16 Management of Outpatient COPD Exacerbations

Key Points
1. COPD exacerbations are associated with an acute worsening of the underlying respiratory symptoms and chronic pulmonary and systemic inflammatory processes.
2. Patients may have a susceptibility phenotype that determines their propensity for exacerbations.
3. Patients with COPD can tell when their baseline symptoms are worsening and can recognize the increases in dyspnea, changes in nature and frequency of cough and sputum, and tachypnea.
4. Early recognition and treatment improves outcomes of COPD exacerbations.
5. Most COPD exacerbations can be safely managed at home with an action plan.
6. Management involves the use of bronchodilators (short acting beta agonists and anticholinergics), steroid therapy, and antibiotics.
7. Between 30% and 50% of COPD exacerbations are associated with a bacterial infection and benefit from antibiotic therapy; antibiotics should be rotated to minimize development of antibiotic resistance.

16.1 Introduction

Chronic obstructive pulmonary disease is an incurable but treatable long term condition that is usually associated with an insidiously progressive loss of lung function and increasing respiratory and systemic symptoms. The course of COPD is often marked by intermittent exacerbations: episodes of increased respiratory symptoms, especially cough, wheezing, phlegm production, and breathlessness, that vary in severity, frequency, duration, and consequence. (See Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD.)

COPD exacerbations may profoundly affect an individual’s health and quality of life and, collectively, exacerbations are the major contributor to the socioeconomic and health-related burden of COPD. Therefore, the treatment and prevention of COPD exacerbations are critical elements in COPD management.

Approximately half of all COPD exacerbations are not reported to healthcare providers and usually are not treated (Wilkinson, 2004). Individuals with COPD may exhibit therapeutic paralysis, attempt to “tough it out” during exacerbations, and do not seek medical attention (Mulhall, 2013). Patients with COPD delay treatment initiation by a median duration of 3.7 days even though each day without treatment prolongs the recovery time by nearly half a day (Wilkinson, 2004). Additionally, those individuals who report exacerbations and are treated have a better quality of life com-
pared with those not treated (Wilkinson, 2004). Thus, although nearly half of all exacerbations are unreported and untreated, earlier recognition and treatment of COPD exacerbations may improve recovery and quality of life.

16.2 Definition and Differential Diagnosis

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report defines a COPD exacerbation as an acute event characterized by a change/increase in the patient’s baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variation (Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines, 2014). Because these symptoms are not specific and may be caused by numerous processes, other causes should be considered during the initial evaluation including myocardial ischemia, heart failure, pneumonia, pneumothorax, pleural effusion, cardiac dysrhythmias, and pulmonary embolism.

In addition to being subjective, the respiratory symptoms that define a COPD exacerbation are patient dependent. To provide more objective measures of COPD exacerbations, various surveys such as the Exacerbations of Chronic Obstructive Pulmonary Disease Tool, a patient-reported outcome (EXACT-PRO), have been developed (Mohan, 2014). The EXACT-PRO is a 14 question survey that is valid and reliable for the objective recognition of COPD exacerbations (Mohan, 2014).

16.3 Prevalence

Using a definition of COPD exacerbation as an event treated with antibiotics and/or corticosteroids, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study monitored exacerbations among 2,138 patients with varying COPD severity for 3 years (Hurst, 2010). During the first study year, the overall exacerbation rate was 1.21 exacerbations/participant and correlated with the severity of airflow limitation: 0.85, 1.34, and 2.00 exacerbations/participant for GOLD stages 2, 3, and 4, respectively (Hurst, 2010). 29% of the study participants had two or more exacerbations in the first year and this proportion increased with disease severity, 22%, 33%, and 47% for GOLD stages 2, 3, and 4, respectively (Hurst, 2010). Approximately half of the patients did not have an exacerbation during the first year. The propensity or resistance to COPD exacerbations was remarkably consistent throughout the study; 71% of patients who had two or more exacerbations in years 1 and 2 had frequent exacerbation in year 3 and 74% of those with no exacerbations in years 1 and 2 had no exacerbations in year 3. Frequent exacerbations were associated with a history of prior events, gastroesophageal reflux or heartburn, worse quality of life, and increased white blood cell count (Hurst, 2010). Thus, the annual frequency of COPD exacerbations ranges from approximately one quarter to one half of individuals
Etiology

16.4 Etiology

COPD exacerbations are characterized by increased inflammation of the entire tracheobronchial tree with increased numbers of macrophages and CD8 T lymphocytes in the airway wall and neutrophils in the airway lumen. Systemic inflammation is also elevated (Wedzicha, 2007). Persistently elevated levels of C reactive protein (CRP) after an exacerbation are associated with failure to recover from that episode and portend another exacerbation within 50 days (Wouters, 2005; Perera, 2007). Elevation of fibrinogen levels is associated with the presence and frequency of COPD exacerbations (Duvoix, 2013). Other biomarkers include procalcitonin and peripheral blood eosinophil count (Brightling, 2013). Elevated levels of von Willebrand’s factor, D dimer, and prothrombin fragment 1+2 during COPD exacerbations suggest damage to endothelial cells and activation of clotting cascades (Polosa, 2011).

70–80% of COPD exacerbations are triggered by respiratory infections, mainly viral and bacterial and the majority of the rest are due to environmental exposures and medication non-adherence (Sethi, 2008). The risk of admission for COPD exacerbation is correlated with the severity of the underlying COPD (Bahadori, 2007) and these risk factors are presented in Table 16.1.

Table 16.1: Risk factors for COPD exacerbation hospitalization and readmission (Bahadori, 2007)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Increased $P_{CO_2}$</td>
<td>is associated with increased risk of COPD hospitalization, readmission and reduced survival</td>
</tr>
<tr>
<td>2. Lower FEV$_1$</td>
<td>is associated with increased risk of COPD hospitalization and readmission</td>
</tr>
<tr>
<td>3. Prior COPD exacerbations 3 or more times in the preceding year</td>
<td>is associated with increased risk of COPD hospitalization and readmission</td>
</tr>
<tr>
<td>4. Inhaled corticosteroid use</td>
<td>is associated with increased risk of COPD hospitalization.</td>
</tr>
<tr>
<td>5. Oral corticosteroid use</td>
<td>is associated with increased risk of COPD hospitalization and readmission</td>
</tr>
<tr>
<td>6. Reported poor health related quality of life</td>
<td>is associated with increased risk of COPD hospitalization and readmission</td>
</tr>
<tr>
<td>7. Long term use of oxygen</td>
<td>is associated with increased risk of COPD hospitalization and readmission</td>
</tr>
<tr>
<td>8. History of COPD for more than 5 years</td>
<td>is associated with a doubling in the risk of readmission</td>
</tr>
<tr>
<td>9. Co-existing comorbidities including coronary artery disease, congestive heart failure, or diabetes</td>
<td>is associated with increased risk of COPD hospitalization.</td>
</tr>
<tr>
<td>10. Severe dyspnea</td>
<td>is associated with increased risk of COPD hospitalization and readmission</td>
</tr>
</tbody>
</table>

Table 16.1: Risk factors for COPD exacerbation hospitalization and readmission (Bahadori, 2007)

1. Increased $P_{CO_2}$ is associated with increased risk of COPD hospitalization, readmission and reduced survival

2. Lower FEV$_1$ is associated with increased risk of COPD hospitalization and readmission

3. Prior COPD exacerbations 3 or more times in the preceding year is associated with increased risk of readmission

4. Inhaled corticosteroid use is associated with increased risk of COPD hospitalization.

5. Oral corticosteroid use is associated with increased risk of COPD hospitalization and readmission

6. Reported poor health related quality of life is associated with increased risk of COPD hospitalization and readmission

7. Long term use of oxygen is associated with increased risk of COPD hospitalization and readmission

8. History of COPD for more than 5 years is associated with a doubling in the risk of readmission

9. Co-existing comorbidities including coronary artery disease, congestive heart failure, or diabetes

10. Severe dyspnea is associated with increased risk of COPD hospitalization and readmission

with COPD depending upon the severity of their airflow limitation and the propensity toward frequent or infrequent exacerbations is stable over a several year period.
16.5 Presentation

Exacerbations are associated with an acute worsening of a patient’s health status and delay in treatment is associated with slower resolution and increased risk of hospitalization (Wilkinson, 2005). Consequently, a patient’s early recognition of exacerbation symptoms and prompt treatment improves exacerbation recovery, reduces risk of hospitalization, and is associated with better health-related quality of life. Patients with COPD can recognize the worsening of their baseline symptoms with each exacerbation and can learn to identify these symptoms. The symptoms depend on the cause of the exacerbation and typical manifestations include cough, sputum production, dyspnea, tachypnea, wheezing, and a decrease in pulmonary function. (Table 16.2)

Table 16.2: Respiratory Symptoms During a COPD Exacerbation

| 1. Greater dyspnea, especially with exertion |
| 2. Increase in frequency and severity of cough |
| 3. Changes in sputum production including increased volume, purulence, and blood |
| 4. Tachypnea |
| 5. Wheezing |

Physical examination findings depend on the severity of the exacerbation and typically include wheezing and tachypnea. In more severe exacerbations, patients develop difficulty speaking, use accessory respiratory muscles, and exhibit paradoxical chest and abdominal wall movements due to asynchrony between the chest and abdomen with respiration. In very severe exacerbations, patients develop hypoxemia and hypercapnia with an increase in lethargy and possible obtundation. They may have fever, chills, or night sweats if there is a precipitating bacterial infection.

16.6 Natural History

The median recovery time from a COPD exacerbation is 6 days for the peak expiratory flow rate (PEFR) and 7 days for daily symptoms; up to 14% of patients do not recover clinically within 35 days and some never return to baseline (Seemungal, 2000). PEFR recovery to baseline values is complete in only 75.2% of exacerbations at 35 days and, in 7.1% of exacerbations, PEFR recovery has not occurred by 91 days (Seemungal, 2000). The rate of decline in forced expiratory volume in one second (FEV1) is 2–8 ml/year greater in frequent COPD exacerbators (two or more exacerbations yearly) compared with infrequent exacerbators (less than two exacerbations annually) (Donaldson, 2002; Vestbo, 2011). Quality of life is significantly affected by COPD exacerbations and, as measured by the St. George’s Respiratory Questionnaire
(SGRQ), is worse in patients with more frequent exacerbations (Seemungal, 1998; Miravitlles, 2004).

16.7 Consequences

The consequences of ambulatory COPD exacerbations are less well studied than more severe exacerbations requiring healthcare encounters but are associated with poor outcomes (Table 16.3).

| Table 16.3: Consequences of Frequent COPD Exacerbations (Qureshi, 2014; Chhabra, 2014) |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Increased risk of future exacerbations | Greater mortality | More frequent healthcare visits | Faster decline in lung function | More inflammation |
| Worse quality of life | Less physical activity | Aggravation of co-morbidities |

16.8 Outpatient Management of COPD Exacerbations

16.8.1 Indications for Home Care

Patients with COPD can recognize the worsening of their baseline symptoms that characterize exacerbations. Common symptoms include a cold or flu, feeling run down or tired, and mood changes, such as feeling down or anxious. When these symptoms are associated with cardinal COPD symptoms including increased shortness of breath and increased amounts of cough and sputum and/or sputum changes from its normal color to a yellow, green or rust color, it is strongly suggestive of a COPD exacerbation. Patients should be given an action plan that explains how to manage exacerbations at home (Figure 16.1 and Table 16.4). The action plan is filled out by the health care provider during routine visits and is individualized for each patient. It includes a list of symptoms to aid the patient in recognizing and assessing the severity of his/her symptoms and lists appropriate next steps.

Other steps include reducing activity, resting frequently, and practicing controlled breathing and relaxation. After resolution of an exacerbation, the patient should see
Table 16.4: Components of a COPD action plan

| 1. Assessment of symptoms and their severity |
| 2. Assessment of the need to inform primary care provider of symptoms or seek more acute medical care |
| 3. Patient initiates prescribed prednisone |
| 4. Patient starts prescribed antibiotic |
| 5. Patient takes 2–4 puffs of their rescue inhaler (albuterol) as needed, up to 4 to 8 times per day for shortness of breath |
| 6. Information about when to seek further medical care |

When you have a COPD exacerbation:
1. Start your action plan as instructed by your Provider
2. If you do not feel better after 48 hours, or if you are getting worse at any time, seek medical attention immediately.
3. Schedule an appointment to see your Provider or contact your Provider to refill and maintain your COPD exacerbation medications - inhalers, antibiotics, and steroids at all times.

Assessment of COPD Disease Activity

<table>
<thead>
<tr>
<th>I am doing well today</th>
<th>I am having a bad day or COPD Exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Usual activity and exercise level</td>
<td>More wheezy and breathless than usual</td>
</tr>
<tr>
<td>Normal amounts of cough or sputum</td>
<td>Feeling run down or tired</td>
</tr>
<tr>
<td>Typical level of breathlessness at rest and with exertion</td>
<td>Increased cough or sputum; change in color of sputum</td>
</tr>
<tr>
<td>Sleeping well at night</td>
<td>Utilizing more reliever medication (albuterol) than usual</td>
</tr>
<tr>
<td>Appetite is good</td>
<td>Swelling of ankles more than usual</td>
</tr>
<tr>
<td><strong>Actions</strong></td>
<td><strong>Actions</strong></td>
</tr>
<tr>
<td>Take daily medicines</td>
<td>Continue daily medications and oxygen</td>
</tr>
<tr>
<td>Use oxygen as prescribed</td>
<td>Use quick relief inhaler (albuterol) 2-4 puffs with spacer every 2-4 hours</td>
</tr>
<tr>
<td>Continue regular exercise/diet plan</td>
<td>Start an oral corticosteroid (Prednisone 40 mg orally daily for 5 days)</td>
</tr>
<tr>
<td>Avoid cigarette smoke and other irritants</td>
<td>Use pursed lip breathing</td>
</tr>
<tr>
<td>Plan activities and pace yourself</td>
<td>Use anxiety/stress management techniques</td>
</tr>
<tr>
<td><strong>I need urgent medical attention</strong></td>
<td><strong>Recent weather change or exposure to air pollution or smog</strong></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Danger Signs - Severe breathlessness, chest pain, fever, agitation, fear, drowsiness, confusion</td>
<td>Call 911 or seek medical care immediately</td>
</tr>
<tr>
<td>Severe shortness of breath even at rest</td>
<td>Show them this plan and say you have severe COPD</td>
</tr>
<tr>
<td>Not able to perform normal activities</td>
<td>Not able to sleep because of breathing</td>
</tr>
<tr>
<td>Fever or chills</td>
<td>Coughing up blood</td>
</tr>
<tr>
<td>Feeling confused or very drowsy</td>
<td><strong>Antibiotic Rotation</strong></td>
</tr>
<tr>
<td>Chest discomfort/pain</td>
<td>After a COPD exacerbation, a different antibiotic may need to be prescribed for your next exacerbation. Help your doctor do this by keeping track of the name of the antibiotic, and when you started taking it for each COPD exacerbation. Bring this information with you to your doctor appointments.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic Name</th>
<th>Date Antibiotic Taken</th>
</tr>
</thead>
</table>

Figure 16.1: Generic COPD Action Plan (American Lung Association accessed December, 2014; Australian Lung Foundation accessed December, 2014; Canadian Medical Association accessed December, 2014)
their primary care provider to obtain a different antibiotic to ensure antibiotic rotation for the next exacerbation (Postma, 1999) and minimize development of antibiotic resistance. A generic action plan derived from recommendations from the American Lung Association, the Canadian Medical Association, and the Australian Lung Foundation (American Lung Association accessed December, 2014; Australian Lung Foundation accessed December, 2014; Canadian Medical Association accessed December, 2014) is presented in Figure 16.1.

### 16.8.2 Indications for a Healthcare Encounter

Patients who are extremely breathless, anxious, panicky, confused, agitated, fearful, or drowsy should seek immediate medical attention. Other patients should start with the action plan but if there is no improvement after 48 hours, or if symptoms worsen at any time, medical attention should be sought immediately (GOLD guidelines, 2014). Other indications to escalate the level of care are presented in Table 16.5.

### 16.9 Management

#### 16.9.1 Home Care

A COPD action plan (Figure 16.1) encourages early intervention by giving patients guidelines to enhance the recognition of an exacerbation and how to initiate early medical management. Action plans with limited or no self-management education (See Educational Programs below) promote patient recognition and initiation of treat-
Management of Outpatient COPD Exacerbations

Figure 16.2: COPD management algorithm, modified from Anthonisen (1987), Hunter (2001) and Siddiqi (2008)

ment for COPD exacerbations but have not been demonstrated to decrease healthcare utilization or improve health-related quality of life (Walters, 2010). The action plan contains advice on how to increase the use of routine COPD medications, to use breathing exercises and relaxation techniques, to change the environment if it is causing the exacerbation, and to increase oxygen use. If the exacerbation is infectious and the dyspnea is accompanied by increased or colored sputum, antibiotics and systemic steroids are indicated (see Figure 16.2). If the condition worsens, patients are advised to visit their physician's office or the emergency department. Follow-up with their physicians either in person or via telephone or electronic communication after the episode is also recommended. Medications used to treat a COPD exacerbation
are reviewed in Table 16.6. Adherence to a written action plan is associated with a reduction in exacerbation recovery time (Bischoff, 2011). Knowing the factors that are associated with proper and prompt utilization of an action plan permits healthcare professionals to direct self-management support to appropriate patients. For those individuals who are unable to adhere with a self-administered action plan, an intensive home care program, including nurse visits, home oxygen, and physical therapy, produces clinical outcomes that are equivalent to hospitalization (Postma, 1999). See discussion of hospital at home below.

**Table 16.6: Pharmacologic therapy in acute exacerbation (Updated from Stoller, 2002)**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Mode of Delivery</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-adrenergic agonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td>Metered-dose inhaler or Nebulizer</td>
<td>100–200 µg 0.5–2.0 mg</td>
<td>4–8 times daily 4–8 times daily</td>
<td></td>
</tr>
<tr>
<td>Anticholinergic agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>Metered-dose inhaler or Nebulizer</td>
<td>18–36 µg 0.5 mg</td>
<td>4 times daily 4 times daily</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>Pill</td>
<td></td>
<td>30–60 mg</td>
<td>Daily for 5 days</td>
</tr>
</tbody>
</table>

**16.9.2 Bronchodilators**

**16.9.2.1 Short Acting Bronchodilators**

**Beta adrenergic agonists:** Inhaled short-acting beta adrenergic agonists (SABA e.g. albuterol) are the mainstay of therapy for an acute exacerbation due to their rapid onset of action and efficacy in producing bronchodilation. After inhalation, the effects of SABAs begin within 5 minutes and reach maximal effect at 30 minutes. SABA’s improve FEV₁ and FVC by 15 to 29% over a period of 60 to 120 minutes. Side-effects include tremors, headache, nausea, vomiting, palpitations, heart rate, and blood pressure variations. There is no added benefit to adding long acting beta-adrenergic agents (LABA e.g. salmeterol) in the treatment of acute exacerbations. Nebulizers and metered dose inhalers (MDI) with spacers have equal efficacy during exacerbations but patients may have difficulty with proper MDI technique during an exacerbation. There has been no demonstrated advantage to the use of a higher cumulative dose of albuterol in patients with acute exacerbation of COPD and 4 times daily dosing is usually adequate (Emerman, 1997).
Anticholinergic agents: Anticholinergic agents (non-selective muscarinic antagonists-SAMA e.g. ipratropium bromide) have an equivalent effect to SABA's and other factors such as the time to peak effect (slightly more rapid for SABA's) and the frequency of adverse effects (fewer and milder with ipratropium bromide – tremors, dry mouth, and urinary retention) may influence the choice of agent for a given patient (Karpel, 1990; Rebuck, 1997; Johnson, 2002). Ipratropium's effect begins within 10–15 minutes and peaks at 30–60 minutes.

The effects of the two classes of short acting bronchodilator agents decline after 2–3 hours but can last as long as 4–6 hours. Both inhaled agents are more effective than all parenterally administered bronchodilators (methylxanthines and sympathomimetics). Unlike the management of stable COPD where the concurrent administration of albuterol and ipratropium is more efficacious than either agent given alone (The COMBIVENT Inhalation Solution Study Group, 1997), a combination of short acting bronchodilators given sequentially in exacerbations does not provide additional benefit (Karpel, 1990; Patrick, 1990; Moayyedi, 1995).

16.9.3 Corticosteroid Therapy

Several randomized, placebo-controlled trials have demonstrated the benefit of systemic corticosteroid therapy in accelerating improvement in airflow, gas exchange, and symptoms, and in reducing the rate of treatment failure (Albert, 1980; Thompson, 1996; Aaron, 2003; Niewoehner, 1999; Aaron, 2003; Davies, 1999; Maltais, 2002). Benefits include a higher FEV₁ on day 1, lower rate of treatment failure at 30 and 90 days, and a shorter hospital stay. The optimal duration of therapy remains uncertain but some studies support a course of 5–10 days (Davies, 1999; Sayiner, 2001; Stanbrook, 2001). Patients with COPD exacerbations continue to have cumulative improvement in FEV₁ during a 10 day corticosteroid course. However, outcomes were no better with an 8 week course of corticosteroids compared with a 15 day course. A Cochrane review found no significant increase in treatment failure with shorter systemic corticosteroid treatment for seven days or less for acute exacerbations of COPD (Walters, 2011). More recently, the REDUCE trial demonstrated that 5 days was not inferior to 14 days of oral 40 mg prednisolone daily and there were no differences in time to the next exacerbation, mortality, restoration of lung function, and adverse events during the 6 months of follow up (Leuppi, 2013).

Oral glucocorticoids are rapidly absorbed with peak serum levels achieved at one hour after ingestion with virtually complete bioavailability. They are as efficacious as intravenous glucocorticoids for treating most exacerbations unless the patient is unable to take oral medications or has poor gastrointestinal absorption.

Most exacerbations can be treated with 30–60 mg prednisone daily for 5–7 days (Gold Guidelines, 2014) and steroid therapy can be stopped without tapering if the duration of therapy is less than 3 weeks (Gold Guidelines, 2014; Niewoehner, 1999).
Longer durations of therapy have no added benefit and a higher risk of adverse effects especially hyperglycemia. More recent findings are suggesting that shorter durations with lower doses are as effective as longer courses with higher doses of corticosteroids.

16.9.4 Antibiotic Therapy

Up to 50% of COPD exacerbations are associated with bacterial infections and antibiotics are indicated for these patients. Clinical criteria (increased dyspnea, sputum volume and sputum purulence) are sufficient to commence a course of antibiotics for a COPD exacerbation and sputum cultures are not usually obtained unless there is a clinical indication. Treatment is usually empirical and a low-cost antibiotic such as trimethaprim-sulfamethoxazole, azithromycin, cefuroxime, or tetracycline is adequate for mild exacerbations in relatively uncompromised patients. For more severe exacerbations, a broader-spectrum antibiotic such as moxifloxacin or levofloxacin that is effective against resistant strains of H. influenzae and S. pneumoniae is recommended. Patients with systemic symptoms such as pneumonia should be treated with a broad-spectrum antibiotic. See Figure 16.2.

16.9.5 Chronic Antibiotic Treatment

Long term antibiotic treatment with azithromycin, erythromycin, clarithromycin, or moxifloxacin has been demonstrated to reduce COPD exacerbations (Herath, 2013). A meta-analysis demonstrated an odds ratio of 0.55 (95% CI, 0.39–0.77) for COPD exacerbations with prophylactic antibiotic treatment and the number needed to treat was 8 (95% CI, 5–18) (Herath, 2013). Both azithromycin and erythromycin have been studied extensively and reduce the time to first exacerbation and exacerbation frequency when administered daily for one year but also adversely impair hearing and increase the prevalence of macrolide resistant bacteria in the sputa of treated patients (Ramos, 2014). Azithromycin therapy has also been associated with a prolonged QTc. (Albert, 2011). The benefit of macrolides has to be balanced against the possible development of antibiotic resistance both in the patient being treated and in other individuals. The exact mechanism of action of macrolides is not known but may be related to their antibacterial, anti-inflammatory, or immunomodulating properties (Martinez, 2008).

16.9.6 Phosphodiesterase 4 (PDE 4) Inhibitors

PDE-4 inhibitors, roflumilast and cilomilast, reduce inflammation and bronchoconstriction by preventing the degradation of cyclic AMP by phosphodiesterase (Beghe,
PDE-4 inhibitors reduce the frequency of COPD exacerbations (OR 0.77, 95% CI 0.71, 0.83) with a number needed to treat for an additional benefit, 20 (95% CI, 16 to 27) (Chong, 2013). Adverse effects of the PDE-4 inhibitors include gastrointestinal symptoms, headache, and weight loss.

16.9.7 Oxygen Therapy

Alterations in oxygenation during COPD exacerbations appear to be associated with the severity of the exacerbation. A prospective study of 40 individuals with moderate to severe COPD not receiving supplemental oxygen demonstrated that the stable mean SpO₂ was 94.8% with a standard deviation of 1% (Hurst, 2010). The maximum reduction in the SpO₂ standard deviation during an exacerbation was only 1.24% suggesting that the SpO₂ did not decline markedly during less severe exacerbations. In contrast, in a prospective study of 2,487 patients presenting to an emergency department with a COPD exacerbation, half had an oxygen saturation < 90% (Quintana, 2014).

Patients with COPD exacerbations are given oxygen to treat hypoxemia with a goal of maintaining adequate levels of oxygenation without precipitating respiratory acidosis or worsening hypercapnia (Brill, 2014). The minimal adequate or safe level of oxygenation has not been defined definitively but most experts suggest a target SpO₂ range of 88–92% (Brill, 2014). The administration of oxygen has potential therapeutic benefits, which include relief of pulmonary vasoconstriction, decrease in right heart strain, and improved myocardial oxygenation. A high FİO₂ is not required to correct the hypoxemia associated with most acute exacerbations and persistent hypoxemia should prompt consideration of pulmonary embolism (PE), acute respiratory distress syndrome (ARDS), pulmonary edema, or severe pneumonia. Oxygen delivery devices include face masks, Venturi masks, nasal cannulae, and non-rebreathing masks. Simple face masks can provide a FİO₂ up to 55% and nasal cannulae up to 40%. Venturi masks provide a precise FİO₂ from 24% to 60% and are the preferred means of oxygen delivery. Non-rebreathing masks can deliver a FİO₂ up to 90%.

Although a “more is better” approach to supplemental oxygen has been adopted by many providers, recent evidence suggests that hyperoxemia (defined as a SpO₂ greater than the target range of 88–92%) is harmful. A British study demonstrated that lower flow oxygen (FİO₂ < 28%) with a goal SpO₂ 88–92% compared with higher flow oxygen delivered while transporting patients with COPD to the hospital reduced the proportion of complicated admissions (defined as the need for aminophylline, invasive or noninvasive ventilation, or death) to 25.2% from 40.8% (Durrington, 2005). In a prospective study comparing untitrated high flow oxygen with oxygen titrated to a target SpO₂ 88–92%, titrated oxygen reduced mortality among those participants with COPD by 78% and among all participants by 58% (Austin, 2010). In patients presenting to an emergency department, hyperoxemia (PaO₂ >100 mmHg) was associ-
ated with a greater risk of adverse outcomes (hypercapnic respiratory failure, assisted ventilation, or death) OR 9.17 (95% CI, 4.08, 20.6) than hypoxemia (PaO₂ < 60 mm Hg) OR 2.16 (95% CI, 1.11, 4.20) (Cameron, 2012).

In patients who do develop hypercarbia after treatment with higher levels of oxygen, rapid cessation of supplemental oxygen may lead to “rebound hypoxemia” due to a greater reduction in the arterial oxygen level compared with the arterial carbon dioxide level upon oxygen withdrawal (Kane, 2011). Therefore, in patients who develop oxygen induced hypercarbia, treatment with invasive or noninvasive ventilation while maintaining low concentration supplemental oxygen should be considered.

16.9.8 Educational Programs

Multiple and varied self-management programs for patients with COPD have been developed and implemented with widely ranging results. A review of COPD educational programs revealed that 53.8% of programs incorporated 10 or more areas of instruction (Stoilкова, 2013). The most common topics were smoking cessation (80.0%), medications (76.9%), exercise (76.9%), breathing techniques (70.8%), exacerbations (69.2%), and stress management (67.7%). Most programs were led by nurses (75.8%) who supplied written information (90.5%) and utilized demonstrations or practice sessions (73.8%). A Cochrane meta-analysis demonstrated that self-management education for patients with COPD reduced hospitalizations, OR 0.57 (95% CI 0.43, 0.75) with a number needed to treat 8 (95% CI, 5, 14) for those with high risk of COPD hospitalization and 20 (95% CI, 15, 35) for those with low risk (Zwerink, 2014). Additional benefits included enhanced quality of life and reduced breathlessness. Integrated disease management incorporating a multidisciplinary team improves quality of life, reduces breathlessness, increases the distance walked in 6 minutes, and decreases the number of hospitalizations and hospitalization duration (Kruijs, 2013). A randomized control trial of a Comprehensive Care Management program to prevent COPD hospitalizations (Fan, 2012) did not demonstrate decreased hospitalizations and was associated with unanticipated excess mortality. This finding may have been related to differences between patients not detectable in data or possibly to undetected delays in care in the intervention group due to a false sense of security.

16.9.9 Hospital at Home

An alternative to hospitalization for an acute COPD exacerbation is hospital at home, a program of intensive management of COPD exacerbations in a patient’s home by visiting healthcare providers. A meta-analysis of patients presenting to the emergency department and then treated with hospital at home for COPD exacerbations
demonstrated a reduction in readmission rates compared with traditional hospitalization, RR 0.76 (95% CI, 0.59, 0.99) and a trend toward reduced mortality, RR 0.65 (95% CI, 0.4, 1.04) (Jeppesen, 2012).

16.9.10 Respiratory stimulants

Respiratory stimulants, measures to increase mucous clearance such as acetylcysteine, nebulized magnesium, and chest physiotherapy are not beneficial in acute exacerbations.

16.10 Prevention of COPD Exacerbations

16.10.1 Pulmonary Rehabilitation

Pulmonary rehabilitation is a multidisciplinary intervention that combines education and exercise to optimize physical conditioning, adherence, and patient involvement in care (Spruit, 2006). When provided in either the stable state or after an acute exacerbation, pulmonary rehabilitation is a highly effective and safe intervention to reduce hospital admissions and mortality and to improve health-related quality of life in COPD patients (Spruit, 2014; Lacasse, 2006; Puhan, 2011). A meta-analysis of pulmonary rehabilitation after a COPD exacerbation revealed reduced mortality (OR 0.28, 95% CI 0.10, 0.84), fewer hospitalizations (OR 0.22, 95% CI 0.08, 0.58) with a number need to treat 4 (95% CI, 3 to 8), and improved quality of life and exercise capacity (Puhan, 2011).

16.10.2 Smoking cessation

A cohort study of 23,971 self-reported previous and current smokers demonstrated that quitting smoking is associated with fewer COPD exacerbations, HR 0.78, (95% CI 0.75,0.87) and that the effect depends upon the length of smoking cessation, 1.04 at less than one year to 0.65 at 10 or more years of smoking abstinence (Au, 2009). Smoking cessation but not smoking reduction is associated with fewer COPD hospitalizations, HR 0.57 (95% CI, 0.33, 0.99) and 0.93 (95% CI, 0.73, 1.18), respectively (Godtfredsen, 2002).
16.10.3 Nutritional support

Although low body mass index and weight loss are risk factors for COPD exacerbations, the effect of nutritional supplementation on exacerbation frequency is not well studied (Hallin, 2006). A meta-analysis showed that nutritional supplementation stimulates weight gain in patients with COPD and the effect is greatest in malnourished patients (Ferreira, 2012). Additional benefits of nutritional supplementation included increases in measures of fat-free body mass, respiratory muscle strength, distance walked in 6 minutes, and health-related quality of life (Collins, 2013; Ferreira, 2012).

16.10.4 Lung Volume Reduction Surgery (LVRS)

In patients who are appropriate candidates, LVRS reduces severe COPD exacerbations (respiratory-related emergency room visits and hospitalizations) by 29% (95% CI, 11–48%) compared with medical management (Washko, 2008). LVRS also increases the time to the first COPD exacerbation in patients with and without a history of exacerbations in the year prior to surgery (Washko, 2008).

16.10.5 Telehealth

Clinical information systems can monitor patients with COPD in their homes using biosensors and questionnaires. This information is transmitted to a central coordination center and reviewed by healthcare providers using data processing algorithms and alerts to monitor daily status, advise individual patients about the goals of maintenance of maximal function and independence, early detection and management of exacerbations and reducing in-person healthcare visits, and provide pulmonary rehabilitation (Goldstein, 2014; McKinstry, 2013). Use of telehealth services for patients with COPD reduces emergency room visits and hospitalizations and exacerbations, does not improve quality of life, and has no effect or may actually increase mortality rates by delaying needed in person care (Kamei, 2013; McLean, 2012; Polisena, 2010). A cost effectiveness review of telehealth for chronic conditions including COPD concluded that telehealth was not cost effective when added to usual care (Henderson, 2013).

16.11 Risk Factors for Relapse

Risk factors for relapse include patients requiring increased doses of nebulized bronchodilators, use of theophylline, use of supplemental oxygen at home, an ED visit in
the preceding week, number of ED and urgent care visits in the past year, self-reported activity limitation, respiratory rate at ED presentation, prior relapse after a hospital visit, and preceding use of glucocorticoids or antibiotics (Kim, 2004). Proven interventions that minimize relapse include smoking cessation, pulmonary rehabilitation, and physical exercise. (See prior sections.) Other strategies to prevent relapse of exacerbations are presented in Table 16.7. Tiotropium, a long acting anticholinergic agent that causes prolonged and persistent bronchodilation, reduces COPD exacerbations and COPD-related hospitalization rates (Anzueto, 2009). Long acting beta adrenergic agonists (LABA) such as salmeterol or formoterol reduce the risk of COPD exacerbations by 23% (Puhan, 2009). Inhaled corticosteroids (ICS) have proven efficacy in reducing the number and severity of exacerbations (Alsaedi, 2002). The combination of LABA and ICS reduces exacerbations by 25% over a one year period (Calverley, 2003).

### Table 16.7: Strategies to Prevent Relapse After an Acute COPD Exacerbation

<table>
<thead>
<tr>
<th>Pulmonary Rehabilitation</th>
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<tbody>
<tr>
<td>Smoking cessation</td>
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<tr>
<td>Self-management plans</td>
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<tr>
<td>LABAs: salmeterol, formoterol</td>
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<tr>
<td>Combination therapy: LABA/ICS</td>
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<tr>
<td>Tiotropium</td>
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<tr>
<td>Influenza vaccine</td>
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<tr>
<td>Physical exercise</td>
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<tr>
<td>LVRS in selected patients</td>
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</tbody>
</table>

Abbreviations: LABA: long-acting β 2-agonist; ICS: inhaled corticosteroid; LVRS: lung volume reduction surgery.

### 16.12 Conclusion

The natural history of COPD is usually punctuated by exacerbations that are characterized by increased respiratory symptoms including breathlessness, cough, wheezing, and sputum production. The frequency, severity, duration, and consequences of each exacerbation vary but patients with COPD appear to exhibit frequent or infrequent exacerbator phenotypes. Nearly half of all exacerbations are not reported by patients but earlier recognition and treatment is associated with more rapid recovery and better quality of life. The main pharmacologic treatments are short acting bronchodilators, antibiotics, and corticosteroids. Factors that reduce relapse of COPD
exacerbations include pulmonary rehabilitation, smoking cessation, long acting anticholinergics and beta agonists, and self-management plans.

16.13 Summary Points

1. COPD exacerbations are interspersed throughout the natural course of COPD but some patients are prone to frequent episodes whereas others have few or infrequent exacerbations.


3. The principal pharmacologic treatments of COPD exacerbations are:
   - Short acting bronchodilators
   - Antibiotics which should be rotated to mitigate the selection of resistant bacteria
   - Corticosteroids which are beneficial in moderate doses (prednisone 40 mg/d orally) and short duration (5 days) that do not require tapering

4. Pulmonary rehabilitation after an acute COPD exacerbation improves survival, reduces subsequent hospitalizations, increases exercise capacity, and improves quality of life.

5. Newer modalities for the ambulatory management of COPD exacerbations include hospital at home and telemedicine.

References


Management of Outpatient COPD Exacerbations


