17 Inpatient Management of Acute COPD Exacerbations

Key Points

1. Acute exacerbations of COPD are a leading cause of morbidity and mortality worldwide. The majority of acute exacerbations of COPD are triggered by bacterial and viral infections.

2. The presence of severe symptoms (breathlessness, cough, wheezing), hemodynamic instability, hypoxemia or hypercarbia, severe underlying disease/comorbidities, and lack of adequate support at home, are some of the factors which should trigger inpatient management as compared to home management of an acute exacerbation.

3. Supplemental oxygen should be provided to target oxygen saturations between 88 – 92%.

4. Moderate dose glucocorticoids for a short duration (40mg prednisone for 5 days) are sufficient for most patients with an acute exacerbation.

5. Use of Noninvasive Positive Pressure Ventilation (NIPPV) reduces mortality and improves outcomes in hypoxemic/hypercapnic patients with acute exacerbations of COPD, and, unless absolutely contraindicated, should be the modality of choice for ventilatory support.

17.1 Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lungs to noxious stimuli or gases (Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines, 2014). It represents a major public health challenge. The prevalence and burden of COPD are projected to increase in the coming years due to continued exposure to COPD risk factors and the aging population (Mathers, 2006). In addition to being a leading cause of mortality and morbidity, COPD poses a significant economic and social burden. In the United States, the estimated direct costs from COPD are 29.5 billion dollars and indirect costs are 20.4 billion dollars (NHLBI Mortality & Morbidity chartbook, 2012). The majority of this cost burden is attributable to COPD exacerbations. In the subsequent sections we will review the salient features of COPD exacerbations and the management of hospitalized patients with COPD exacerbations.
17.2 Definition and Risk Factors

A COPD exacerbation is defined as an acute event characterized by worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication (GOLD guidelines, 2014). It is accompanied by a change in one or all of the following symptoms:
1. Increase in cough severity and frequency
2. Change in sputum color or consistency
3. Increase in baseline dyspnea

17.3 Risk Factors for COPD Exacerbations

Multiple studies have attempted to identify factors which might predispose patients to frequent exacerbations. In an observational study, Miravitlles et al (Miravitlles, 2000) found that increasing age, severity of FEV₁ impairment, and presence of chronic mucus hypersecretion were independently associated with the risk of having 2 or more exacerbations per year. Additionally, the severity of FEV₁ impairment and the presence of co-morbid conditions were associated with a higher risk of hospitalization (Miravitlles, 2000). In another study, chronic cough and sputum production were associated with frequent COPD exacerbations including frequent hospitalizations for severe exacerbations (Burgel, 2009). Niewoehner et al (Niewoehner, 2007) created a multi-variate model and found that older age, severity of FEV₁ impairment, productive cough, duration of COPD, hospitalization for COPD in the previous year, and theophylline use at baseline predicted a higher risk of future exacerbations. In the same study, older age, percentage of predicted FEV₁, unscheduled clinic/emergency department visits for COPD in the prior year, any cardiovascular comorbidity, and prednisone use at baseline were associated with a greater risk of hospitalization (Niewoehner, 2007).

Perhaps the best appraisal of COPD exacerbations comes from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study (Hurst, 2010). This study followed more than 2000 patients with COPD for a period of 3 years and observed the frequency of COPD exacerbations. They found that exacerbations became more frequent and more severe as the severity of COPD increased. The **single best predictor of exacerbations, across all GOLD stages, was a history of prior exacerbations**. Other factors associated with an increased frequency of exacerbations were the presence of gastroesophageal reflux disease (GERD), poorer quality of life, and elevated white blood cell (WBC) count (Hurst, 2010).

COPD is frequently characterized by evidence of increased low grade systemic inflammation (Gan, 2004). Recently, Thomsen et al hypothesized that elevated levels of inflammatory biomarkers in patients with stable COPD are associated with an increased risk of exacerbations. They identified 6574 patients with COPD from the
participants of Copenhagen City Heart Study and the Copenhagen General Population Study and followed them prospectively to assess for exacerbations. They found that elevated levels of inflammatory biomarkers at baseline (CRP, Fibrinogen and WBC count) were associated with an increased risk of future exacerbations, even in patients with mild disease and no prior history of exacerbations (Thomsen, 2013).

### 17.4 Etiology of COPD Exacerbations

COPD exacerbations can be triggered by several factors. The most common cause of an acute exacerbation is a respiratory tract infection (viral or bacterial). Bacterial pathogens are believed to be responsible for up to 50% of the COPD exacerbations (Sethi, 2008). Rosell et al performed bronchoscopic sampling of lower airways and found clinically significant bacterial concentrations in 54% of patients with COPD exacerbations as opposed to 4% of healthy adults (Rosell, 2005). Acquisition of new bacterial strains may play a central role in the pathogenesis of COPD exacerbations (Sethi, 2008). Respiratory viral infections can account for exacerbations in up to one-third of patients (Mohan, 2010). A range of respiratory viruses are linked to COPD exacerbations. The most common viruses associated with exacerbations of COPD are rhinoviruses, but in more severe exacerbations requiring hospitalization, influenza is more common (Seemungal, 2001; Rohde, 2003; Greenberg, 2000).

Air pollution can trigger exacerbations in patients with COPD (Ling, 2009). In up to 30% of patients with an acute exacerbation, no particular etiology is identified (Sapey, 2006). Recent evidence suggests that pulmonary embolism (PE) might account for a significant proportion of these exacerbations. A single center prospective cohort...
study found that in patients requiring hospitalization secondary to a severe COPD exacerbation, PE was identified in 25% cases (Tillie-Leblond, 2006). These results were further supported by a meta-analysis (Rizkallah, 2009).

### 17.5 Triage to Home Versus Hospital for Management of Exacerbations

The assessment of a patient with COPD exacerbation begins with a complete medical history and physical examination. It is important to have a broad initial set of differential diagnoses when evaluating a patient with COPD presenting with worsening dyspnea. Alternate diagnoses to consider include congestive heart failure, pulmonary thromboembolism, pneumonia, pneumothorax and worsening anemia. Zvezdin et al (Zvezdin, 2009) reviewed the medical records of 43 patients who died within 24 hours of admission for an acute exacerbation of COPD. The primary cause of death was heart failure (37%), pneumonia (28%), and pulmonary thromboembolism (21%); respiratory failure due to COPD progression occurred in only 14% of the patients (Zvezdin, 2009).

The medical history should include an assessment of COPD severity (usually based upon prior spirometry measuring the FEV₁ % predicted), presence/worsening of new/existing symptoms, and their comorbidities. Physical examination should focus on identifying signs which might suggest acute decompensation, such as the use of accessory muscles of respiration, paradoxical movement of the chest and abdomen, development of cyanosis, peripheral edema, change in mental status, and hemodynamic instability. In addition, the following tests may be of additional value to assess severity of the exacerbation and exclude alternate diagnoses:

1. Pulse oximetry and arterial blood gas measurement to analyze oxygenation and acid-base status

### Table 17.2: Common etiologies responsible for acute exacerbations of COPD

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial infections</td>
<td><em>Haemophilus influenza</em>, <em>Streptococcus pneumonia</em>, <em>Moraxella catarrhalis</em>, <em>Pseudomonas aeruginosa</em>, <em>Chlamydia pneumonia</em>, <em>Mycoplasma pneumonia</em></td>
</tr>
<tr>
<td>Viral infections</td>
<td>Rhinovirus, Influenza and Parainfluenza virus, Respiratory syncytial virus, <em>Coronavirus</em>, <em>Adenovirus</em>, <em>Human metapneumovirus</em></td>
</tr>
<tr>
<td>Air pollution</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Comorbid conditions such as congestive heart failure, pneumonia</td>
<td></td>
</tr>
<tr>
<td>Other/Idiopathic</td>
<td></td>
</tr>
</tbody>
</table>
Inpatient Management of Acute COPD Exacerbations

1. Chest radiographs are especially useful as they can help exclude alternate diagnoses such as heart failure, pneumonia and pneumothorax. A clear chest radiograph might provide a clue to the presence of pulmonary thromboembolism, especially if the dyspnea and hypoxemia seem out of proportion to the degree of cough/sputum production.

2. Electrocardiogram to diagnose arrhythmias or cardiac ischemia.

3. Complete blood count to look for polycythemia, leukocytosis, thrombocytopenia or anemia.

4. Metabolic panel to evaluate electrolytes and blood sugar.

The first question to answer in the management of COPD exacerbations is to determine whether the patient needs hospitalization or can they be safely managed at home. Over 80% of exacerbations can be safely managed at home with antibiotics, corticosteroids, and bronchodilators (Hurst, 2010; Tashkin, 2008). Intensive home care or “Hospital at home” programs for management of COPD exacerbations deliver similar clinical outcomes compared with hospitalization but provide substantial financial savings (Ram, 2004). However, such an approach requires a dedicated support team and resources which are not widely available at the current time.

Overall, there is a paucity of literature when it comes to guidance in making the decision to hospitalize a patient with an acute exacerbation of COPD. To some extent this decision has to be individualized based on the available hospital and community resources. In general, criteria that might trigger hospitalization are provided by the GOLD guidelines (GOLD guidelines, 2014). These criteria can be divided into clinical, laboratory/radiologic, and psychosocial factors. Clinical examination findings such as hemodynamic instability, altered mental status, use of accessory muscles of respiration, new oxygen requirement, presence of cyanosis, severe underlying COPD, history of frequent exacerbations, failure of outpatient management, and significant comorbid conditions should prompt consideration of hospitalization. Laboratory findings such as respiratory acidosis, elevated white blood cell count, and chest radiograph showing a lobar pneumonia or significant pulmonary edema should also

Table 17.3: Criteria to trigger hospitalization for patients with COPD exacerbations.

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
- Severe underlying COPD
- Onset of new physical signs (e.g. peripheral edema, cyanosis)
- Failure of outpatient/emergency room management
- Presence of other co-morbidities (e.g. heart failure, arrhythmias)
- History of frequent exacerbations
- Older age
- Inadequate home support
- Change in mental status
prompt consideration of inpatient admission. Finally, psychosocial factors, such as older age, presence or absence of support at home, and availability of outpatient appointments for quick follow up should be evaluated prior to discharging patients from the emergency room or office.

Once a decision has been made to admit a patient with an acute exacerbation, the next step is to decide whether the patient can be safely managed on the ward or requires an ICU admission. Patients with a life threatening exacerbation should be promptly triaged to the ICU. Presence of hemodynamic instability, respiratory muscle fatigue, respiratory acidosis, persistent severe hypoxemia, need for mechanical ventilation, and altered mental status should prompt admission to the ICU. Table 17.4 summarizes the indications that warrant ICU admission for patients with an acute exacerbation of COPD. Patients not meeting these indications can generally be safely triaged to the wards. Patients with a mild exacerbation and good social support at home can be admitted under observation (less than 48 hour hospital stay) with a plan to complete the remainder of their therapy at home. This decision can be further guided by the emergency department course of these patients. Patients who start to show improvement in their symptoms in the emergency department after a few hours of treatment can generally be safely admitted for observation. However, patients with more severe exacerbations, especially patients with severe underlying disease, history of frequent exacerbations, and presence of significant cardiovascular comorbidities should be admitted to the inpatient setting with a plan to monitor them for a few days until they start to show signs of clinical improvement/stabilization.

Table 17.4: Indications for ICU admission for patients with acute exacerbations of COPD

- Changes in mental status
- Persistent and/or worsening hypoxemia (pO₂ < 40 mmHg) despite supplemental oxygen
- Presence of respiratory acidosis
- Hemodynamic instability
- Need for mechanical ventilation

17.6 Hospital Management of COPD Exacerbations

The major components of management in COPD exacerbations include reversal of airflow obstruction with short acting bronchodilators and systemic glucocorticoids, identifying and treating the trigger(s) of the exacerbation, especially treating infectious processes with antibiotics, and ensuring adequate oxygenation. In the following sections we will cover the pharmacologic management of COPD exacerbations, followed by the role of mechanical ventilation in the management of COPD exacerbations.
17.6.1 Pharmacologic Therapies for the Management of COPD Exacerbations

17.6.1.1 Supplemental Oxygen

Supplemental oxygen is a key therapy for management of COPD exacerbations. However, the use of supplemental oxygen should be judicious. Administration of high flow oxygen can lead to worsening hypercapnia and worse outcomes. The exact mechanisms for worsening hypercapnia after administration of supplemental oxygen are not clear, but likely include a combination of the following factors:

1. Worsened ventilation-perfusion matching due to attenuation of hypoxic pulmonary vasoconstriction (Aubier, 1980).
2. Haldane effect – release of carbon dioxide bound to hemoglobin due to rightward displacement of CO2-hemoglobin dissociation curve in the presence of increased oxygen saturation (Christiansen, 1914).
3. Decreased minute ventilation (Robinson, 2000).

In a prospective, randomized trial, paramedics treating patients with COPD exacerbations provided either high flow oxygen irrespective of the patient’s pulse oximeter saturations (SpO2) or supplemental oxygen titrated to achieve SpO2 between 88 – 92%. The mortality rate in the high flow oxygen group was 9% whereas mortality rate in the oxygen titration group was 4%. Thus, in patients with an acute exacerbation of COPD, using supplemental oxygen titrated to maintain SpO2 between 88 – 92% reduced mortality by 58% compared with unconstrained high flow oxygen (Austin, 2010). This trial forms the basis of our recommendation to titrate supplemental oxygen to a SpO2 of 88 – 92% in patients with COPD exacerbations.

17.6.1.2 β Adrenergic Agonists

Inhaled short acting β-adrenergic agonists (albuterol, levalbuterol) are the mainstays of pharmacological management to reverse air flow obstruction. They can be administered via a metered dose inhaler (MDI) with/without a spacer or via nebulization. Current evidence suggests that both approaches (nebulization versus MDI) are equivalent in terms of drug delivery and treatment of bronchospasm (Turner, 1997). Despite this evidence of clinical equivalency and increased cost, clinicians tend to prefer nebulized therapy on the pretext of a more uniform/reliable drug delivery.

Typical doses of albuterol are 2.5 mg by nebulizer every one to four hours as needed, or four to eight puffs (90 mcg per puff) by MDI with a spacer every one to four hours as needed. Increasing the dose of nebulized albuterol to 5 mg or using continuous nebulized β-agonists does not have a significant impact on spirometry or clinical outcomes (Nair, 2005), but might lead to increased adverse effects such as tachycardia, tremors, and hypokalemia.

Patients with severe COPD are at higher risk of hypercapnia with supplemental oxygen (discussed in the section above). This phenomenon has been observed with
the use of oxygen-driven nebulizers (Edwards, 2012). Thus, bronchodilators to be administered via nebulization should be given via compressed air nebulization rather than oxygen driven nebulization (O’Driscoll, 2008).

17.6.1.3 Anticholinergic Agents
Short acting inhaled anticholinergic agents (ipratropium) are commonly employed in conjunction with β-adrenergic agonists for treatment of COPD exacerbations. The typical dose for ipratropium in this setting is 500 mcg by nebulizer every four – six hours as needed. Alternatively, two to four puffs (18 mcg per puff) can be administered by MDI with a spacer every four – six hours as needed.

The evidence for this practice is conflicting. There are studies showing an additive bronchodilator effect by adding short acting anticholinergics to inhaled β-agonists (O’Driscoll, 1989). However, there is contrasting evidence that showed no additive bronchodilation was observed with the addition of inhaled anticholinergics to β-agonists (McCory, 2002).

We recommend giving a trial of inhaled anticholinergics in conjunction with β-agonists to see if patients derive symptomatic benefit. However, in the absence of robust clinical evidence behind this practice, caution should be exercised in administering anticholinergics to elderly patients with a history of benign prostatic hyperplasia. They should not be given any more frequently than every 4 hours in order to prevent anticholinergic side effects.

17.6.1.4 Glucocorticoids
Systemic corticosteroids, when given in conjunction with bronchodilators, can improve symptoms and shorten the hospital length of stay for patients with an acute exacerbation of COPD (Niewoehner, 1999; Quon, 2008). Corticosteroids have a nearly 100% oral bioavailability and, thus, should be administered orally unless patients are unable to take oral medications (e.g. intubated and mechanically ventilated patients). De Jong et al (De Jong, 2007) compared intravenous prednisone to oral prednisone in patients admitted with COPD exacerbation and found no difference in the rates of treatment failure, spirometric and quality of life improvement, and length of hospital stay.

The optimal dose and duration of corticosteroids for treatment of COPD exacerbations has been a subject of debate for the past few years. De Jong et al (De Jong, 2007) and Lindenauer et al (Lindenauer, 2010) compared low dose oral prednisone to high dose intravenous prednisone and found similar outcomes. Niewoehner et al (Niewoehner, 1999) conducted a double blind, randomized trial comparing a 2 week with an 8 week course of steroids for COPD exacerbations. They found that a 2 week course of steroids was similar in efficacy and outcomes to an 8 week course. This trial formed the basis for the standard 14 day steroid course for COPD exacerbations over the past decade. More recently, the 14 day steroid course was compared with a 5 day
course and the authors found similar outcomes and less corticosteroid exposure from a 5 day steroid course (REDUCE trial) (Leuppi, 2013). The dose of prednisone used in the REDUCE trial was 40 mg prednisone daily. Nebulised budesonide alone may be an alternative to systemic corticosteroids in the management of hospitalized patients with acute exacerbations of COPD (Maltais, 2002; Gunen, 2007).

Tapering of systemic corticosteroids, although a common practice, is unnecessary in most circumstances. The risk of hypothalamic-pituitary-adrenal-axis suppression is negligible when low dose, short duration corticosteroid regimens are used. No evidence exists to suggest that abruptly stopping a low-dose steroid regimen will increase the risk of disease relapse. In addition, patients find tapered regimens confusing which commonly leads to incorrect dosing (Vondracek, 2006). We recommend not initiating a tapering course of steroids unless the duration of treatment will exceed 14 days.

In summary, the trend in corticosteroid dosing is shifting to a paradigm of low to moderate doses given for a relatively short duration. Based upon the findings from the REDUCE trial (Leuppi, 2013) and the GOLD guidelines (GOLD guidelines, 2014), oral 40 mg prednisone daily for 5 days should suffice for most patients with acute exacerbations of COPD.

17.6.1.5 Antibiotics
While the utility of antibiotics is less established for mild exacerbations managed in the outpatient setting, the role of antibiotics is more established in moderate-severe exacerbations requiring hospitalization. Anthonisen (Anthonisen, 1987) compared antibiotic administration with placebo in patients with acute exacerbations of COPD and found a higher treatment success rate in patients who received antibiotics with no increase in adverse effects. Nouira et al (Nouira, 2001) compared oral ofloxacin to placebo in mechanically ventilated patients with COPD exacerbation and showed that the combined frequency of death and need for additional antibiotics, as well as duration of hospital stay and mechanical ventilation were lower in the group treated with ofloxacin. Similar improvements in outcomes after administration of antibiotics have been reported by multiple other studies (Roede, 2009; Rothberg, 2010; Daniels, 2010; and Stefan, 2013). Vollenweider et al (Vollenweider, 2012) conducted a meta-analysis of all randomized control studies on this subject and found high quality evidence supporting the role of antibiotics in the management of severe COPD exacerbations requiring hospitalization, especially patients admitted to the ICU or requiring mechanical ventilation. Similar benefit was not found in cases of mild exacerbations managed in the outpatient setting.

Based upon the above data, the GOLD guidelines recommend antibiotic administration to patients with COPD exacerbations requiring mechanical ventilation (invasive or non-invasive) or patients with increased sputum volume or purulence (GOLD guidelines, 2014). The recommended length of therapy is 5 days for most patients.
Falagas et al (Falagas, 2008) performed a meta-analysis comparing short duration antibiotic courses (5 days) with longer duration courses (7 – 10 days) and found similar treatment success rates in both groups. Additionally, patients treated with a shorter course of antibiotics had fewer adverse events.

The optimal choice of antibiotic for use in COPD exacerbations is not well established, and to some extent is dependent upon the local bacterial resistance pattern. Usual first line therapy should target the common bacterial pathogens (*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*) and consists of a macrolide antibiotic, penicillin, or doxycycline (Dimopoulos, 2007). In patients with severe disease, history of frequent exacerbations and/or history of exacerbation requiring mechanical ventilation, consideration must be given to the possibility of resistant organisms such as *Pseudomonas* species which will not be adequately covered by the above antibiotics. Cultures from sputum and/or lung should be performed in these high risk patients and broad spectrum antibiotics administered with a plan to de-escalate based upon the culture and susceptibility results (Soler, 1998; Miravitlles, 1999).

Measurement of serum procalcitonin should be considered in patients with acute exacerbations of COPD. Serum procalcitonin is elevated in response to bacterial infections and thus can be a useful biomarker to help decide initiation/duration of antibiotics. A recent Cochrane analysis found that use of serum procalcitonin measurement in cases of respiratory tract infections (including COPD exacerbations) did not affect mortality or treatment failure but led to a significant reduction in antibiotic exposure (Schuetz, 2012). This practice could reduce the overall cost of treatment, prevent unnecessary adverse events associated with exposure to antibiotics and also prevent emergence of resistant organisms.

### 17.6.1.6 Other Therapies

Adjuvant therapies in addition to the above measures that might benefit a hospitalized patient with an acute exacerbation of COPD include the following:

1. **Smoking cessation:** Hospitalization provides a great opportunity to get patients to quit smoking. The admission itself can act as a strong deterrent against continued active smoking (Rigotti, 2008; Keenan, 2009). Intensive counseling for smoking cessation during hospitalization (at least one contact during the hospital stay with continued support for at least one month after discharge) increased the likelihood of smoking cessation (relative risk (RR) 1.37, 95% confidence interval (CI) 1.27–1.48) (Rigotti, 2012). Addition of nicotine replacement therapy to the counselling can further increase the rates of smoking cessation (RR 1.54, 95% CI 1.34–1.79) (Rigotti, 2012).

2. **Thromboprophylaxis:** PE accounts for a significant proportion of acute exacerbations of COPD. As discussed earlier in this chapter, PE is the trigger for up to a quarter of COPD exacerbations in patients without an identified exacerbation
cause or in patients with non-resolving symptoms (Tillie-Leblond, 2006; Rizkallah, 2009). Additionally patients with COPD are at increased risk for development of venous thromboembolism and PE (Bertoletti, 2012). Adequate pharmacologic measures should be taken to prevent this complication in hospitalized patients (Kahn, 2012). Physicians should maintain a high index of suspicion to look for a deep vein thrombosis (DVT) or PE in cases of COPD exacerbations.

3. **Nutritional support**: Patients with an acute exacerbation of COPD tend to have negative nitrogen balance and use of nutritional supplements to target a daily caloric intake of 1.5 times their resting energy expenditure leads to modest improvements in lung function and general well-being scores (Saudny-Unterberger, 1997).

4. **Management of comorbidities**: COPD coexists with multiple other comorbidities which can negatively affect patients’ prognosis (Barnes, 2009). Cardiovascular disease is the most frequent comorbidity in patients with COPD and frequently complicates the hospital course and management of patients admitted with a COPD exacerbation (Almagro, 2012). The major cardiovascular comorbidities coexisting with COPD include hypertension, ischemic heart disease (IHD), heart failure (CHF), and atrial fibrillation (Almagro, 2012). Distinction between heart failure and COPD exacerbation can sometimes be difficult based on history, and further investigations such as chest radiographs, serum brain natriuretic peptide (BNP), and echocardiography may be helpful in distinguishing the two conditions. In general, these comorbidities should be managed according to their respective guidelines, as there is no evidence to suggest that these manifestations should be treated differently in the presence of COPD (GOLD guidelines, 2014).

   There is an increased risk of myocardial ischemia in patients admitted with acute exacerbations of COPD (Donaldson, 2010). The biggest management conundrum in the presence of combined COPD and cardiovascular disease is the ability to use β-blockers. β-blockers have a significant mortality benefit in cases of ischemic heart disease and congestive heart failure (Hunt SA, 2009; Kushner FG, 2009), and are under-utilized because of concern for worsening bronchospasm (Stefan, 2012). Multiple studies have shown that selective b₁-blockers can be safely administered to patients with COPD (Stefan, 2012; Salpeter, 2005). In a cohort study of patients with COPD, Quint et al (Quint, 2013) found that use of β-blockers either started at presentation for MI or continuation of previously prescribed β-blockers was associated with a reduction in mortality. Thus, the benefits of β-adrenergic blockade in cases of IHD or CHF far outweigh any concerns for worsening bronchospasm and should not be withheld from patients with COPD exacerbations.

5. **Other therapies such as mucolytic agents e.g. N-acetylcysteine, methylxanthines e.g. theophylline and aminophylline, and chest physiotherapy** have not been shown to be beneficial in management of COPD exacerbations, and, thus, should not be routinely used for these patients (Black, 2004; Snow, 2001).
17.6.2 Mechanical Ventilation for Acute Exacerbations of COPD

17.6.2.1 Noninvasive Positive Pressure Ventilation (NIPPV):
NIPPV refers to positive pressure ventilation delivered via a noninvasive interface (nasal mask, oral mask or nasal prongs) as opposed to an invasive interface (endotracheal tube, tracheostomy). The use of NIPPV is becoming more common as we realize the benefits offered by this modality compared to invasive mechanical ventilation.

Perhaps, the best studied use of NIPPV has been in cases of hypoxemic and hypercapnic respiratory failure from COPD exacerbations. NIPPV reduces arterial carbon dioxide levels, corrects acidosis, decreases work of breathing, decreases hospital length of stay, and avoids complications of mechanical ventilation such as ventilator associated pneumonia. More importantly, use of NIPPV improves overall survival compared with invasive mechanical ventilation (Brochard, 1995; Plant, 2000; Chandra, 2012; Ram, 2004; Conti, 2002). In a meta-analysis by Ram et al (Ram, 2004), the use of NIPPV for COPD exacerbations was associated with almost 50% reduction in mortality (11% versus 21%). Thus, NIPPV is probably the treatment modality offering the largest mortality benefit in cases of acute exacerbations of COPD.

An oronasal mask might confer the most physiologic advantage in these patients (Navalesi, 2000) but, in reality, the choice of mask is more dependent upon patient comfort. A starting inspiratory pressure (IPAP) of 8–12 cms H$_2$O, and an end expiratory pressure (EPAP) of 4–6 cms H$_2$O is a reasonable start for most patients. Further titration of inspiratory and expiratory pressures is based on the clinical condition and gas exchange parameters. Patients initiated on NIPPV should be closely monitored and a repeat blood gas obtained after 1–2 hours of NIPPV. Improvement of pH and carbon dioxide within this time frame portends a good prognosis (Anton, 2000). As a corollary to this, if patients fail to show improvement/stabilization in their gas exchange parameters or clinical condition within the first two hours after initiation of NIPPV, they should be intubated and placed on invasive mechanical ventilation.

Table 17.5: Indications for initiation of Noninvasive Positive Pressure ventilation (NIPPV)

<table>
<thead>
<tr>
<th>At least one of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Respiratory acidosis (Arterial pH ≤ 7.35, or PaCO$_2$ &gt; 45 mmHg)</td>
</tr>
<tr>
<td>- Severe persistent hypoxemia (Arterial PaO$_2$ &lt; 40 mmHg)</td>
</tr>
<tr>
<td>- Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue</td>
</tr>
<tr>
<td>- Increased work of breathing, as evidenced by use of accessory muscles of respiration, paradoxical motion of abdomen, or intercostal muscle retraction</td>
</tr>
</tbody>
</table>
17.6.2.2 Invasive Mechanical Ventilation

Endotracheal intubation and invasive mechanical ventilation is typically reserved as the last resort in the management of COPD exacerbations, and are used when patients have either failed or not tolerated a trial of NIPPV or there are contraindications to the use of NIPPV (Table 17.6). The goals of invasive mechanical ventilation are the same as NIPPV and include reduction in work of breathing, correction of acidosis, and prevention of dynamic hyperinflation. Volume controlled modes of ventilation are most commonly used for this purpose with assist control mode (AC) being the most common mode of mechanical ventilation.

With mechanical ventilation, careful attention has to be given to avoid overventilation that can lead to air trapping and dynamic hyperinflation. Dynamic hyperinflation can lead to barotrauma and decreased venous return causing cardiovascular collapse and death (Tobin, 2001). Dynamic hyperinflation is characterized by increased levels of intrinsic positive end expiratory pressure (Auto-PEEP). Auto-PEEP is very common in patients with COPD (MacIntyre, 1997) and can lead to significantly increased work of breathing (Coussa, 1985). An indication of the presence of auto-PEEP can be the presence of one or more of the following: 1) ineffective triggering on the ventilator, 2) increasing peak pressures, 3) the beginning of inspiratory flow before expiratory flow reaches zero (Ranieri, 1995). Auto-PEEP can be quantitatively assessed by measuring the airway opening pressure during an end-expiratory pause (Pepe, 1982). The quantitative measurement might be helpful as it provides a guide to the amount of extrinsic PEEP that should be used. As a rough estimate, the applied or extrinsic PEEP should be approximately 80% of the auto-PEEP (Ranieri, 1993). Other strategies to reduce auto-PEEP include reducing the minute ventilation and prolong-

**Table 17.6: Contraindications for use of Noninvasive Positive Pressure ventilation (NIPPV)**

<table>
<thead>
<tr>
<th>Contraindications for use of NIPPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one of the following:</td>
</tr>
<tr>
<td>Aspiration risk</td>
</tr>
<tr>
<td>Altered mental status</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
</tr>
<tr>
<td>Cardiac/respiratory arrest</td>
</tr>
<tr>
<td>Severe agitation</td>
</tr>
</tbody>
</table>

**Table 17.7: Indications to initiate invasive mechanical ventilation**

<table>
<thead>
<tr>
<th>Indications to initiate invasive mechanical ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to tolerate NIPPV</td>
</tr>
<tr>
<td>Contraindications to the use of NIPPV</td>
</tr>
<tr>
<td>Failure to improve gas exchange parameters after trial of NIPPV (2 hours)</td>
</tr>
<tr>
<td>Massive aspiration</td>
</tr>
<tr>
<td>Inability to handle respiratory secretions</td>
</tr>
</tbody>
</table>
Hospital Management of COPD Exacerbations

Table 17.8: Summary of management of hospitalized patients with an acute exacerbation of COPD.

- Diagnostic testing
  - Assess oxygen saturation with pulse oximetry
  - Routine labs such as CBC, Renal panel
  - Chest x-ray to assess for pneumonia, heart failure, pneumothorax etc
  - Arterial blood gas in severe exacerbations or patient exhibiting signs of respiratory distress

- Supplemental oxygen: Titrate to keep oxygen saturation between 88 – 92%

- Inhalers:
  - β-adrenergic agonists (Albuterol) and anticholinergic agents (Ipratropium).
  - Avoid aggressive use of anticholinergic agents to prevent side effects especially in elderly patients.
  - Use compressed air nebulizers rather than oxygen driven nebulizers

- Glucocorticoids:
  - Moderate dose glucocorticoids are as effective as high dose.
  - Oral steroids have similar efficacy to intravenous steroids

- Antibiotics:
  - Macrolide, or respiratory fluoroquinolone as first line agents
  - May have to alter antibiotic choice based on likely pathogens and local antibiograms

- Mechanical Ventilation:
  - Noninvasive positive pressure ventilation (NIPPV), is the preferred mode of mechanical ventilation, unless absolute contraindications exist
  - Consider for patients with respiratory acidosis, hypoxemia, or signs of respiratory distress/fatigue
  - Close monitoring to assess for need of invasive mechanical ventilation
  - Use NIPPV to assist with weaning from invasive mechanical ventilation

Close attention must be paid to the size of the endotracheal tube in mechanically ventilated patients with COPD. Whenever possible, avoid smaller diameter endotracheal tubes as increased resistance through the smaller tube can contribute to Auto-PEEP. Occasionally, patients can present with severe auto-PEEP causing decreased venous return and cardiovascular collapse. Immediate, short duration disconnection from the ventilator (to allow “deflation” and reduction in hyperinflation) can be a lifesaving maneuver in this circumstance. Mechanical ventilation can then be resumed with reductions in minute ventilation and the addition of extrinsic PEEP.

COPD exacerbations that require mechanical ventilation are associated with worse outcomes and increased mortality (Seneff, 1995). Thus, every effort should be made to identify the patient’s wishes (advance directives or living will) prior to initiating mechanical ventilation.

Weaning from mechanical ventilation can be difficult in patients with COPD. The major determinant in a patient’s ability to be liberated from the ventilator is the
ability of the respiratory muscles to cope with the ventilatory load (Purro, 2000). Use of NIPPV to facilitate weaning can significantly improve the chances of successful extubation (Nava, 1998). In addition, early use of NIPPV in patients with hypercapnia following a spontaneous breathing trial reduced the risk of respiratory failure and improved 90 day mortality (Ferrer, 2009).

### 17.7 Hospital Discharge and Follow up

The optimal duration of inpatient stay for management of COPD exacerbations is unclear. Length of stay of 6–7 days has been quoted based on the results by Mushlin et al (Mushlin, 1991). However, in today’s age, with better organized transitions of care between inpatient and outpatient teams, the optimal length of stay is likely shorter for most patients. A patient’s home medications should be initiated prior to discharge to ensure efficacy of the regimen. It might be prudent to continue inhaled corticosteroids even in the presence of systemic steroids, in order to emphasize adherence and ensure continuity of the home regimen after systemic steroids are discontinued. The requirement for supplemental oxygen should be addressed at rest and with exertion prior to discharge.

**Table 17.9: Items to assess prior to discharge from hospital**

- Smoking cessation
- Ensure efficacy of home inhaler regimen
- Reassess inhaler technique
- Need for supplemental oxygen, at rest and with exercise
- Adequate outpatient follow up
- Management and follow up plan for other comorbidities
- Ensure patient and/or home caregivers understand the management plan and provide written instructions for the same

The goal after hospital discharge is to prevent future exacerbations and hospitalizations. Prior hospital admissions, use of oral corticosteroids, long term oxygen use, poor health related quality of life, and lack of physical activity are associated with an increased rate of readmissions (Bahadori K, 2007). Effective communication between hospital providers, patient/family, and outpatient physicians is critical to prevent future readmissions. These patients should be reassessed 4 – 6 weeks after hospital discharge. Smoking cessation, effectiveness of the outpatient medical regimen, inhaler technique and vaccination status should be addressed during this follow up. In patients with frequent exacerbations, long term use of macrolides such as azithromycin (Albert, 2011), or phosphodiesterase inhibitors such as roflumilast (Chong, 2013) should be considered in order to reduce the frequency of exacerbations. When compared to conventional care, pulmonary rehabilitation after an acute exac-
Acute exacerbations of COPD reduce mortality by 72% and readmission by 78% with a number needed to treat of only 6 and 4, respectively (Puhan, 2011). Health-related quality of life and exercise capacity were increased above the minimally important difference (Puhan, 2011).

17.8 Conclusion

Acute exacerbations of COPD are a leading cause of morbidity and mortality worldwide. The majority of these exacerbations can be successfully treated in the outpatient setting; however, severe cases require hospitalization. Detailed investigations to determine etiology of exacerbations as well as management of underlying comorbidities is essential for successful management of these patients. Careful attention must be paid to the presenting symptoms and underlying comorbidities in order to properly triage these patients from the emergency room. The use of NIPPV has led to significant reduction in mortality from acute exacerbations of COPD. Effective communication between inpatient providers, patients, families and primary care providers is essential in order to prevent recurrent hospitalizations from COPD exacerbations.

17.9 Summary Points

1. Acute exacerbations of COPD are significant contributing factors to the morbidity and mortality burden of COPD.
2. The distinction between COPD exacerbations and underlying cardiovascular comorbidities can be difficult but must be done promptly as it can have a significant impact on management and subsequent mortality.
3. History of frequent exacerbations, severity of underlying disease, and the presence of significant cardiovascular comorbidities are the main factors predicting future exacerbations as well as increased risk of hospitalization.
4. Avoid excessive use of anticholinergic inhalers in order to prevent adverse effects, especially in elderly patients.
5. Administration of β-blockers is safe in patients with COPD and should not be withheld, especially in patients with significant cardiac history.
6. Early use of NIPPV should be considered in severe exacerbations for initial mechanical ventilator support as well as to facilitate weaning and liberation from invasive mechanical ventilation.
References


