Diagnosis and Management of COPD in the Primary Care Setting

Learning Objectives
After participating in this educational activity, participants should be able to:

1. Follow the recent guidelines in the use of spirometry and understand how to use a spirometer

2. Advise patients about the benefits of exercise and pulmonary rehabilitation programs as the potential benefits relate to the severity of COPD symptoms

3. Educate patients about treatment options and manage the side effects of current treatments

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**Introduction**

Chronic obstructive pulmonary disease (COPD) is a treatable disease characterized by progressive airflow limitation. The most distressing symptoms for patients with COPD are dyspnea and the progressive inability to engage in activities of daily living. These clinical manifestations of COPD lead, ultimately, to poor health-related quality of life. COPD is a disease of multiple components and is no longer considered a disease of bronchoconstriction only. Airway inflammation and structural changes in the airway due to small airway inflammation and loss of elastic recoil due to destruction in the terminal lung are also very important components. Airway inflammation is triggered by the exposure to inhaled noxious particles and gases, and is present throughout the airways, parenchyma, and pulmonary vasculature and may contribute to disease progression. Several studies have demonstrated that this airway inflammation may persist even when patients with COPD stop smoking although to a much lesser extent than in those who continue smoking. Macrophages, CD8+ T lymphocytes, and neutrophils are increased in various parts of the lung in COPD. Activated inflammatory cells release a variety of mediators including leukotriene B4, interleukin 8, tumor necrosis factor, and other inflammatory mediators capable of damaging lung structures and/or sustaining neutrophilic inflammation.

The worldwide impact of COPD is of major concern as it continues to be a significant health problem and a leading cause of morbidity and mortality. COPD is currently the third leading cause of death and 12th leading cause of morbidity in the United States.[1-3] A recent longitudinal study calculated that North Americans have 27.6% lifetime risk of physician-diagnosed COPD.[4] Prevention of disease progression, improvement of symptoms, exercise tolerance and health status, and decrease in exacerbations and mortality are the main goals of management of COPD. As the primary point of contact for many patients with COPD, primary care clinicians play an important role in COPD prevention, early diagnosis, and appropriate management.

**Case Study 1.**

KJ is a 52-year-old woman who presents with increasing shortness of breath on exertion over the past 2 years. She reports that she used to walk 9 holes of golf with her women’s group every Wednesday morning, but has needed to use a golf cart over the past year because she feels fatigued. She attributes this decline to getting old. She also reports occasional cough. She was told 3 years ago that she had “a touch of asthma” for which she was given a short-acting inhaler to use when she was symptomatic. She is wondering if her asthma is getting worse. Medical history: Mild hypertension on atenolol 50mg daily, Osteoporosis taking calcium supplements, GERD on the counter antacids.

**Smoking history:** Smoked a pack per day for about 15 years, but stopped 15 years ago

**Family history:** Mother had diabetes and died of heart failure at age 70

**P/E:** BMI: 24.5kg/m2, HR 73, BP 138/86, RR 18 / min, Lungs: decreased breath sounds. Heart: normal. Rest of exam: normal
1. The most likely diagnosis for KJ is:
   a. Asthma
   b. COPD
   c. Asthma and COPD
   d. Deconditioning
   e. Cannot be determined at this point

2. All the following are important initial work-up tests for KJ except:
   a. Pulse oximetry
   b. Chest X-ray
   c. EKG
   d. Spirometry
   e. High resolution CT scan

3. Which of the following helps differentiate between asthma and COPD?
   a. Asthma symptoms are usually episodic while COPD symptoms are slowly progressive
   b. Asthma has an inflammatory component, but COPD is a disease characterized by airway obstruction
   c. Asthma affects mostly women, while COPD is a disease of old men
   d. Significant acute bronchodilator response to albuterol is seen in asthma, but not in COPD
   e. COPD mainly affects patient older than 65 years of age while asthma mainly affects younger individuals

COPD: Diagnostic Considerations
COPD is often underdiagnosed and undertreated because it is often confused with other conditions. Early diagnosis of patients with COPD is essential to ensure optimal interventions. For many years, COPD was considered a disease of “old men”, but current data from many countries demonstrate that it is becoming more common in women and in middle-aged individuals. COPD should be considered in any individual over 40 years old who reports history of exposure to risk factors: tobacco, occupational dust, chemicals, and who reports progressive dyspnea or activity limitation, chronic cough, and chronic sputum production.

Several factors play a role in the delayed diagnosis of COPD; patients frequently misinterpret the origin of their breathing problems and may often attribute them to aging. In addition, symptoms of COPD are non-specific and can occur long after a person has stopped smoking, and in some cases, in the absence of a smoking history. Furthermore, because the disease has a very slow progressive course, symptoms are often undetermined by patients who tend to modify their activities to accommodate their slow decline in exercise tolerance. Activity limitation and fatigue are very common early symptoms in patients with COPD and should be evaluated with further testing accomplished by conducting a complete evaluation of the patient. Some validated questionnaires may help identify patients who are at increased risk and who may benefit from spirometry. The Lung Function Questionnaire (LFQ) was recently developed as a tool to aid in COPD screening.[5,6] The LFQ is a 5-item self-administered questionnaire, where a
total score of ≤18 suggests an increased risk of airflow obstruction. Another self-scored questionnaire for identifying patients with possible COPD is the COPD Population Screener questionnaire (COPD-PS).[7]

COPD may mimic other airway diseases such as asthma, bronchiectasis, and non-pulmonary diseases such as congestive heart failure. Although COPD and asthma symptoms may overlap, some features of asthma may help differentiate it from COPD (Table 1).

Table 1. Clinical Features That May Help Differentiate Asthma from COPD

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>SUGGESTIVE FEATURES</th>
</tr>
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</table>
| COPD      | Mid-life onset (Age >40 years)  
Slowly progressing symptoms  
Long history of smoking  
Fatigue and activity limitation |
| ASTHMA    | Early onset  
Varying symptoms (episodic)  
Symptoms during the night/early morning  
Presence of allergy, rhinitis, and/or eczema  
Presence of family history |

Assessment of COPD

Case Study 1. KJ (cont’d)
4. Appropriate assessment of this patient’s COPD should focus on:
   a. Assessing her lung function impairment  
b. Determining the impact of her disease on her health status 
c. Assessing her risk for future exacerbation  
d. Looking for and appropriately treating comorbidities  
e. All of the above

The updated GOLD guidelines stipulate that assessment of a patient with COPD should be based on evaluation of symptoms and health status, risk of exacerbation and lung function.[8-10] In addition assessment and management of comorbid conditions are important.

Evaluation of Symptoms
In evaluating patients with COPD, assessment of symptoms in identifying those who are very symptomatic versus those with minimal symptoms is an important step in the progress. This is
especially important since symptoms and lung function do not always correlate. The GOLD guidelines suggest the use of either the Modified Medical Research Council (mMRC) Dyspnea scale (Figure 1) or the COPD Assessment Test questionnaire (CAT)[11,12] (Figure 2). An mMRC of 2 or more or a CAT score of 10 or more signify the presence of severe symptoms.

Case Study 1. KJ (cont’d)
5. Upon further questioning, KJ states that on level ground, she walks slower than people of the same age because of breathlessness, or has to stop for breath when walking at her own pace. Accordingly her mMRC dyspnea grade is:
   a. 1  
   b. 2  
   c. 3  
   d. 4  
   e. 0

Figure 1. Modified Medical Research Council (mMRC) Dyspnea Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description of Breathlessness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>I only get breathless with strenuous exercise</td>
</tr>
<tr>
<td>1</td>
<td>I get short of breath when hurrying on level ground or walking up a slight hill</td>
</tr>
<tr>
<td>2</td>
<td>On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace</td>
</tr>
<tr>
<td>3</td>
<td>I stop for breath after walking about 100 yards or after a few minutes on level ground</td>
</tr>
<tr>
<td>4</td>
<td>I am too breathless to leave the house or I am breathless when dressing</td>
</tr>
</tbody>
</table>
Figure 2. COPD Assessment Test (CAT) Questionnaire

Evaluation of Lung Function

The GOLD guidelines recommend that a diagnosis of COPD, which is confirmed using spirometry (post-bronchodilator FEV1/forced vital capacity [FVC] ratio of < 0.70), should be considered in patients with symptoms of COPD (eg, dyspnea, chronic cough, or sputum production) and/or exposure to risk factors for the disease.[10] Recent COPD guidelines issued by the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society recommend against using spirometry for COPD screening in patients who do not have respiratory symptoms.[13,14] However, if patients have symptoms of COPD, but do not recognize them, they would fail to meet criteria for spirometry screening.
which may lead to a delay in diagnosis. Given the substantial burden of the disease and the benefits of early treatment intervention, it is essential that detailed questioning of individuals at risk be done.

**Figure 3. Case Study 1. KJ Underwent Spirometry Testing with the Results Shown Below (cont’d)**

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
<th>Pre- % Predicted</th>
<th>% Predicted</th>
<th>Post- % Predicted</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>2.29</td>
<td>2.18</td>
<td>95%</td>
<td>2.29</td>
<td>100%</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.77</td>
<td>1.15</td>
<td>65%</td>
<td>1.35</td>
<td>76%</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>82%</td>
<td>53%</td>
<td>59%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. Examining her spirometry, you determine that KJ suffers from:
   a. COPD, Stage II (moderate)
   b. Moderate Persistent Asthma
   c. Asthma and COPD
   d. Cannot determine based on data given
   e. COPD, Stage III (severe)

7. Important factor that can help differentiate asthma from COPD in this case is:
   a. Presence of hyperinflation on chest X-ray
   b. Change in FEV₁ post bronchodilator administration by >12% and 200 mL
   c. Post-bronchodilator FEV₁/FVC ratio on spirometry <70%
   d. Positive allergy skin test
   e. None of the above

Spirometry is an important tool in the diagnosis and staging (Figure 4) of the disease in the primary care setting.[15-20] Unfortunately, it continues to be underutilized in many practices because of many misconceptions including the cost, long time commitment and lack of reimbursement.[21]
The extent of spirometric response to acute bronchodilator administration is not usually helpful in differentiating asthma from COPD as many patients with COPD demonstrate significant bronchodilator response (>12% and 200 mL change in FEV1 and FVC). However, the post-bronchodilator value of FEV1/FVC will continue to show airway obstruction (<0.7).[22,23]

**Evaluation of Exacerbation Risk**

The course of COPD is complicated by exacerbations defined as episodes of worsening symptoms that necessitate escalation of therapy including either use of antibiotics, systemic steroids, ER visits and hospitalization. Prevention of exacerbation is a major goal for the management of COPD and several interventions can help prevent exacerbations.

8. **The risk of future exacerbations in COPD is predicted by:**
   a. Severity of airflow limitation
   b. History of previous exacerbations
   c. History of daily cough and sputum
   d. History of GERD
   e. All of the above

The GOLD guidelines stipulate that assessment of COPD should include identifying high risk patients for future exacerbations. Patients with ≥2 exacerbations in the preceding year are at highest risk. Data from the ECLIPSE study and other studies have described predictors of future exacerbations; these include past history of exacerbations, severity of airway obstruction, history of poor quality of life and GERD, and presence of chronic bronchitis.[24,25] In summary assessment of COPD should focus on three main issues summarized in (Figure 5) below.
Figure 5. Assessment of COPD based on GOLD Recommendations

Based on this assessment patients are grouped according to symptoms, risks and lung function into Groups A, B, C, D. Management strategies are recommended according to this grouping (discussed below).

Assessing Comorbidities

9. Which of these medical conditions are commonly encountered in patients with COPD?
   a. Hypertension
   b. Depression
   c. Osteoporosis
   d. Hypertension and depression
   e. All of the above
Case Study 2.

A 56-year-old man with known chronic obstructive pulmonary disease as a result of cigarette smoking presents to the emergency department with severe chest pain. He is admitted to the coronary care unit for observation, where his symptoms improve on treatment with nitrates. The attending cardiologist wants to begin treatment with a beta-blocker before the patient leaves the hospital and is concerned about the possible effects on lung function. Spirometry in the outpatient setting demonstrated an FEV of 1.9 L (58% of predicted normal value) and a vital capacity of 3.4 L (72% predicted), with no improvement after 4 puffs of inhaled albuterol. The FEV measured during the current admission is 1.8 L.

1. Which of the following would be the best advice to give to the cardiologist?
   a. Do not begin treatment with a beta-blocker because of the risks of bronchoconstriction
   b. Begin treatment with the most cardio-selective beta-blocker available
   c. Begin treatment with any beta-blocker, as there is no risk of bronchoconstriction in a patient with COPD
   d. Wait until a methacholine inhalation challenge has been performed to determine whether the patient has asthma
   e. Wait until a trial of an oral corticosteroid has been completed to establish whether the patient has reversible airflow obstruction before beginning a beta-blocker

COPD also is associated with clinically relevant extrapulmonary effects, including poor nutritional status, reduced BMI, and impaired skeletal muscle function, which may contribute to disease severity in some patients.[10,26-30] Other comorbidities can also contribute to disease severity and/or complicate COPD management. COPD patients in a recent study had a five-fold increased risk of cardiovascular disease, a three-fold increased risk of stroke, and two-fold increased diabetes risk.[28] Considering that 20% of Medicare beneficiaries have ≥5 chronic conditions and half are prescribed ≥5 medications for comorbid diseases, it is critical that physicians screen for comorbidities and implement disease management programs that consider the “whole patient”.[31]

Systemic inflammation has been proposed as a pathogenic link between COPD and certain comorbidities.[32-34] Categories of comorbidities include those with common pathways, including other smoking-related diseases, such as ischemic heart disease and lung cancer, and those considered to be complications of COPD, including pulmonary hypertension and heart failure. Coexisting coincidental comorbidities, such as bowel or prostate cancer, depression, diabetes, dementia, Parkinson’s disease, and arthritis, are pathogenically unrelated, but they can complicate COPD management. Intercurrent comorbidities, including upper respiratory tract infections, are acute illnesses that may have a more severe impact in COPD patients compared with those without COPD. Because systemic inflammation may be an important contributor to the systemic effects and comorbidities associated with the disease, novel systemic anti-inflammatory therapies may play a role in treating these extrapulmonary effects of COPD in the future.[35]
Comorbidities of COPD are associated with poor clinical outcomes, although their severity and impact on patient health vary with time and among patients. Data from the National Hospital Discharge Survey from 1979 to 2001 indicate that rates of in-hospital mortality due to various cardiovascular, pulmonary, and thoracic conditions are higher in patients with COPD versus those without COPD.[36] COPD is currently the third leading cause of death in adults in the United States; however, results from several studies suggest that patients with COPD may be more likely to die from comorbid conditions than COPD, in particular those related to cardiovascular disease. The use of beta-blockers to treat cardiac comorbidities in COPD have traditionally been contraindicated in COPD but recent studies have demonstrated that cardioselective agents can safely be used in this situation.[10]

**Management Considerations in COPD**

**Goals of Management**
The main goals of therapy of COPD are focused on relieving symptoms, improving health status, preserving lung function from decline, improving exercise performance, preventing exacerbations,[37] and decreasing mortality.[10] These goals should be reached with minimal side effects from treatment. Traditional COPD therapies have focused on improving symptoms and aim to alleviate the problems of reduced airflow and declining lung function. However with our improved knowledge about the multicomponent nature of the disease, therapeutic approaches aim to target both the symptoms and the inflammation that underlies and drives COPD.

**Nonpharmacologic Interventions**

**Vaccination**
Reducing risk of infection is important to prevent worsening of the course of COPD. Yearly influenza vaccination can reduce more-severe forms of influenza and acute exacerbations of COPD as well as rates of hospitalization for pneumonia. Pneumococcal vaccination reduces invasive pneumococcal disease and is recommended in COPD patients.

**Smoking Cessation**
2. Smoking cessation in COPD is associated with all the following except:
   a. Improved survival
   b. Prevention of progression of disease (decline in lung function)
   c. Improvement in lung function
   d. Decrease risk of lung cancer
   e. Complete resolution of airway inflammation

Smoking cessation is the single most effective and cost-effective intervention to reduce the progression of COPD and should be attempted in all patients.[15,38] Unfortunately, even with the best intervention strategies, less than a third of smokers become sustained quitters. Once patients develop demonstrable airflow obstruction, their symptoms and airway inflammation...
can persist even after smoking cessation. Several effective therapies for tobacco dependence are available and should be considered in patients interested in quitting smoking. These include behavioral techniques, support groups, and pharmacotherapy including nicotine supplements, bupropion, and nicotine-receptor partial agonists like varenicline.[39,40]

**Exercise and Pulmonary Rehabilitation**

Pulmonary rehabilitation is currently recommended for the management of patients with moderate or severe COPD.[41-50] Pulmonary rehabilitation is an individualized multidisciplinary program that aims to optimize patients’ performance and self-control. The program includes upper and lower body aerobic workout and breathing exercises; nutritional, psychological, and behavioral interventions; and education. Pulmonary rehabilitation produces significant improvement in respiratory symptoms, exercise capacity, quality of life, and health care utilization.

**Surgical Therapies**

Lung volume reduction surgery (LVRS) includes resection of severely emphysematous areas of the lungs. The procedure can be performed through thoracoscopy or median sternotomy. In the National Emphysema Treatment Trial (NETT), LVRS improved spirometry, lung volumes, exercise tolerance, dyspnea, and quality of life.[51] Subjects with upper lobe disease and low baseline exercise capacity had improved longevity when compared to optimal medical therapy. In contrast, NETT showed that patients with very advanced COPD including FEV1 of 20% or less, diffusing capacity of 20% or less, or diffuse emphysema, had shorter longevity with LVRS. LVRS can help COPD patients with severe lung disease as long as it is performed in centers with experience in this type of surgery. Bronchoscopic lung volume reduction using valves and coils are being investigated, but not yet approved for use in the US.

COPD patients with giant bulla (>1/3 hemithorax) might benefit from bullectomy with improvement in symptoms (dyspnea), lung function, oxygenation and ventilation, exercise capacity, and quality of life. In selected patients with advanced COPD, a lung transplant can improve pulmonary function, exercise capacity, and quality of life.

**Pharmacologic Interventions**

Evidence-based guidelines for COPD emphasize the comprehensive and stepwise approach to the management of COPD and stipulate that all patients who are symptomatic merit a trial of pharmacologic intervention.

**Bronchodilators**

3. Which of the following statements about bronchodilator response in COPD is correct?
   a. Lack of response to one class of drug does not imply non-responsiveness to another class
   b. Short-term lung function response may underestimate long-term response
   c. Patients with an “irreversible” FEV1 acute bronchodilator response may still have a beneficial lung volume response
d. Approximately 65% of patients with COPD demonstrate significant bronchodilator response to acute administration of short acting beta2-agonists

e. All are correct

4. Regular Treatment with Long-Acting Beta-agonists in COPD:
   a. Is not different from short acting bronchodilators in improving lung function
   b. Reduces the number of disease exacerbations
   c. Is associated with significant tolerance of effect
   d. Should always be given with inhaled corticosteroids
   e. Is associated with significant cardiovascular complications and should be avoided

Bronchodilators work through their direct relaxation effect on airway smooth muscle cells, although many have non-bronchodilator activities that might contribute to their beneficial effects in COPD.[52,53] Three classes of bronchodilators—beta2-agonists, anticholinergics, and theophylline—are currently available and can be used individually or in combination. The use of theophylline in COPD has been restricted because of its potential systemic side effects. Inhaled short-acting bronchodilators are currently recommended as the preferred drugs for rescue of symptoms in patients with mild disease, while inhaled long-acting bronchodilators (beta2-agonists and anticholinergics) are recommended as first-line agents for maintenance therapy in patients with moderate and severe disease and those with daily symptoms. When symptoms are not sufficiently controlled by the use of one bronchodilator, combining bronchodilators of different classes may be a more effective approach. In addition, combining a long-acting beta2-agonist with an inhaled corticosteroid has also been shown to be more effective than the use of either agent alone.

Several issues need to be considered when assessing the response to bronchodilator therapy. First, the lack of acute response to one class of bronchodilator does not necessarily imply nonresponsiveness to another. One further consideration is that a patient’s FEV1 response to acute bronchodilator therapy does not predict long-term response to bronchodilator therapy and can vary from day to day. The clinical efficacy of bronchodilators has traditionally been assessed by the degree of improvement in FEV1. However, other physiologic measures, such as the change in inspiratory capacity (IC), correlate better with change in symptoms, such as dyspnea and exercise tolerance. This suggests that assessment of bronchodilator treatment is using indices of hyperinflation or air trapping, might provide a better indicator of efficacy. Although changes in lung volumes are independent of changes in FEV1, several studies have demonstrated that the more-sustained airway patency offered by long-acting bronchodilators reduces air trapping.[54,55]

Though the strength of the data varies, there is increasing evidence that the use of long-acting beta2 agonists (salmeterol, formoterol, and indacaterol), long-acting anticholinergic agents (tiotropium) inhaled corticosteroids, and combination inhalers either delay the time to next exacerbation and/or reduces the frequency of exacerbation and severity of individual exacerbations.[56] The effects of long-acting bronchodilators on health status have been well documented in several clinical trials. Most clinical trials have demonstrated superiority of long-acting agents over short-acting bronchodilators.
Tiotropium is a long-acting anticholinergic with 24 hour duration of action and so can be used once daily, studies have demonstrated its super efficacy to ipratropium bromide. Tiotropium exerts its effects by activating M1, M2, and M3 muscarinic receptors in the airway, but has a long half-life at the M3 receptor. Although tiotropium failed to slow the decline in lung function over the 4 years of the study, it had a significant effect on improving health status and reducing exacerbations.

Aclidinium bromide is the newest inhaled anticholinergic that works by inhibiting the M3 receptor in smooth muscle, resulting in bronchodilation. Aclidinium bromide has been shown to lead to significant improvements in bronchodilation, health status, and COPD symptoms, with a low incidence of adverse events. It does require twice daily inhalations. To achieve maximal benefit, all bronchodilators must be correctly delivered to the airway using a proper technique. Inhaled bronchodilators have traditionally been delivered to the lung using a metered dose inhaler (MDI). However, a significant number of patients with COPD cannot effectively coordinate their breathing using an MDI. This problem may be remedied by the use of a dry-powder device (DPI), an MDI with a spacer device, or a nebulizer. Two long-acting nebulized beta2-agonists are currently approved for twice daily maintenance treatment of COPD (arformoterol and formoterol).

Inhaled Corticosteroids
6. The TORCH study demonstrated that the long-term use of inhaled corticosteroids/long-acting beta2-agonists combination in COPD may be associated with all except:
   a. Reduction of exacerbations
   b. Improvement of health status (quality of life)
   c. Short-term improvement in lung function
   d. **Reduction in mortality**
   e. Increased risk of pneumonia

Given the prominence of airway inflammation in COPD, highly potent, but nonspecific anti-inflammatory agents such as corticosteroids could be expected to have some effect on lung function and health outcomes of COPD patients. Current guidelines recommend the use of regular treatment with ICS for symptomatic patients who suffer frequent exacerbations and whose FEV1 is less than 50% of predicted. Several large, 3-year randomized trials have failed to show a significant effect of ICS on the rate of decline of FEV1, compared with placebo. Although both ICS and long-acting beta 2-agonists (LABAs) are effective by themselves in improving lung function and reducing exacerbations, their beneficial effects are amplified when they are given together. There is a large, growing body of experimental and clinical evidence supporting the use of combination therapy with inhaled corticosteroids and LABAs for the long-term treatment of COPD patients with severe disease. The use of ICS and LABA combination products has been shown to improve lung function, symptoms, and health status and reduce exacerbations in patients with moderate to severe COPD. The 3-year study, TOWARDS A Revolution in COPD Health (TORCH) study, demonstrated a significant effect of therapy with salmeterol fluticasone combination (SFC) over 3 years on several COPD outcomes including moderate to severe exacerbations and quality of life. SFC had a 2.6% absolute risk reduction in all-cause mortality compared to placebo but this difference was not statistically significant.
(P = 0.052). A fluticasone and vilanterol combination is a newer once daily LABA and ICS inhalation powder approved in 2013 for once daily use in COPD with the indication to maintain airflow or reduce exacerbations in those with a history of exacerbations. It has been shown to have similar efficacy to the older salmeterol fluticasone combination.[66] Recent data suggests, but has yet to confirm that the triple combination of ICS/LABA with tiotropium may provide additional clinical benefits.[67]

**Roflumilast**

Roflumilast is an oral phosphodiesterase-4 inhibitor (PDE4). It is indicated as an add-on therapy to existing COPD medication in patients with history of severe disease, chronic bronchitis, and history of exacerbation.[68-70] It is administered as once daily dose and inhibits cyclic-AMP and thus may have an anti-inflammatory effect. Roflumilast studies in severe COPD patients demonstrated a significant reduction in moderate to severe exacerbations and a modest effect on lung function.

**Oxygen**

Supplemental long-term oxygen therapy (LTOT) has been associated with a variety of beneficial effects in patients with severe COPD who are hypoxemic in room air.[40,41,71] These include prolonged survival, reduced secondary polycythemia, improved cardiac function during rest and exercise, reduction in the oxygen cost of ventilation, and improved exercise tolerance. Patients with partial pressure of oxygen (PaO2) less than 55 mm Hg (SaO2 <88%) whose disease is stable despite receiving otherwise comprehensive medical treatment are candidates for LTOT. Patients whose PaO2 is 55 to 59 mm Hg (SaO2 89%) are eligible to receive LTOT if they show signs of pulmonary hypertension, cor pulmonale, erythrocytosis, edema from right heart failure, or impaired mental state. If oxygen desaturation only occurs during exercise or sleep, then oxygen therapy should be considered specifically under those conditions.

**Mucolytics**

Mucus impaction contributes to worsening of symptoms of patients with COPD. A number of studies investigating the role of existing mucolytics such as potassium iodide and guaifenesin failed to demonstrate significant clinical efficacy of these agents in the management of patients with COPD, although some have shown some decrease in COPD exacerbations. A variety of new agents addressing mucociliary clearance and mucus production are under investigation.

**Antibiotics**

Although empiric treatment with antibiotics has been shown to be beneficial in COPD exacerbations, their role in chronic management is not well defined and their use is currently not recommended. The role of chronic azithromycin therapy in preventing COPD exacerbations has recently been examined. Administration of daily azithromycin (250 mg) for 1 year in patients with severe COPD at risk of exacerbation reduced the subsequent risk for exacerbation.[72] Current guidelines do not recommend the routine use of such agents at this point, and care should be taken because of the possibility of cardiac toxicity with long-term use. The use of prophylactic use of fluoroquinolones has also been examined and may have a role in some patients at risk of exacerbation.
Augmentation Therapy for α1-Antitrypsin Deficiency
Replacement therapy with α1-proteinase inhibitor has been approved for patients with emphysema due to the α1-antiprotease deficiency. Given in weekly infusions to patients with ZZ or null AAT phenotypes, therapy can increase serum levels above the target threshold of 11 mm and can provide protective levels within the epithelial lining of the lung. Although AAT augmentation therapy has a sound theoretical basis, proof of its efficacy has been difficult to document. However, available evidence supports the use of this therapy in patients with AAT serum levels less than 11 mm and FEV1 between 30% and 65% predicted, but it might not be useful in other subsets of patients with COPD.[73]

Stepwise Approach to Therapy
The GOLD guidelines recommend a stepwise approach to the management of COPD according to the patient’s group based on lung function, symptoms and risk of exacerbations (Figure 6 and 7).

Figure 6. Non-pharmacologic Interventions

<table>
<thead>
<tr>
<th>PATIENT GROUP</th>
<th>ESSENTIAL</th>
<th>RECOMMENDED</th>
<th>DEPENDING ON LOCAL GUIDELINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Smoking cessation (can include pharmacologic treatment)</td>
<td>Physical activity</td>
<td>Flu vaccination</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pneumococcal vaccination</td>
</tr>
<tr>
<td>B, C, D</td>
<td>Smoking cessation (can include pharmacologic treatment) Pulmonary rehabilitation</td>
<td>Physical activity</td>
<td>Flu vaccination</td>
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<tr>
<td></td>
<td></td>
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<td>Pneumococcal vaccination</td>
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Figure 7. Pharmacologic Therapy

<table>
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<tr>
<th>PATIENT GROUP</th>
<th>RECOMMENDED FIRST CHOICE</th>
<th>ALTERNATIVE CHOICE</th>
<th>OTHER POSSIBLE TREATMENTS</th>
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<tbody>
<tr>
<td>A</td>
<td>SAMA prn or SABA prn</td>
<td>LAMA or LABA or SABA and SAMA</td>
<td>Theophylline</td>
</tr>
<tr>
<td>B</td>
<td>LAMA or LABA</td>
<td>LAMA and LABA</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
<td>LAMA and LABA or LAMA and PDE4-inh. or LABA and PDE4-inh.</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA or LAMA</td>
<td>ICS + LABA and LAMA or ICS+LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.</td>
<td>Carbocysteine SABA and/or SAMA Theophylline</td>
</tr>
</tbody>
</table>

LABA = Long-acting beta2-agonists, SABA = Short-acting beta2-agonists, LAMA = Long-acting antimuscarinic agents (anticholinergics), SAMA= short-acting antimuscarinic agents, PDE4-inh = Roflumilast, ICS= Inhaled corticosteroids

Novel Targets of Therapy
Several novel therapies are now in different stages of development for use alone or in combination with other agents. Most of these agents include refined once daily LABAs or LAMAs delivered through novel easy to use devices. In addition multiple formulations of combinations of once daily LABAs and LAMAs are under development.[74-87] In addition once daily LABA/ICS formulations are being investigated. One such combination has now been approved in the U.S. (Indacaterol/Fluticasone furoate).[88] A large long term study investigating this drug in patients with cardiovascular risk factors is currently underway.[89]

Other targets include agents that target airway inflammation in COPD, drugs with anti-oxidant effects such as acetylcysteine and carbocysteine, drugs that may have effects on lung regeneration (retinoids), and mucoactive drugs.[35,79,90-94]

Drugs which are commonly used to manage comorbidities of COPD may have an effect on the course of the disease itself. The role of statins on COPD exacerbations is currently being investigated in an ongoing large multicenter study.
Safety of COPD Medications

Safety of COPD medications should be considered upon prescribing a medication. This topic was recently reviewed.[9] Because patients with COPD often have underlying comorbidities such as cardiac disease, care should be taken upon prescribing medications that may have cardiovascular adverse effects such as the commonly used bronchodilators. The use of Inhaled corticosteroid use may be associated with thrush, dysphonia, increased risk of fractures, and pneumonia. Roflumilast may be associated with GI adverse effects (nausea and vomiting) as well as weight loss. While the long-term safety of existing medications has been examined in long-term studies, patients enrolled in such studies may not be good representatives of those in “real life” and thus treatment should be individualized by weighing risks and benefits.

Management of COPD Exacerbations (AECOPD)

Case Study 3.

58-year-old former smoker with severe COPD, diabetes, and ischemic heart disease. Seen in your clinic with chief complaint: severe dyspnea. Also has 4 days of increased cough productive of green sputum. Afebrile, RR 28. Cyanotic, pulse oximetry saturation of 82%. Moderate respiratory distress with pursed-lip breathing. Lungs with wheezing, no crackles, I:E of 1:5. Heart regular, no extra heart sounds. No edema No fever or chest pain. ABG: pH=7.12, PaCO₂=80 mm Hg, PaO₂=50 mm Hg

1. What would be your next step of management?
   a. Start a short course of systemic steroids
   b. Send sputum culture and start broad spectrum antibiotics
   c. Arrange for home oxygen
   d. **Transfer to the closest hospital via ambulance**
   e. Discuss end-of-life issues with family and patient

2. Because of the high morbidity and mortality associated with COPD, you are asked to assist in the development of a clinical practice guideline for your hospital network. Of the following recommendations, which is LEAST likely to improve outcome in patients with exacerbation of COPD with respiratory failure requiring hospitalization in an ICU?
   a. Oral antibiotics for 7-14 days
   b. Systemic steroids for 7 days
   c. **Chest physiotherapy for 48 to 72 hours**
   d. Noninvasive positive pressure ventilation for 48 to 72 hours
   e. Aerosolized albuterol for 48 to 72 hours

An acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is associated with worsening quality of life and faster decline of lung function. AECOPD has a 10% in-hospital mortality rate and up to 25% mortality in patients admitted to an ICU. Although AECOPD is usually caused by bacterial or viral infections, environmental pollution, and lack of compliance...
with medications, in many cases the cause is not clear. Differential diagnosis of AECOPD includes pneumonia, myocardial ischemia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, cardiac arrhythmias, and noncompliance with medications.

The evaluation of patients during AECOPD should include the severity of COPD, comorbid medical conditions, and history of prior AECOPD and its outcomes, including hospitalization and intubation. Effect of AECOPD on respiratory and hemodynamic function should be evaluated and considered for severity classifications. Initial diagnostic procedures, depending on the severity of AECOPD, include saturation of oxygen, chest radiography, electrocardiogram (ECG), and routine blood tests, including complete blood count (CBC) and basic metabolic panel. Other diagnostic tests may be indicated to rule out other diagnoses.

Early treatment of AECOPD is associated with faster recovery. Main pharmacotherapy includes increased short-acting bronchodilators, antibiotics, and short course of systemic steroids.[96-101] Short-acting beta2-agonists and anticholinergics offer similar benefits. Several studies have shown reduction in treatment failure and improved outcomes (especially for inpatient treatment) with the use of antibiotics for AECOPD. Systemic corticosteroids reduce treatment failure and length of hospital stay and improve FEV1, but are associated with increased side effects particularly hyperglycemia. Correction of hypoxemia is essential step in management and occasionally ventilator support (non-invasive) may be needed in those with impending respiratory failure.

First-line antibiotic therapy in low risk patients includes macrolides, doxycycline, and cephalosporins. However in patients with severe exacerbation and in those with high risk, respiratory fluoroquinolones or amoxicillin-clavulanate is recommended.

**Practical Strategies for COPD Management–Individualizing Patient Needs and Preferences**

**Phenotypic Characterization**
Management of COPD is complex; COPD symptoms and presentation are heterogeneous and progressive, and patients frequently have other comorbidities. In addition, response to therapy in COPD may be related to the underlying phenotype of the patient.[25, 32,102-107]

**Individualize Treatment Plan to Ensure Adherence**
Patient-physician communication and patient education are critical to management of COPD because patients’ disease perceptions can affect outcomes, including quality of life.[108-111] In addition, study findings showed greater treatment adherence in patients with compassionate doctors who spent adequate time with them and patients with greater understanding of their disease and disease management options.[111]
Choice of Medication and Delivery Device

3. When monitoring a patient with COPD who has experienced worsening symptoms or increased frequency of exacerbation, it is important to consider inhaler technique as it is estimated that up to __ percent of patients make at least one error while using their MDI.

   a. 38%
   b. 48%
   c. 58%
   d. 76%
   e. 90%

The inhaled route is the usual preferred method to deliver COPD medications. However, many patients are not comfortable and do not master their use of inhaler devices even dry powder devices.[112,113] One study estimated that 76% of MDI users and 49%-55% of DPI users made at least one error in using their inhaler device.[114] This is especially true in patients with cognitive or physical dysfunction which prevent them from handling the correct technique needed to ensure adequate drug delivery. This is true for most metered dose inhalers (MDIs) and some DPIs which require an adequate inspiratory flow rate for the drug to be dispersed. In such situations, consideration of a nebulized platform may be a good alternative.[115,116] Therefore it is essential for a clinician to consider these issues when prescribing a medication for COPD. Other factors include patient’s preference, cost of acquisition, and insurance coverage of the medication as well as its efficacy and tolerability in the specific patient.
References


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