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Chronic Obstructive Pulmonary Disease: Inpatient Management

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- Chronic obstructive pulmonary disease
- Inpatient management
- Acute exacerbation of COPD
- Global Initiative for COPD guidelines

HOSPITAL MEDICINE CLINICS CHECKLIST
1. Acute exacerbations of chronic obstructive pulmonary disease (COPD) are common in the course of chronic COPD, and are associated with substantial morbidity.
2. There are numerous guidelines, but literature suggests that there is substantial variation in care in patients with acute exacerbations of COPD.
3. Key components of acute therapy for most patients include oral steroids, antibiotics, nebulizers, oxygen, and early consideration of noninvasive ventilation.
4. Adjuvant components of care include venous thromboembolism prophylaxis, appropriate immunizations, counseling for smoking cessation, and consideration of pulmonary rehabilitation.

DEFINITIONS AND BURDEN OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND EXACERBATIONS

How is chronic obstructive pulmonary disease defined and diagnosed?

Chronic obstructive pulmonary disease (COPD) is an acquired and progressive pulmonary disorder. The principal physiologic lesion is airflow limitation, demonstrated on pulmonary function testing. Pathophysiologically, COPD is marked by evidence of chronic airway inflammation, loss of airway elasticity, and destruction of the alveoli.

COPD develops over years of exposure to noxious substances. At least 80% of the overall risk is considered attributable to smoking and exposure to smoking. Air pollution and other environmental agents may cause or contribute to COPD, in addition to unusual inherited disorders such as \text{\alpha}1-antitrypsin deficiency.

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In the clinical setting of symptoms and appropriate history, the diagnosis requires demonstrating persistent airflow limitation after treatment with a bronchodilator, defined as a ratio of forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) of less than 0.70.

What is an acute exacerbation of COPD?

Acute exacerbations of COPD (AECOPD) occur commonly in the natural course of COPD. The diagnosis of an acute exacerbation is a clinical one that is based on history and absence of alternative explanations. The Global Initiative for COPD (GOLD) defines an exacerbation as:

- A worsening of symptoms, which is
- Beyond normal day-to-day variation, and which
- Leads to a change in medication

Episodes are typically marked by increasing dyspnea, cough, and/or sputum production or quality.

What is the epidemiology and burden of COPD?

Worldwide, COPD is more prevalent in smokers, in men, and in individuals older than 40 years, and carries a substantial health and economic cost. The World Health Organization reports that COPD accounted for 5.8% of deaths worldwide in 2008, making it the fourth leading cause of death. The direct costs of COPD in the United States have been recently estimated to be $29.5 billion, with another $20.4 billion in indirect costs.

AECOPD merits special attention. In 2009, COPD as a primary diagnosis accounted for 739,000 hospital discharges in the United States. Hospitalizations and acute care costs constitute the bulk of the direct costs of COPD in the United States, and have a deleterious impact on lung function and on patients’ quality of life. One study found the 3-year risk of mortality after hospitalization for AECOPD to be nearly 50%. Other studies suggest that the in-hospital mortality of patients admitted for AECOPD with respiratory acidosis is approximately 10%. As airflow limitation worsens, the risks of exacerbation, hospitalization, and death increase.

Despite near unanimous agreement among treatment guidelines for AECOPD, there remains substantial variation in the delivery of guideline-concordant therapies to hospitalized patients. In a 2006 retrospective study of more than 70,000 patients admitted with AECOPD, only 66% received the full complement of evidence-based therapies, and more than 40% received at least one therapy contraindicated by guidelines and literature. The investigators concluded there are “widespread opportunities to improve quality of care and to reduce costs by addressing problems of underuse, overuse, and misuse of resources and by reducing variations in practice across institutions.”

In addition, transitioning from hospitalization to self-care is fraught with the risk for rehospitalization and potentially ineffective care. In 2009, Jencks and colleagues reported the 30-day rehospitalization rate for patients discharged from a COPD hospitalization was 22.6%, with the most frequent causes of rehospitalization being respiratory conditions.

What are the causes of AECOPD?

Most AECOPD are thought to be incited by bacterial or viral infections of the respiratory tree, or by exposure to environmental pollutants. Roughly one-third of AECOPD remain cryptogenic.
Other conditions may present similarly or concomitantly to AECOPD, such as pulmonary embolism, pneumonia, cardiac ischemia, or congestive heart failure. These entities must be identified promptly; however, from a clinical perspective further pursuit of the etiology is usually not relevant to the approach to acute treatment (but may be of value in preventing subsequent episodes and in improving chronic symptoms and treatment).

INITIAL EVALUATION AND DECISION FOR ADMISSION

What other conditions need to be considered in the evaluation of AECOPD?

The presentation of AECOPD is nonspecific, and must be distinguished from other life-threatening cardiopulmonary conditions including congestive heart failure, cardiac ischemia, pneumonia, and pulmonary embolism. This last condition has received some attention in recent literature. An analysis published in 2009 suggested that the prevalence of pulmonary embolism among patients hospitalized for acute COPD was 25%, although the limitations of the studies and analysis make clinical interpretation and application of these findings difficult.7

What tests are supported by guidelines?

The initial approach to AECOPD should be to determine the physiologic severity of respiratory distress, to evaluate for concomitant (or contributory) cardiac and pulmonary conditions, and to make an accurate triage decision for further care. In addition to the history and physical examination, basic laboratory studies, and electrocardiogram, the following diagnostic interventions may be considered, in descending order.

- Chest radiographs are recommended by existing guidelines in the evaluation of AECOPD, based on data from observational studies of patients presenting with presumed AECOPD; up to 21% of such patients' chest films suggest a change in treatment or alternative or concomitant diagnosis (eg, heart failure or pneumonia).8
- Arterial blood gas analysis should be performed in most patients to assess the degree of hypoxemia and hypercarbia, to assess indications for noninvasive ventilation, and to assess the effectiveness of supplemental oxygen therapy.
- Testing for influenza viruses may be seasonally appropriate and could affect choice of treatment.

In addition, sputum culture is generally not indicated because of the lack of specificity of findings, chronic colonization of COPD patients’ airways, and ubiquity of contamination. Likewise, spirometry is of dubious benefit because there are only limited data to show that clinical outcomes correlate with spirometry in the acute setting.

Are there established criteria to guide the decision to admit patients with AECOPD?

There are no evidence-based guidelines or “severity indices” that sufficiently and accurately distinguish patients who can be safely treated as outpatients from those who benefit from hospitalization. Therefore, the decision to admit patients to the hospital is a clinical decision. The initial clinical determination should assess for actual or imminent respiratory failure or other end-organ instability, which could prompt assisted ventilation and admission to intensive care.
In 2004, the American Thoracic Society published guidelines to guide the decision to hospitalize patients with AECOPD:

- High-risk comorbidities including pneumonia, cardiac arrhythmia, heart failure, diabetes mellitus, renal or liver failure
- Inadequate response of symptoms to outpatient management
- Marked increase in dyspnea
- Inability to eat or sleep owing to symptoms
- Worsening hypoxemia
- Worsening hypercapnia
- Changes in mental status
- Inability to care for oneself (lack of home support)
- Uncertain diagnosis

EVIDENCE-BASED TREATMENT

What therapies for AECOPD are supported by evidence?

There are numerous guidelines available to guide therapy for AECOPD in hospitalized patients. The principal therapies for the majority of patients include bronchodilators, corticosteroids, antibiotics, oxygen therapy, and early consideration for noninvasive positive-pressure ventilation (NIPPV). In addition, prophylaxis against venous thromboembolism (VTE) and evaluation for influenza and pneumococcal vaccination are appropriate and evidence based.

Bronchodilators

Which bronchodilators should be administered?

Short-acting bronchodilators alleviate dyspnea and improve airflow obstruction during AECOPD. Either β2-adrenergic agonists or anticholinergic agents may be administered in this setting. Both types of agents act rapidly and may be administered in nebulized form or in a metered dose inhaler (MDI). There is no compelling evidence that nebulizers are superior to MDI, although administration of nebulizers to anxious and dyspneic patients may be easier and better tolerated.

A systematic review of methylxanthine bronchodilators in AECOPD suggested a trend toward shorter length of stay (LOS) in hospital but also more symptomatic relapses at 1 week, and more adverse effects such as nausea, palpitations, and arrhythmias.10

The anticholinergic ipratropium bromide is also effective in AECOPD. Combination therapy with both β2-agonist and anticholinergic agents has not consistently shown a benefit in AECOPD, and a 2008 systematic review concluded that there was no evidence to support simultaneous therapy, or to suggest superiority of β2-agonists over anticholinergics.11

Is there evidence to support the choice or dose of bronchodilator?

The optimal dose and interval of bronchodilators has not been established by formal study. Albuterol is a common β2-agonist, administered via nebulizer as a 2.5-mg dose. Increasing the dose to 5 mg has not been shown to improve lung function or reduce hospital LOS.
In hospitalized patients with AECOPD, what are the expected benefits of treatment with systemic glucocorticoids?

Even before there were data to support the practice, systemic corticosteroid treatment was adopted as a standard part of the treatment of AECOPD. This decision was based, presumably, on the clinical similarities between COPD and asthma, and the recognition of the important role that systemic corticosteroids played in reversing the airway inflammation in asthma. However, over time it became clear that the inflammatory processes involved in these 2 diseases were different, and that the clinical effect of glucocorticoids in COPD was much smaller than in asthma.12

In the largest randomized controlled trial addressing this question (a trial sponsored by the Veterans Administration [VA] published in 1999),13 271 patients hospitalized for an AECOPD were randomized to receive systemic glucocorticoid treatment or placebo. All were treated with broad-spectrum antibiotics and bronchodilators. The primary outcome was treatment failure, defined as 1 of the following: death from any cause, need for intubation/mechanical ventilation, readmission for COPD, or intensification of pharmacologic treatment. The results showed that patients treated with systemic glucocorticoids experienced a lower rate of treatment failure, but this was mostly related to the need for intensification of treatment in the placebo group (mainly adding glucocorticoids). Therefore the benefit of adding systemic corticosteroids early was, primarily, that one would avoid having to add them later. However, the steroid group also had a 1.2-day shorter LOS and a significant improvement in FEV1 on the day after enrollment, but also had significantly higher rates of hyperglycemia requiring medical therapy, in comparison with the control group. The investigators concluded that glucocorticoids offer a modest benefit in patients hospitalized with COPD, at the cost of significant hyperglycemia in some patients.

There have been several other studies and meta-analyses examining the use of glucocorticoids in the treatment of AECOPD that have, for the most part, supported similar conclusions.14,15 A Cochrane Collaboration meta-analysis14 found that patients with AECOPD who were treated with systemic glucocorticoids experienced significantly fewer treatment failures (odds ratio [OR] 0.5, 95% confidence interval [CI] 0.36–0.69) than those treated with placebo (Fig. 1). Based on these data, 10 patients with AECOPD would need to receive steroids to prevent 1 treatment failure.16–18 Another meta-analysis found that patients with AECOPD treated with systemic glucocorticoids experienced shorter hospital LOS (1.22 days shorter, 95% CI 2.26–0.18). Some studies have also found steroids to be associated with improvements in FEV1, decreases in breathlessness, and improvements in blood gas abnormalities in this population. However, steroids have never demonstrated any mortality benefit in AECOPD.

Most of the studies of glucocorticoids in AECOPD have been performed in noncritically ill populations. However, recently, a study of patients in the intensive care unit demonstrated a decreased rate of noninvasive ventilation failure and a shorter duration of mechanical ventilation in those treated with glucocorticoids compared with placebo, suggesting that the benefits of this treatment extend to this population as well.19

What are the risks associated with glucocorticoid treatment in AECOPD?

The use of systemic glucocorticoids in this patient population is not without risks. The adverse effects of these drugs include psychosis, osteoporosis, hyperglycemia, muscle wasting, insomnia, and increased appetite/weight gain.14,20
Fig. 1. Forest-plot comparison of systemic corticosteroids (SCS) versus placebo for the outcome of treatment failure in the treatment of acute exacerbations of COPD. CI, confidence interval. (From Walters JA, Gibson PG, Wood-Baker R, et al. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2009;(1):CD001288. http://dx.doi.org/10.1002/14651858.CD001288.pub3; with permission.)
One in every 6 patients treated with glucocorticoids will experience an adverse effect, the most common of which is hyperglycemia (1 in every 13 patients).

**Which patients should receive glucocorticoids during an AECOPD?**

Overall, systemic glucocorticoids have a modest but significant treatment benefit in AECOPD, but are complicated by relatively frequent, but often manageable complications. For every 10 patients treated, a treatment failure will be prevented (and hospitalization duration will be reduced) but nearly 2 medication complications will occur (with hyperglycemia being most common).

The 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that glucocorticoids be prescribed for hospitalized patients with AECOPD. The authors concur with this recommendation for most patients, although clinical judgment is required for situations whereby the risk/benefit ratio is altered (eg, a clinically mild exacerbations coupled with a high risk for side effects from glucocorticoids).

**What are the optimal glucocorticoid dose, duration, and route of delivery for the treatment of patients hospitalized with AECOPD?**

The questions about dose and duration are especially important, because many of the adverse effects of glucocorticoid use, including psychiatric effects, osteoporosis, and hyperglycemia, correlate with the degree of exposure to the glucocorticoid medications. Therefore, it is prudent to use the lowest dose and the shortest course of these medications that will achieve the desired benefit. Unfortunately no clinical trials have directly compared the efficacy of high-, medium-, or low-dose regimens. Doses ranging from 30 mg of methylprednisolone daily up to 125 mg of solumedrol every 6 hours (followed by a tapering dose) have shown beneficial effects. A large observational study (which examined data on almost 80,000 patients) did not find any difference in outcomes (including initiation of mechanical ventilation, mortality, or readmission) in patients treated with high-dose (equivalent to 120–800 mg/d prednisone) versus low-dose (equivalent to 20–80 mg/d prednisone) glucocorticoids for the first 2 days of admission.

These data suggest that very high initial doses of glucocorticoids are not advantageous, but the optimal dosing of glucocorticoids in AECOPD remains uncertain. The GOLD guidelines recommend 30 to 40 mg of oral prednisolone daily. Optimal duration of treatment is also unknown based on the available evidence. The VA study (discussed earlier) compared a 2-week course of treatment with an 8-week course of treatment, and found no benefit with the longer course. A small study of hospitalized patients demonstrated that a 10-day course of glucocorticoids resulted in better improvements in spirometric measurement, dyspnea on exertion, and PaCO₂ levels than did a 3-day course. A Cochrane Collaboration meta-analysis was able to identify only 4 studies that compared the duration of corticosteroid treatment in AECOPD, 2 of which were only published as abstracts.

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Therefore, the available data do not allow for firm conclusions regarding the optimal duration of glucocorticoid treatment in AECOPD. The GOLD guidelines recommend 7 to 10 days.

**Which glucocorticoid type and route is best?**

There is no evidence that any steroid preparation is better than another when used at equivalent dosing. It is also not clear if the route of administration (eg, intravenous vs
oral) is important. Oral glucocorticoids are highly bioavailable, and the intravenous administration of these medications should be reserved for when the patient is unable to take the medications by mouth, or when there is suspicion that the oral medication might not be absorbed for some other reason.20 The large observational study (discussed earlier) was not able to show a difference in outcomes when comparing oral and intravenous treatments.21

- The GOLD guidelines recommend a standard course of 30 to 40 mg of oral prednisolone daily for 7 to 10 days.1

Should glucocorticoids be gradually tapered when they are prescribed for AECOPD, or can they be discontinued abruptly?

This question has not been well studied, and applies to many other diseases that are treated with brief bursts of glucocorticoid medications. Although even brief courses of glucocorticoids do suppress the pituitary-adrenal axis, this suppression is not likely to be of clinical significance, and appears to be of short duration.24–26 Therefore, glucocorticoid regimens for AECOPD that are comparable to the one recommended here do not require a taper and can be abruptly discontinued at the end of the course.20

**Antibiotics**

What are the most frequent bacteria implicated in AECOPD?

Bacterial infections are the most frequently identified precipitant of acute exacerbations of COPD, and are implicated in up to 50% of cases.27,28 The 3 most common are *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*.29–31 *Pseudomonas aeruginosa* is an important pathogen in patients with severe COPD (FEV₁ <50% of predicted).32 Atypical bacteria, such as *Chlamydophila*, *Legionella*, and *Mycoplasma*, are uncommon pathogens, as is *Staphylococcus aureus*, which is not frequently isolated from patients with acute exacerbations of COPD. Acquisition of new bacterial strains is correlated with exacerbations of COPD.33 Viral infections are also frequent contributors to acute exacerbations of COPD;34–36 rhinovirus is most frequently isolated, and seasonal influenza, parainfluenza, and coronavirus are also frequent contributors.

When should patients with acute exacerbations of COPD be treated with antibiotics?

Because up to half of all acute exacerbations of COPD are triggered by bacterial infections,29–31 most patients hospitalized for acute exacerbations of COPD should be treated with antibiotics. The exact indications and patient selection remain controversial, as many previous studies did not differentiate between acute and chronic bronchitis, lacked an adequate assessment for pneumonia, or did not have a placebo control. The major guidelines differ slightly in their recommendations for initiation of antibiotic therapy for acute exacerbation of COPD.

The GOLD guidelines1 explicitly address the decision to initiate antibiotics in their most recent update, advocating for the use of antibiotics in acute exacerbations of COPD in 3 scenarios:

1. Patients presenting with all 3 cardinal symptoms of AECOPD: increased sputum purulence, increased sputum volume, and worsened dyspnea
2. Patients presenting with increased sputum purulence plus either increased sputum volume or worsened dyspnea
3. Severe exacerbation requiring mechanical ventilation (either NIPPV or invasive endotracheal ventilation)

The American Thoracic Society differs slightly in their recommendations by suggesting antibiotics be initiated in hospitalized patients who have a change in either sputum purulence or sputum volume. Practically speaking, the majority of patients hospitalized with acute exacerbation of COPD will have an increase in either sputum purulence or sputum volume, and treatment with antibiotics would be indicated.

It is important to differentiate acute exacerbations of COPD from bacterial pneumonia, because atypical bacterial infections are less frequent triggers for COPD exacerbations, and many of the common antibiotic regimens for acute exacerbations of COPD do not provide adequate coverage for these atypical pathogens.

What are the benefits of antibiotics in patients with acute exacerbations of COPD?

Based on the finding that the majority of acute exacerbations of COPD are triggered by infections, antibiotics have been used in the treatment of AECOPD for decades. One of the earliest trials of antibiotics in AECOPD showed a 23% relative increase in the rate of treatment success and a 48% decrease in the risk of deterioration in ambulatory patients treated with antibiotics. Since this landmark article, numerous published studies have shown decreases in mortality, duration of mechanical ventilation, readmissions, and treatment failure. An early meta-analysis of randomized trials of antibiotics for exacerbations of COPD showed a small but significant benefit of antibiotics. The benefit of antibiotics seems to be greatest in patients with more severe exacerbations of COPD.

What are the appropriate antibiotics for the treatment of acute exacerbations of COPD?

Antibiotic selection for patients with acute exacerbations of COPD requires integration of an understanding of the microbiologic pathogenesis of COPD exacerbations, patient-specific risk factors for resistant pathogens, and knowledge of the local microbiologic resistance patterns. In general, a more severe exacerbation of COPD requires broader empiric antibiotic coverage.

- For moderate exacerbations of COPD in patients without risk factors for  \textit{P. aeruginosa}, monotherapy with a macrolide, respiratory fluoroquinolone, or a second- or third-generation cephalosporin are frequently recommended.

A recent meta-analysis of randomized controlled trials comparing macrolide antibiotics with fluoroquinolone antibiotics showed no difference in the rate of treatment failure between the groups but a lower incidence of side effects with macrolide antibiotics. In patients aged 65 years or older, those with severe COPD, 3 or more exacerbations per year, or who have received recent antibiotic therapy (within the past 90 days), the risk for resistant pathogens increases; broader coverage and sputum culture is suggested for these patients.

Because of its virulence and rapid acquisition of antibiotic resistance,  \textit{P. aeruginosa} is a particularly important pathogen in acute exacerbations of COPD. Risk factors for  \textit{P. aeruginosa} are detailed in Box 1. In patients presenting with one or more of these risk factors, coverage with an antibiotic with known activity against  \textit{P. aeruginosa}, such as an antipseudomonal \(\beta\)-lactam, fluoroquinolone, or aminoglycoside, is indicated. Selection of an appropriate antibiotic should be guided by local resistance patterns and the patient’s prior sputum culture sensitivities, when available.
How long should antibiotics be continued for acute exacerbations of COPD?

The ideal duration of antibiotic therapy for acute exacerbations of COPD is unknown. The GOLD guidelines recommend 5 to 10 days of antibiotic therapy.1 This recommendation is based on consensus opinion, however, and should be interpreted with caution. A recent meta-analysis comparing 5 days with 7 days of therapy showed no difference in outcome but fewer adverse events, with a shorter duration of therapy.45 In practice, the duration of antibiotic therapy is adjusted based on initial response to therapy and severity of underlying disease, with longer durations reserved for patients with delayed clinical responses or severe airflow obstruction at baseline. For this reason, close follow-up after discharge from hospital is particularly important for patients with acute exacerbations of COPD.

Should prophylactic antibiotics be prescribed for prevention of AECOPD?

Long-term antibiotic prophylaxis for the prevention of acute exacerbations of COPD is controversial. A large meta-analysis46 showed no reduction in acute exacerbations with long-term prophylaxis and a mean of 1 day of disability avoided per month of treatment. Two recent trials have renewed interest in antibiotic prophylaxis, particularly in high-risk patients.47,48 The first showed a decreased risk of exacerbation in patients treated with pulsed moxifloxacin (400 mg daily for 5 days every 8 weeks), with a greater effect in those with purulent sputum at baseline.47 The second demonstrated a 27% reduction in exacerbations and increased the time to first exacerbation by 3 months using a regimen of azithromycin, 250 mg daily, in patients at high risk for exacerbation. However, this regimen increased the risk of hearing loss.48

- Long-term prophylaxis should be considered in patients with frequent exacerbations despite optimal medical therapy, while carefully weighing the risks of increased antibiotic resistance and adverse drug reactions.

Noninvasive Positive-Pressure Ventilation

What are the indications for noninvasive positive-pressure ventilation in acute exacerbations of COPD?

Noninvasive positive-pressure ventilation (NIPPV) helps to facilitate alveolar gas exchange and has the potential to improve both ventilation and oxygenation in patients with acute respiratory failure. The indications for initiation of NIPPV in
AECOPD are primarily for those patients with acute hypercarbic respiratory failure. The GOLD guidelines suggest using NIPPV in patients with either:

- Respiratory acidosis (arterial pH $\leq 7.35$ and/or arterial carbon dioxide tension $[\text{PaCO}_2] \geq 45$ mm Hg), or
- Severe dyspnea with signs of respiratory muscle fatigue or increased work of breathing (use of accessory respiratory muscles, paradoxic abdominal movement, or retraction of intercostal muscles)$^1$

The indications for NIPPV in patients with acute exacerbations of COPD and hypoxemic respiratory failure are less clear. The 2001 International Consensus Conference in Intensive Care Medicine recommend that NIPPV be considered for patients with hypoxemic respiratory failure, but do not specifically recommend it for the subset of patients with acute exacerbations of COPD and hypoxic respiratory failure.$^{49}$

**What are the contraindications for NIPPV in AECOPD?**

The 2001 International Consensus Conference Statement of Noninvasive Positive Pressure Ventilation$^{49}$ defined contraindications to NIPPV, including:

- Cardiac or respiratory arrest
- Other acute severe organ failure (such as hemodynamic instability, severe encephalopathy, or severe upper gastrointestinal hemorrhage)
- Recent esophageal anastomosis, facial surgery, trauma, or deformity
- Upper airway obstruction
- Inability of the patient to protect their airway, high aspiration risk, or inability to clear oropharyngeal secretions.

Many patients with severe or very severe COPD have advanced directives outlining clear limits on invasive mechanical ventilation. It is prudent to initiate a discussion of these limits, particularly as they apply to noninvasive ventilation, at the time of admission to the hospital for all patients with acute exacerbations of COPD, because of the potential benefits of NIPPV in avoiding the need for invasive mechanical ventilation.

**What are the main risks of NIPPV in AECOPD?**

The primary risk of NIPPV in AECOPD is aspiration of gastric or oropharyngeal contents. Unlike invasive mechanical ventilation, NIPPV has no mechanism to prevent aspiration of gastric contents. In addition, the positive airway pressure creates a pressure gradient, which can facilitate passage of oropharyngeal or gastric contents into the lower airway.

Other complications of NIPPV include:

- Facial irritation
- Gastric distension
- Sinusitis
- Conjunctival irritation (from an improper mask seal)
- Patient discomfort$^{50}$

**What are the main benefits of NIPPV in AECOPD?**

Numerous prospective randomized trials have demonstrated the benefits of NIPPV in acute exacerbations of COPD$^{51-53}$:

- Reduces the need for invasive mechanical ventilation by up to 80% to 85%$^{53-55}$
• Improves respiratory mechanics\textsuperscript{56}
• Reduces both in-hospital and 30-day mortality

A large meta-analysis\textsuperscript{57} showed a reduction in in-hospital mortality, less need for endotracheal intubation, and less treatment failure compared with standard medical care. The benefits of NIPPV are much less clear in patients with mild to moderate COPD exacerbations.\textsuperscript{58}

*What mode of NIPPV should be selected for patients with acute exacerbations of COPD?*

Clinicians have several choices of mode when initiating NIPPV in patients with acute exacerbation of COPD. Assist control, pressure support ventilation, and proportional assist ventilation have all been shown to improve respiratory physiology and decrease respiratory distress in patients with acute exacerbations of COPD.\textsuperscript{59,60} Bilevel positive airway pressure provides a higher inspiratory pressure coupled with a lower expiratory pressure, and is generally well tolerated by patients. Very little evidence supports one mode of NIPPV over another.

*How should patients initiated on NIPPV for acute exacerbations of COPD be monitored?*

After initiation of NIPPV, patients should be monitored closely for signs of clinical improvement. A repeat arterial blood gas analysis should be obtained within 2 hours of initiation, as improvement of pH and \( \text{PaCO}_2 \) after 2 hours predicts success of NIPPV.\textsuperscript{61,62} In certain patients, NIPPV is poorly tolerated or can worsen respiratory distress, and such patients must be identified early to facilitate an expeditious transition to alternative modes of ventilation.

**Important Comorbidities Affecting the Treatment of AECOPD**

*What are the common cardiac comorbidities in patients with AECOPD?*

Patients with COPD have a high incidence of cardiovascular disease. Coronary artery disease is common in this population, probably related to the shared risk factor of tobacco smoking; one study of a population of patients with COPD found cardiovascular disease was a more common cause than lung disease of hospitalization and death.\textsuperscript{63} Supraventricular arrhythmias (including atrial fibrillation and multifocal atrial tachycardia) are also common in patients with AECOPD, possibly related to the hypercarbia, hypoxemia, and hemodynamic changes that occur in this condition, or as a side effect of medications used its the treatment, such as methylxanthine medications (eg, theophylline) and glucocorticoids.\textsuperscript{64,65} Because of these associations, hospitalists often must simultaneously manage AECOPD and acute cardiovascular diseases.

*What are the key treatment considerations when managing concomitant cardiovascular disease in patients with acute exacerbations of COPD?*

When managing AECOPD in the hospital, the hospitalist must be aware of cardiovascular comorbidities, including underlying coronary artery disease, acute cardiac ischemia, and atrial arrhythmias. When acute heart and lung disease occur together, some special considerations arise. First, the urgency of controlling the patient’s lung
disease increases in the setting of concomitant cardiovascular disease. Second, the medications used for treatment may need to be altered when treating acute cardiac and pulmonary problems simultaneously.

In the case of coronary artery disease, attention to hypoxemia is critical in maximizing myocardial oxygen delivery. Moreover, in the case of atrial arrhythmias, the reversal of hypoxemia and acidosis caused by the underlying lung disease may eliminate the arrhythmia altogether.

However, the treatment of atrial fibrillation or cardiac ischemia and the simultaneous treatment of AECOPD sometimes require the use of medications that have opposite effects, especially in the case of adrenergic and antiadrenergic medications. Specifically, β-blockers are often used to control the heart rate in atrial fibrillation or myocardial O₂ demand in acute cardiac ischemia, whereas β-agonists are typically used to combat bronchospasm in AECOPD. Therefore, a hospitalist may encounter situations whereby both a β-agonist and a β-antagonist might be indicated, although seemingly contradictory.

In theory, the effects of β-agonists might be undesirable in the setting of cardiac disease. Despite their relative selectivity for β2 receptors, β2-agonists do cause tachycardia, especially when used at high doses. However, a significant association with arrhythmias other than sinus tachycardia has not been clearly demonstrated. Clinicians have to balance the risks of tachycardia against the benefits of β-agonist treatment in the acute setting, and there is little evidence to guide the decision. It may be prudent to use non-β-agonist bronchodilators (eg, anticholinergics) preferentially in situations where tachycardia and cardiac ischemia are major concerns. The 2006 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of atrial fibrillation recommend that β-agonists be avoided in patients with bronchospastic illness if they develop atrial fibrillation. However, there is insufficient evidence of harm from β-agonist therapy in this setting to preclude its use, if it is thought to be essential to a patient’s care.

Can β-blockers be safely used in patients with AECOPD?

Nonselective β-blockers do cause significant bronchoconstriction, but this pulmonary effect is not seen in β1-selective β-blockers. One meta-analysis examined 22 trials in which “cardioselective” (β1-selective) β-blockers were prescribed to patients with COPD, and examined effects on spirometric measurements and symptoms, and the effect of bronchodilator medications when patients were given β-blockers. The study concluded that there is no effect on any of the studied parameters, and that β-blocker medications appear to be entirely safe in in patients with COPD. Of note, the patients in these studies all had COPD, and some had severe disease. However, none of the studies targeted patients with AECOPD.

- This meta-analysis offers strong evidence that the pulmonary effects of β1-selective β-blockers are minimal, and that the common practice of withholding these medications from patients with stable COPD is unwarranted.

In addition, 2 large observational studies have suggested that β-blockers may even be beneficial for patients with COPD. The first of these examined a large population of COPD patients, and demonstrated a lower risk of death and acute exacerbation of COPD associated with the use of β-blockers. The second study examined COPD patients during a hospitalization for a COPD exacerbation, and demonstrated a lower risk of death associated with the use of β-blockers during that hospitalization. Although these studies challenge the conventional wisdom that β-blockers are to be
avoided in COPD, they should be interpreted with caution. These observational studies are almost certainly tainted by selection bias (eg, with patients who exhibit the most severe bronchoconstriction being the least likely to be treated with a β-blocker). Although both of these studies used statistical methods to correct for this bias, these methods are imperfect, and any conclusions based on them must acknowledge this methodologic limitation.

The available studies do not clearly delineate how an acutely ill patient with active bronchoconstriction might react to the initiation of a β-blocker medication. It may therefore be prudent to use alternative medications (eg, nondihydropyridine calcium-channel blockers or digoxin) to control heart rate in the setting of acute bronchoconstriction, if there is no strong indication for a β-blocker medication. The ACC/AHA 2006 guidelines for the management of atrial fibrillation recommend avoiding β-blockers in the treatment of patients with atrial fibrillation who also have bronchospastic lung disease. However, if there is a strong indication for a β-blocker medication (eg, cardiac ischemia), or if alternative medications are not providing the desired effect, it is appropriate to prescribe β1-selective β-blockers, even in the face of acute bronchoconstriction.

Methylxanthine medications (eg, theophylline, aminophylline) should also be avoided in patients with atrial arrhythmias, as they are known precipitants of these arrhythmias.

Is multifocal atrial tachycardia associated with COPD?

Multifocal atrial tachycardia (MAT) is an arrhythmia that appears to be secondary to abnormal automatic or triggered atrial activity. The rhythm is recognized when 3 or more distinct p-wave morphologies can be observed on an electrocardiogram demonstrating a ventricular rate of greater than 100 beats per minute. MAT is much less common than atrial fibrillation, but is more closely associated with COPD. Most patients with MAT have significant underlying lung disease, and nearly 20% of patients with acute respiratory failure will demonstrate this arrhythmia. The hypoxemia, hypercarbia, and hemodynamic changes related to AECOPD, and treatment with methyxanthines, all may contribute to the development of this rhythm. However, MAT is also associated with a variety of other clinical conditions, including heart disease, hypokalemia, and hypomagnesemia.

How should multifocal atrial tachycardia be treated?

MAT is typically a transient rhythm, and often resolves with treatment of the underlying disease. Patients with MAT in the setting of AECOPD should therefore be treated aggressively for their lung disease; methyxanthine medications should be avoided, and hypokalemia and hypomagnesemia should be corrected. In small studies, the intravenous administration of magnesium often slowed or terminated the rhythm, even in patients with normal serum concentrations of magnesium, so this might be considered as an early intervention in those patients without contraindications. If MAT is persistent or problematic, pharmacologic treatment can also be prescribed, with the goal of slowing and/or terminating the rhythm. Both verapamil and metoprolol are effective in achieving each of these goals, with a small comparative trial suggesting that metoprolol may be the more effective of the two. The use of β-blocking medications in patients with AECOPD and bronchospasm is discussed above. Of note, cardioversion has not been shown to effectively treat this arrhythmia, but atrioventricular nodal ablation has been used to control the rhythm in refractory cases.
PREVENTIVE CARE

Which preventive interventions should be addressed when a patient is hospitalized with AECOPD?

In addition to venous thromboembolism prophylaxis, smoking cessation should be emphasized, and appropriate vaccinations should be provided.

Smoking Cessation

Smoking cessation is probably the most important preventive health intervention that can be delivered for a smoking patient. Although tobacco abuse and dependence is a chronic disease, it is widely believed that recurrent, brief counseling interventions will increase the likelihood of cessation. Hospitalization creates an unusual set of circumstances whereby the patient is temporarily not allowed to smoke, and is in direct contact with health care workers who can provide education and support. In addition, many hospitalized patients are treated with nicotine replacement therapy to curb the symptoms of nicotine withdrawal. Therefore, hospitalization is a perfect opportunity to encourage smoking cessation. A systematic review of studies of smoking cessation in hospitalized patients from 2008 demonstrated that counseling interventions in the hospital did result in improved cessation rates at 6 and 12 months (OR 1.65, 95% CI 1.44–1.9), but only if the intervention continued (as phone or face-to-face contacts) for more than a month after discharge. Counseling efforts that were limited to the hospital stay, or persisted for less than 1 month after discharge, did not appear to improve cessation rates. This review also found that nicotine replacement therapy, when added to counseling, resulted in a trend toward improved cessation rates (OR 1.47, 95% CI 0.92–2.35).

- Therefore, hospitalists should recommend smoking cessation to all smokers who are hospitalized.

It is also reasonable to use nicotine replacement therapies in the hospital to treat nicotine withdrawal symptoms, and to continue as such after discharge, if the patient expresses an intention to quit. If inpatient smoking-cessation consultation services are available, hospitalists should also use these services to benefit the patient.

Vaccinations

The United States Center for Disease Control and Prevention recommends an annual influenza vaccination and a pneumococcal vaccination for patients with COPD. In this patient population, influenza vaccination results in a fewer COPD exacerbations, and may also lead to decreased hospitalizations and death. Pneumococcal vaccination has not been shown to reduce these complications, but does appear to reduce invasive pneumococcal disease in a general population of patients.

Efforts to improve vaccination rates to these organisms has led to the development of “standing-order vaccine programs,” which allow for hospitals and other facilities to provide these vaccinations to appropriate patients, without an individual physician order. These programs have resulted in improvements in vaccination rates, and hospitalized patients now commonly receive vaccination to these organisms (although this is often accomplished without direct input from the hospitalist). For hospitalists practicing in hospitals without standing-order programs, it is reasonable to recommend these vaccinations at the time of hospital discharge for these patients.
HOSPITAL DISCHARGE

When discharging a patient after hospitalization for an AECOPD, what are the essential elements of postdischarge care that the hospitalist should consider?

When discharging a patient after hospitalization for an AECOPD, hospitalists should consider the need for close follow-up, long-term oxygen therapy, and pulmonary rehabilitation.

When should a follow-up appointment be scheduled after hospitalization for an AECOPD?

Close outpatient follow-up after discharge is recommended for this population of patients. Approximately 20% of patients hospitalized with an AECOPD are readmitted within 30 days. Although the best means of reducing readmissions in this population remain uncertain, one large, retrospective cohort study demonstrated that the rate of readmissions was lower in those patients who attended a follow-up visit with either their primary care physician or their pulmonologist within 30 days of discharge.

A causal link between follow-up appointments and readmissions cannot be deduced from this study, but it has certainly raised awareness of the potential benefits of timely follow-up appointments in these patients. The optimal timing of follow-up after an AECOPD is not clear, but the GOLD guidelines suggest that it be scheduled for 4 to 6 weeks after discharge.

Which patients should be discharged with continuous oxygen therapy after hospitalization for an AECOPD?

Patients who continue to require oxygen therapy to maintain adequate oxygenation at the time of discharge should be discharged with continuous oxygen therapy. Long-term oxygen therapy has been shown to reduce mortality and hospitalizations in patients with severe hypoxemia. Guidelines from the American Thoracic Society and the European Respiratory Society recommend that patients with hypoxemia be treated with long-term oxygen therapy (Fig. 2). Patients with an AECOPD often meet the criteria for long-term oxygen therapy at the time of hospital discharge, and hospitalists should prescribe oxygen in these cases. However, some of these patients who are discharged with home oxygen therapy after an AECOPD will have improved oxygenation as they recover from the acute illness, and will be able to eventually discontinue oxygen therapy. Reassessment of a patient’s oxygen status is one important goal of the follow-up appointment already discussed. It is also worth noting that patients who use long-term oxygen therapy chronically (i.e., they are using it at the time of admission) should generally continue that therapy after discharge, even if they appear not to meet criteria for it at the time of discharge. It is thought that long-term oxygen therapy may have a reparative effect over time in patients with chronic hypoxemia that leads to augmented oxygenation, which may be undone by discontinuing the oxygen therapy.

Should hospitalists refer patients to pulmonary rehabilitation programs after hospitalizations for AECOPD?

Pulmonary rehabilitation is an established part of the treatment of COPD. These programs include multiple interventions (which might include strength and endurance
Fig. 2. A flow chart for prescribing long-term oxygen therapy (LTOT). ABG, arterial blood gases; PaO$_2$, arterial oxygen tension; SaO$_2$, arterial oxygen saturation. (Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. American Thoracic Society: American Thoracic Society/European Respiratory Society Task Force. Standards for the diagnosis and management of patients with COPD [Internet]. Version 1.2. New York: American Thoracic Society; 2004 [updated 2005 September 8]; with permission. Available at: http://www.thoracic.org/go/copd. Accessed August 6, 2012. This document was published in 2004 and is currently in revision. Certain aspects of this document may be out of date and caution should be used when applying these in clinical practice or other usages.)
training, breathing exercises, smoking cessation, education, psychosocial interventions, and so forth), but a core part of this treatment involves training the muscles of ambulation. These programs decrease dyspnea, improve quality of life, and decrease hospitalization in COPD patients. Several studies have looked at the value of pulmonary rehabilitation, specifically in the context of an AECOPD. A Cochrane Collaboration meta-analysis of 9 studies of pulmonary rehabilitation after AECOPD (not all requiring hospitalization) demonstrated significant reduction in rates of hospitalization and death in those patients randomized to early pulmonary rehabilitation. Some quality-of-life measures were also improved in this group. Most of these studies started the rehabilitation within 10 days of discharge for those patients who were hospitalized, and the mean FEV₁ was less than 40% predicted in most studies (range, 32%–52% predicted). Individually the studies in this meta-analysis were small and of modest methodologic quality, but taken together the findings are compelling.

- Hospitalists should consider early referral to pulmonary rehabilitation programs when arranging post-hospital care for their patients after an AECOPD.

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