory infection being the most common. Various viruses account for about 30% of these infections.[18] The viral pathogens most commonly implicated, in order of frequency, include rhinovirus, respiratory syncytial virus, coronavirus, and influenza.[19] The prevalence of specific pathogens may vary geographically and seasonally. Bacterial infections also incite exacerbations. Causative bacteria tend to differ, depending on the severity of the underlying disease. *Haemophilus influenzae* and *Moraxella catarrhalis* predominate in patients with milder COPD, while *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* are found more commonly in patients with more severe underlying respiratory disease.[18]

Poor adherence to home medications is another notable factor that contributes to COPD exacerbations. One study that used data from a large COPD medication trial showed a clear correlation between adherence to COPD medications and clinical outcomes. The authors found that poor adherence was associated with both a higher rate of exacerbations necessitating hospitalization and greater mortality.[20] Air pollution, cold weather, and gastroesophageal reflux disease are other factors postulated to play a role in triggering exacerbations, although data for some of these factors are inconclusive.[18,21]

Clinical Features

Symptoms commonly associated with COPD include dyspnea and productive cough. Sudden worsening of these symptoms may herald an acute exacerbation, for which patients may seek treatment from their primary care physician or in the ED.[6]

When assessing a patient with a suspected exacerbation, look first for signs of severe illness that require immediate intervention. For example, identify signs of respiratory distress, such as breathing through pursed lips, inability to speak in complete sentences, leaning forward, diaphoresis, and use of accessory muscles of respiration. Examine the patient's chest and abdomen to determine the use of accessory muscles of respiration.[22] Look also at the neck, because a deviated trachea could signify a tension pneumothorax. Take note of the vital signs, paying special attention to the respiratory rate and oxygen saturation to identify tachypnea and hypoxia, respectively. Tachycardia may signify a tachydysrhythmia or simply reflect the sympathetic response to a distressing situation. A fever may indicate an infectious process, such as pneumonia. A decrease of 10 mmHg or more in the patient's systolic blood pressure associated with inspiration would be concerning for pulsus paradoxus.[23] Speak with the patient to assess his or her mental status, since acute hypercarbic respiratory failure can cause patients to appear somnolent or even agitated and uncooperative.

If no threat to life requiring immediate action is identified on this initial evaluation, take the time to perform a thorough history and physical examination. In addition to the basic elements of the history of present illness, pertinent

historical questions should be asked. If the patient has a standing diagnosis of COPD, find out what medications he or she uses at home and whether the patient requires supplemental oxygen. Ask about the rate of oxygen, usually reported as liters/minute, and whether that rate has increased during this acute exacerbation. Ask about the duration of oxygen use during the day, such as 24 hours or only at bedtime. Increased flow rate and hours of use indicate an exacerbation of underlying disease. Ask about oxygen source, either concentrator or pressurized tanks, and whether the oxygen supply has been lost due to delayed delivery or electrical power loss. Inquire about a history of exacerbations and if the patient has ever required noninvasive ventilation (NIV), intubation, or admission to the intensive care unit (ICU).

Because respiratory infections and environmental exposures are common causes of exacerbations, ask about infectious symptoms, such as fever and cough, as well as potential exposures. Ask whether the patient's cough is productive, and if so, how the current sputum compares to the color and volume of sputum the patient usually has. Also include a pertinent review of systems, emphasizing symptoms like chest pain that, when endorsed, can suggest a serious complication of an exacerbation or an alternate diagnosis.

Examine the patient's neck for jugular venous distention, which may suggest emergent conditions like acute heart failure or cardiac tamponade, but that also may be present in COPD patients who have cor pulmonale and other forms of chronic heart failure. The lung examination may reveal adventitious sounds, such as wheezes or rhonchi.[24] Patients in extremis may have significantly decreased air movement and, thus, might not have appreciable wheezes or rhonchi on lung examination. Diminished or absent unilateral breath sounds may indicate a pneumothorax. Cardiac gallops and murmurs can indicate heart failure or valvular disease. However, because of the lung hyperinflation that often accompanies COPD, heart sounds may be difficult to auscultate.

Look at the patient's fingers and perioral area for cyanosis, which may be present in severe hypoxia. Examine the lower extremities as well. Bilateral edema may be present in patients with heart failure, whereas unilateral swelling in a dyspneic patient would suggest venous thromboembolism.[25]

Diagnostic Studies

Basic laboratory studies, such as a complete blood count (CBC) or basic metabolic panel (BMP), often are ordered. The CBC may disclose anemia that could be contributing to the patient's dyspnea, although anemia itself does not appear to affect exacerbation risk.[26] The CBC also may show leukocytosis if there is an infectious process present, but this is a nonspecific finding. The BMP is useful for evaluating the patient's bicarbonate, which may be low in the setting of respiratory acidosis.

Further evaluation of the patient's acid-base state can be achieved with blood gas analyses. Guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend obtaining serial arterial blood gases (ABG) in patients with severe exacerbations, but this is probably unnecessary in patients with less severe symptoms.[13,27] In fact, a combination of continuous pulse oximetry and venous blood gases (VBG) may be sufficient to monitor oxygenation status in milder exacerbations. One meta-analysis showed acceptable agreement between oxygen saturation readings from pulse oximeters and the arterial oxygen pressure as determined by ABG when the patient's oxygen saturation was above 70%.[28]

Two other studies showed that a partial pressure of carbon dioxide (pCO_2) greater than 45 mmHg on VBG identifies hypercarbia, which was defined as an arterial pCO_2 greater than 50 mmHg, with perfect sensitivity, suggesting that the VBG can be used to screen for significant hypercarbia. However, because arterial and venous pCO_2 values differ substantially, an ABG would be required to evaluate the specific level of arterial pCO_2 after a screening VBG identifies that some level of hypercarbia exists.[29,30] The VBG also gives a pH and bicarbonate that are similar to those obtained from arterial blood.[31]

It is important to remember that laboratory values, while helpful, provide only part of the picture. Key management decisions, such as initiating NIV or intubating the patient, should take into account the patient's overall clinical status and not be driven solely by the patient's blood gases.[27]

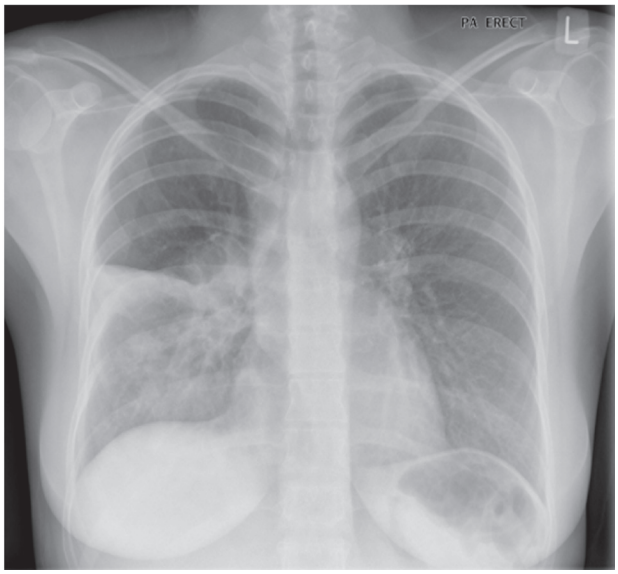
If there is concern for a cardiac cause of the patient's symptoms based on the medical history and clinical presentation, it may be reasonable to obtain an electrocardiogram (ECG), cardiac biomarkers, or brain natriuretic peptide. Guidelines from the National Institute for Health and Care Excellence (NICE) in the United Kingdom recommend an ECG for all patients.[32] In addition to showing ischemic changes, the ECG will detect cardiac rhythm disturbances. Arrhythmias, including atrial fibrillation, atrial flutter, and ventricular tachycardia, are observed more commonly in patients with COPD. There is some suggestion that exacerbations may incite multifocal atrial tachycardia. The occurrence of arrhythmias during an exacerbation has been associated with higher mortality.[33,34] Elevated cardiac biomarkers in the setting of a COPD exacerbation, even in the absence of an acute coronary syndrome, also are associated with a higher 30-day mortality.[35]

Chest radiographs often are ordered when a patient presents with symptoms suggestive of a COPD exacerbation.[36] Radiographs are particularly useful in equivocal cases because they can provide strong evidence for alternate etiologies, such as pulmonary edema and pleural effusions in a patient with a heart failure exacerbation, or an air-filled pleural space in a patient with pneumothorax. As previously discussed, some COPD exacerbations are caused by bacteria, and the chest radiograph can provide evidence to support this diagnosis in the form of a lobar consolidation. Figure 1 demonstrates a chest radiograph from a COPD patient with a consolidation suggesting a lobar pneumonia.[37] Further laboratory workup of a patient with a COPD exacerbation may include inflammatory markers to guide treatment. This will be discussed later.

Differential Diagnosis

A history of COPD exacerbations is a key indication that the patient

Figure 1. COPD Chest X-Ray



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may be experiencing a recurrent acute exacerbation. However, other causes of dyspnea that present similarly should always be considered. The differential diagnosis for a patient presenting with dyspnea is extensive and includes some critical diagnoses that can be fatal if not promptly identified and treated. Myocardial infarction and acute heart failure are two important considerations because, as previously discussed, coronary artery disease and heart failure are frequent comorbidities among COPD patients.[7,38] Pneumothorax also is a notable cause of acute dyspnea in patients with COPD.[39] Another consideration in the differential diagnosis is pulmonary embolism (PE). Patients with severe COPD are at higher risk for developing PE, which can present similarly to an acute COPD exacerbation.[40] This means that correctly diagnosing PE may be more challenging in this cohort.[41] It may be appropriate to strongly consider PE in a patient with pleuritic chest pain, no clear infectious symptoms, or failure to improve with typical COPD therapy.[27,42] A high-sensitivity D-dimer is recommended as a screening test, and those with a value above the threshold established by the test manufacturer should undergo imaging with computed tomography (CT) pulmonary angiography to detect pulmonary emboli or duplex ultrasound to detect thrombi in the leg veins.

Management

Treatment for COPD exacerbations generally includes supplemental oxygen, bronchodilators, systemic steroids, and antibiotics. Key treatment points discussed in the following sections are summarized in Table 1.

Oxygenation

Assessment of the patient's airway patency and oxygenation status is the most important first step. Patients who are hypoxic should be given supplemental oxygen. Usually, this is accomplished with a nasal cannula or non-rebreather mask connected to an external oxygen source. Evidence shows that both hypoxia and hyperoxia are harmful in COPD, and, therefore, the literature currently recommends targeting an oxygen saturation of 88% to 92%.[43]

Traditional teaching cautioned against the use of high supplemental oxygen concentrations because of the belief that this would suppress the hypoxic respiratory drive in the COPD patient and potentially lead to apnea. Excessive oxygen administration can lead to hypercapnia and, therefore, should be avoided. However, the primary driving force behind this effect is not thought to be suppression of the respiratory drive. Instead, reversal of hypoxic vasoconstriction and increased delivery of oxygenated air to dead-space areas of the lung are thought to be the driving forces.[44]

For patients who require greater respiratory support but not endotracheal intubation, NIV with continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) is indicated. Specifically, guidelines recommend NIV for patients who are acidemic, who are in respiratory distress, or who exhibit hypoxia refractory to supplemental oxygen.[13] Using NIV in these patients may help to avoid intubation, and is associated with shorter lengths of stay and improved mortality.[45]

Guidelines from the British Thoracic Society recommend initiating BiPAP with an inspiratory positive airway pressure (IPAP) of about 15 cm H_2O and an expiratory pressure of about 3 cm H_2O. They also recommend gradually increasing the IPAP to 20 to 30 cm H_2O, depending on the patient's clinical status, respiratory rate, and blood gas values.[46] However, note that caution is advised when raising the IPAP above 20 cm H_2O because of the risk of gastric distention at these elevated pressures.[47]

Avoidance of intubation is a notable benefit of NIV associated with lower mortality, shorter length of stay, and less cost compared to invasive mechanical ventilation.[48] Some novel therapies are under investigation to assist patients failing NIV in an attempt to improve their respiratory status and prevent intubation. One large, prospective study examined the use of a gaseous mixture of helium and oxygen. This mixture, commonly known as heliox, did not improve the NIV failure rate compared to oxygen alone, although it did show beneficial effects on respiratory rate and pCO_2.[49] Another rescue strategy under investigation is veno-venous extracorporeal carbon dioxide removal. There is some evidence to suggest that initiating this therapy in patients who are failing BiPAP may reduce the degree of hypercarbia and help to avoid intubation. However, extracorporeal carbon dioxide removal is associated with serious complications, including life-threatening bleeding.[50] Guidelines from the British Thoracic Society caution that this

Table 1. Key Treatment Points

Treatment	Mechanism of Action	Key Points
Supplemental oxygen	Improves hypoxemia	• Titrate to SpO_2 of 88% to 92%[43] • NIV reduces intubation rates and mortality[45]
Bronchodilators	Produce bronchodilation by relaxing smooth muscle in bronchi, effect lasts four to six hours[67]	• SABAs are first line • Nebulizer and MDI are both effective delivery methods[65]
Steroids	Reduce airway inflammation and enhance bronchodilation[74]	• PO is equivalent to IV in efficacy[76,77] • Preferred duration is five to seven days[81,82]
Antibiotics	Treat underlying bacterial infections	• Recommended when there are signs of infection or in severe exacerbations (*see Table 2*)

SpO_2 = oxygen saturation; NIV = noninvasive ventilation; SABAs = short-acting beta-2 agonists; MDI = metered dose inhaler; PO = by mouth; IV = intravenous

therapy is experimental and requires specialized training to implement.[46] It is not included in the GOLD guidelines.[13]

Despite its clear benefits in COPD exacerbations, disadvantages to NIV include the discomfort of the tight-fitting mask and the limitations on oral intake and speaking while undergoing treatment. High-flow nasal cannula (HFNC), which provides humidified air at up to 60 liters per minute through nasal prongs, is a proposed alternative to NIV.[51] Compared to NIV modalities such as BiPAP, HFNC is associated with similar intubation rates and short-term mortality in COPD exacerbations.[52-54] It also has been shown to be superior to standard nasal cannula and approximately equal to NIV in improvement of hypercarbia, although there are conflicting findings in the literature.[52,54-57] The ability of HFNC to flush air forcefully from the anatomical dead space of the upper airway in a flow rate-dependent manner appears to be the primary mechanism behind this reduction in the arterial carbon dioxide pressure.[58,59] Studies also indicate that HFNC is better tolerated than BiPAP and even more comfortable than the standard nasal cannula.[52,56,57] The comparable efficacy and superior tolerability suggest that HFNC could be an acceptable alternative if the patient has difficulty tolerating NIV.

Although avoiding intubation is preferred, sometimes intubation and mechanical ventilation are necessary in patients experiencing severe COPD exacerbations. The alterations in respiratory physiology that characterize COPD patients at baseline have significant implications for ventilator management. The central issue is dynamic hyperinflation, whereby inspired air becomes trapped in the lungs because of the great resistance to air flow in the constricted and inflamed bronchioles. This process causes the end-expiratory volume to increase with ventilator-delivered breaths. The result is the development of intrinsic positive end-expiratory pressure, which is reflected by increasing plateau pressures. The higher lung volumes created by this dynamic hyperinflation make it harder for the patient to draw spontaneous breaths, decrease cardiac output, and increase the risk of pneumothorax.

There are two primary strategies to mitigate dynamic hyperinflation. The first strategy involves the use of steroids and bronchodilators to open the airways and reduce the expiratory obstruction, allowing more air to exit the lungs. The second way to reduce dynamic hyperinflation is to increase the amount of time spent in expiration, which can be done in the mechanically ventilated patient either by decreasing the respiratory rate or adjusting the inspiratory to expiratory (I:E) ratio. Some degree of hypercapnia and acidosis is acceptable in patients who maintain a respiratory acidosis at baseline, as attempting to normalize the patient's blood gas values may make successfully extubating the patient more challenging.[60]

Prone positioning has been studied as an intervention in patients who require mechanical ventilation as a result of a COPD exacerbation. This method has been shown to improve mortality in patients with acute respiratory distress syndrome.[61] Although there is no evidence of a similar mortality benefit in COPD exacerbations, prone positioning does appear to enhance oxygenation and reduce dynamic hyperinflation.[62-64] However, the few studies examining this intervention were small, so prone positioning in COPD exacerbations likely will require further study to clarify its potential benefits.

Bronchodilators

Short-acting beta-2 agonists (SABAs), such as albuterol, are recommended as first-line bronchodilators for COPD exacerbations.[13] Regarding the choice between nebulizers and metered dose inhalers (MDI) for bronchodilator delivery, there is no high-quality evidence that favors one mode over the other.[65] However, for practical purposes, the nebulizer system may be more efficient because it can be worn as a mask and does not require patient operation. Doses commonly used are 2.5 mg and 5 mg. One study that compared these two doses of nebulized albuterol for treatment of mild-to-moderate exacerbations in inpatients found no difference in length of stay or time until respiratory improvement between the two groups, suggesting that the higher dose does not offer additional benefit.[66]

Be aware of the adverse effects of SABAs, which include tachycardia, palpitations, hyperglycemia, hypokalemia, and tremor. Nebulization of SABAs is associated with a higher likelihood of adverse effects than drug delivery by MDI.[67] Adding a short-acting anticholinergic agent, such as ipratropium

bromide, has not been shown to enhance the bronchodilator effect or prevent hospitalization.[68,69] However, GOLD guidelines still recommend combining SABAs and anticholinergic drugs in severe exacerbations.[13]

Magnesium

Sometimes magnesium is used along with bronchodilators in COPD exacerbations, and it can be administered either intravenously or by nebulization. There is some evidence that intravenous magnesium sulphate modestly enhances air flow in some patients when used adjunctively with SABAs. However, the addition of magnesium has not been shown to affect patient-centered outcomes, such as need for admission, length of stay, and mortality.[70-72] Nebulized magnesium has not been shown to be effective in improving lung function or avoiding hospital admission.[73] Magnesium is not included as a recommended adjuvant treatment in either the GOLD or NICE guidelines.[13,32]

Corticosteroids

Systemic corticosteroids act to both reduce airway inflammation and enhance bronchodilation.[74] They have been shown to reduce both the risk of treatment failure and length of hospitalization during a COPD exacerbation, and they are associated with accelerated improvement in lung function.[75,76]

Patients who can tolerate oral intake, including those who require hospital admission, can be given steroids by mouth because there is evidence that oral steroids are equally effective to those given parenterally,[76,77] and in fact are associated with a shorter length of stay for inpatients.[78] Guidelines from the European Respiratory Society and American Thoracic Society (ERS/ATS) affirm this evidence, recommending oral over intravenous steroids when oral intake is tolerated.[79] The typical dose of daily oral prednisone ranges from 20 mg to 60 mg.[78] Evidence suggests that prednisone doses greater than 80 mg per day do not provide more benefit than lower doses, including in inpatients.[80] GOLD guidelines recommend a five-day course of prednisone 40 mg.[13]

Longer steroid courses only expose the patient to more potential harms without providing any observable benefit.[81,82] One of the most clinically relevant short-term adverse effects associated with steroids is hyperglycemia.[76] Although the effect of this transient hyperglycemia may be negligible for many patients, it can be problematic in those with diabetes,[83] which is estimated to be present in up to 23% of those with COPD.[7]

When parenteral steroids are provided, either methylprednisolone or dexamethasone often is chosen. In one head-to-head study of ED patients who were admitted to the hospital, methylprednisolone appeared more effective in treating cough, while dexamethasone was more effective for dyspnea and hypoxia. However, these differences appear small, and there is no compelling evidence to recommend one over the other.[84]

One cohort study examined dosing strategies for patients requiring admission to the ICU as the result of a COPD exacerbation. The researchers found that an initial daily dose of 240 mg or less of methylprednisolone, which is equivalent to 60 mg given every six hours, was associated with a shorter length of stay and less time requiring invasive mechanical ventilation compared to higher doses. This suggests that lower doses are preferred even in critically ill COPD patients, although specific dosing recommendations for this population require further study.[85]

Antibiotics

Sometimes antibiotics are prescribed in COPD exacerbations. GOLD guidelines recommend antibiotics in three clinical scenarios. These are outlined in Table 2, along with recommended classes of empiric antibiotics.[13] In addition, patients with signs of bacterial pneumonia, such as a lobar consolidation on chest X-ray, should receive antibiotics.

Table 2. Antibiotic Recommendations[13]

Patients with the indications below can be treated with any one of the three recommended agents.

Indications	Recommended Agents*
• Increased dyspnea, sputum volume, and sputum purulence • Increased dyspnea and sputum purulence • Increased sputum volume and sputum purulence • Patient needs noninvasive ventilation or intubation	• Aminopenicillin with clavulanic acid • Macrolide • Tetracycline

* Other antibiotic classes may be appropriate depending on local and patient-specific resistance factors.

Research shows that antimicrobial therapy is associated with a lower risk of treatment failure in outpatients and patients requiring ICU care. Improved mortality and shorter lengths of stay are additional benefits associated with antibiotic use in ICU patients.[86] Sputum cultures for patients treated outside the hospital do not appear to be helpful and are not recommended routinely, unless the patient has risk factors for *P. aeruginosa* infection, including repeated exacerbations.[13,32,87]

Although antibiotics are shown to provide some benefit in COPD exacerbations, the indiscriminate and excessive use of antibiotics is a widely recognized problem with significant, deleterious downstream effects. Therefore, there is great incentive to prescribe antibiotics appropriately.[88] To this end, there has been interest recently in determining whether inflammatory biomarkers can predict a need for antibiotics in COPD exacerbations. Most investigation to date has focused on C-reactive protein (CRP) and procalcitonin.

CRP is an acute phase protein that is thought to play a part in the inflammatory response to microbial infection by triggering the complement cascade.[89] The use of CRP testing to guide antibiotic prescribing for outpatients has been

Table 3. Selected Indications for Hospitalization[13,32]	
Symptoms	• Severe dyspnea • Rapid onset of symptoms
Signs	• High respiratory rate • Confusion or drowsiness • Acute respiratory failure • New physical signs, such as cyanosis or peripheral edema
Diagnostic studies	• SpO_2 < 90% • Changes on chest X-ray • Arterial pH < 7.35
Medical history	• Presence of serious comorbidities
Social factors	• Insufficient home support • Lives alone
Emergency department course	• Failure to respond to initial treatment

shown to decrease antibiotic use without compromising care.[90,91]

The other biomarker of interest, procalcitonin, is the precursor to the hormone calcitonin. Although the primary purpose of this pathway is to maintain calcium homeostasis, microbial lipopolysaccharides and inflammatory interleukins can upregulate the production of procalcitonin and, therefore, make it a potential marker for bacterial infection. In clinical practice, procalcitonin often is preferred over CRP for identifying infections.[92]

Regarding procalcitonin use in COPD exacerbations, some studies have shown an association of procalcitonin with fewer antibiotic prescriptions without adversely affecting outcomes.[93-95] However, others have found that procalcitonin does not reduce overall antibiotic exposure,[96] and still others have challenged the ability of these biomarkers to differentiate bacterial from viral infections in COPD exacerbations.[97,98] Because of these conflicting findings, GOLD neither endorses nor discourages the use of biomarkers in prescribing decisions.[13] The role of these biomarkers in guiding treatment decisions in COPD exacerbations likely will require more study and clarification.

Exacerbation Prevention

GOLD guidelines recommend optimizing outpatient therapy after an exacerbation in an effort to prevent subsequent exacerbations.[13] Whether this is done in the ED, on hospital discharge, or by the patient's primary care physician may vary by provider preference and practice location. Combination inhalers have become common and generally are more effective than single-medication inhalers. Specifically, the inhaler most effective at reducing the risk of future exacerbations appears to be a long-acting beta-2 agonist (LABA) combined with a long-acting muscarinic antagonist (LAMA).[99] Inhaled corticosteroids (ICS) are used frequently in combination with LABAs. Although this combination improves quality of life,[100] the ICS component appears to increase the risk for developing pneumonia.[101,102] Regarding monotherapy, ERS/ATS guidelines indicate a preference for LAMAs over LABAs.[103]

Disposition

Disposition decisions are relatively straightforward regarding patients on either end of the severity spectrum. Addressing those who reside between the extremes becomes more challenging. To inform those decisions, it is important to note which clinical features are associated with worse outcomes. Patients with comorbidities, such as heart failure and diabetes, tend to have higher readmission and mortality rates.[104,105] A visible consolidation on the chest radiograph during a COPD exacerbation is associated with more frequent administration of supplemental oxygen, greater degree of acidemia, longer hospitalization, and higher mortality. Not surprisingly, these patients frequently also have purulent sputum and receive antibiotics.[106] Selected indications for admission from GOLD and NICE guidelines are combined in Table 3. They include some of the high-risk factors discussed previously.

Several COPD-specific clinical decision rules in the literature are intended to help this decision-making process. One rule, called DECAF, combines dyspnea severity, eosinopenia, radiographic consolidation, acidemia, and atrial fibrillation to estimate both in-hospital and 30-day mortality. Dyspnea is graded based on the extended Medical Research Council dyspnea score.[107] It was shown to be a better predictor of in-hospital and 30-day mortality than prior decision rules, such as CURB-65, BAP-65, and CAPS,[108] although this conclusion has been challenged recently.[109] One caveat to DECAF is that it was studied only in the inpatient population and is meant to help identify patients who may be safely discharged early from an inpatient unit. Therefore, it is unclear how this decision rule applies to patients in the ED.

To address this gap, the Ottawa COPD Risk Scale (OCRS) was designed specifically for aiding disposition decisions in the ED. OCRS uses 10 factors to predict the risk of short-term adverse events, and is meant to help determine which patients are sufficiently low-risk that they can be discharged safely from the ED with outpatient follow-up.[110,111] The authors declined to recommend a cutoff value that would differentiate patients who should be admitted from those who are safe for discharge, deferring to clinician judgment. Remember that decision rules are meant to be factored into the milieu of clinical data that inform decision-making and are not intended to serve as stand-alone deciding factors.

Summary

Acute exacerbations frequently prompt patients with COPD to present to the ED, so it is crucial for emergency physicians to understand how to assess and treat these patients effectively. Viral and bacterial respiratory infections are the most common causes of exacerbations, but nonadherence to home medications also is a significant contributing factor. Because comorbidities are common in

those with COPD, consider other serious causes for the patient's symptoms, such as myocardial infarction, acute heart failure, and pulmonary embolism.

In the evaluation of a patients with milder symptoms, continuous pulse oximetry and venous blood gases may be sufficient to monitor oxygenation status without an arterial blood gas. Even though venous and arterial carbon dioxide pressures differ, evidence suggests that a venous blood gas can be used to screen for hypercarbia.

Treatment of COPD exacerbations often involves supplemental oxygen, bronchodilators, and systemic corticosteroids. Titrate the supplemental oxygen to achieve an SpO_2 of 88% to 92%. For patients who require more respiratory support than a nasal cannula or non-rebreather mask, NIV has been shown to reduce intubation rates and mortality. Patients who do not improve on NIV or cannot tolerate it should be intubated, although there is some evidence to suggest that high-flow nasal cannula is tolerated better and can improve hypercarbia and help to avoid intubation.

Ventilator management of COPD patients is focused on reducing intrinsic positive airway pressure and dynamic hyperinflation. This can be accomplished by administering medications to reduce airway inflammation and bronchoconstriction, reducing the respiratory rate, and adjusting the I:E ratio on the ventilator to allow for greater expiratory time.

Short-acting bronchodilators, such as albuterol, can be delivered effectively by either nebulizer or MDI. An outpatient steroid course of about five days is appropriate for patients who are discharged. Use steroids with caution, especially in patients with a history of diabetes, because they can cause hyperglycemia.

Antibiotics generally are recommended when there are signs of bacterial infection, such as purulent sputum, and in patients requiring mechanical ventilation. Inflammatory markers, such as CRP and procalcitonin, are being investigated as indicators for antimicrobial therapy in COPD exacerbations, but there is not yet enough evidence to recommend their routine use for this purpose.

Guidelines recommend assessing the patient's long-term regimen after an exacerbation and making adjustments as needed to reduce the risk of subsequent exacerbations. Patients with severe symptoms, those who do not respond appropriately to treatment in the ED, and those with significant comorbidities should be admitted, while it may be reasonable to allow those with milder symptoms and good social support to go home with close follow-up. Clinical decision rules can be used to assist disposition decisions.

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CME/CE Questions

1. What is the most common cause of chronic obstructive pulmonary disease (COPD) exacerbations?
   a. Seasonal changes
   b. Pulmonary emboli
   c. Gastroesophageal reflux disease
   d. Respiratory infections
2. Which of the following statements regarding bronchodilators is true?
   a. Bronchodilators are delivered more effectively by nebulizer than metered dose inhaler.
   b. Short-acting beta-adrenergic agonists combat bronchospasm by relaxing airway smooth muscle.
   c. Long-acting beta-2 agonists are recommended over short-acting beta-2 agonists for emergent treatment of exacerbations.
   d. A potential side-effect of bronchodilators is hyperkalemia.
3. Which of the following factors has been associated with poor prognosis in COPD exacerbations?
   a. Younger age
   b. Presence of comorbidities
   c. First-ever exacerbation
   d. No visible consolidation on chest X-ray
4. Which long-term therapy is associated with increased risk of developing pneumonia?
   a. Inhaled corticosteroids
   b. Long-acting beta-adrenergic agonists
   c. Long-acting muscarinic antagonists
   d. Prophylactic antibiotics
5. Which of the following statements regarding noninvasive ventilation (NIV) is true?
   a. NIV is contraindicated prior to an intubation attempt.
   b. NIV is contraindicated in the patient who remains hypoxic on nasal cannula.
   c. NIV is contraindicated in the acidemic patient.
   d. NIV is contraindicated in the somnolent patient.
6. According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, which of the following is an indication for antibiotics?
   a. Need for intubation and mechanical ventilation
   b. Need for intravenous corticosteroids
   c. Presence of purulent sputum alone
   d. Presence of increased sputum volume alone
7. Which of the following statements regarding corticosteroids is true?
   a. Inhaled corticosteroids are indicated in an acute exacerbation.
   b. Intravenous corticosteroids are more effective than oral steroids.
   c. Hyperglycemia is an adverse effect of steroids.
   d. Longer courses (14 days) of oral steroids are more effective than shorter courses (five days).
8. Which of the following factors alone generally is considered an indication for admission?
   a. The patient has new peripheral edema on physical examination.
   b. The patient has normal sinus rhythm on electrocardiogram.
   c. The patient lives with supportive family.
   d. The patient responds well to bronchodilators in the emergency department.
9. Which of the following statements regarding COPD exacerbations is true?
   a. Exacerbations have no effect on progression of disease.
   b. Patients with a history of exacerbations are less likely to experience future exacerbations.
   c. Exacerbations have no effect on mortality.
   d. Exacerbations are associated with a decline in lung function.
10. Which of the following changes to ventilator settings will reduce dynamic hyperinflation?
    a. Increasing inspiratory to expiratory ratio
    b. Decreasing respiratory rate
    c. Increasing positive end-expiratory pressure
    d. Increasing respiratory rate

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Chronic Obstructive Pulmonary Disease Exacerbations

Key Treatment Points

Treatment	Mechanism of Action	Key Points
Supplemental oxygen	Improves hypoxemia	• Titrate to SpO_2 of 88% to 92%[43] • NIV reduces intubation rates and mortality[45]
Bronchodilators	Produce bronchodilation by relaxing smooth muscle in bronchi, effect lasts four to six hours[67]	• SABAs are first line • Nebulizer and MDI are both effective delivery methods[65]
Steroids	Reduce airway inflammation and enhance bronchodilation[74]	• PO is equivalent to IV in efficacy[76,77] • Preferred duration is five to seven days[81,82]
Antibiotics	Treat underlying bacterial infections	• Recommended when there are signs of infection or in severe exacerbations (*see Table 2*)

SpO_2 = oxygen saturation; NIV = noninvasive ventilation; SABAs = short-acting beta-2 agonists; MDI = metered dose inhaler; PO = by mouth; IV = intravenous

Antibiotic Recommendations

Patients with the indications below can be treated with any one of the three recommended agents.

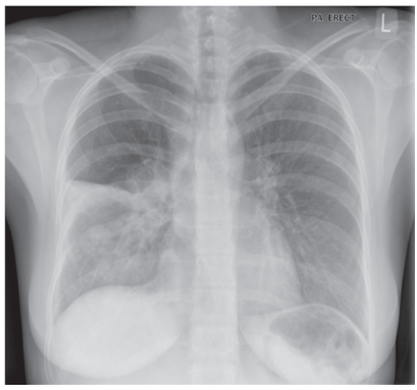
Indications	Recommended Agents*
• Increased dyspnea, sputum volume, and sputum purulence • Increased dyspnea and sputum purulence • Increased sputum volume and sputum purulence • Patient needs noninvasive ventilation or intubation	• Aminopenicillin with clavulanic acid • Macrolide • Tetracycline

* Other antibiotic classes may be appropriate depending on local and patient-specific resistance factors.

Selected Indications for Hospitalization

Symptoms	• Severe dyspnea • Rapid onset of symptoms
Signs	• High respiratory rate • Confusion or drowsiness • Acute respiratory failure • New physical signs, such as cyanosis or peripheral edema
Diagnostic studies	• SpO_2 < 90% • Changes on chest X-ray • Arterial pH < 7.35
Medical history	• Presence of serious comorbidities
Social factors	• Insufficient home support • Lives alone
Emergency department course	• Failure to respond to initial treatment

COPD Chest X-Ray



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