

Louisiana Drug Utilization Review (LADUR) Education

Chronic obstructive pulmonary disease (COPD)

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Issues...

- COPD airflow limitation is usually progressive and is associated with an abnormal inflammatory response in the lungs to noxious agents.
- It is the fourth leading cause of death in the United States.
- In 2002, the treatment of COPD in the US was estimated to cost approximately \$32.1 billion.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response in the lungs to noxious agents. It is the fourth leading cause of death in the United States, with more than 10 million adults in the United States having physician diagnosed COPD, and morbidity and mortality associated with COPD is expected to increase in the next decade. This is particularly disturbing when one considers that exposure to tobacco smoke is the primary cause of COPD, accounting for 80-90% of the risk for disease development.

In 2002, the treatment of COPD in the US was estimated to cost approximately \$32.1 billion. Of these costs, \$18.1 billion was attributed to direct costs and \$14.1 billion was attributed to indirect costs. In 1998, the World Health Organization and the National Heart Lung and Blood Institute held a consensus workshop that resulted in the 2001 publication of a report entitled the "Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global strategy for diagnosis management and prevention of chronic obstructive pulmonary disease." This publication was updated in 2003, and it is the purpose of this article to summarize the GOLD 2003 report. The report recommends four components to the management of COPD: 1) Assess and monitor disease, 2) Reduce Risk Factors, 3) Manage stable COPD, and 4) Manage exacerbations.

Goals of Disease Management

The goals of the disease management process is to

1. Prevent disease progression

2. Relieve symptoms
3. Improve exercise tolerance
4. Improve health status
5. Prevent and treat complications
6. Prevent and treat exacerbations
7. Reduce mortality

| Host Factors | Exposures |
|---|----------------------------------|
| Genes (α_1 .antitrypsin deficiency) | Tobacco Smoke |
| Airway Hyperresponsiveness | Occupational Dusts and Chemicals |
| | Outdoor and Indoor Air Pollution |
| | Infections |
| | Socioeconomic Factors |

Component 1: Assess and Monitor Disease

As stated previously, COPD is characterized by a fixed limitation in airflow that may be partially reversible. In addition, it is characterized by an age related decline in pulmonary function that exceeds that of patients without COPD. The diagnosis should be considered in any patient with a history of exposure to risk factors (Table 1) and symptoms of cough, sputum production and /or shortness of breath. Chronic cough is usually the first symptom to develop and may or may not be associated with airflow limitation. Signs of airflow limitation are usually not present on physical exam until significant lung impairment has occurred. Because of this, patients with a suspected diagnosis of COPD should have the diagnosis confirmed by spirometry, and a post bronchodilator forced expiratory volume in 1 second (FEV1) < 80% predicted and an FEV1 to forced Vital Capacity ratio of < 70%. Based on the level of symptoms, severity of pulmonary function defects as measured by spirometry and the presence of complications, COPD may be classified into several severity classifications (Table 2).

| Stage | Characteristics |
|--------------|---|
| 0: At Risk | <ul style="list-style-type: none"> • Normal spirometry • Chronic symptoms such as cough, sputum production |
| I: Mild COPD | <ul style="list-style-type: none"> • $FEV_1/FVC < 70\%$ • $FEV_1 \geq 80\%$ predicted • With or without chronic symptoms (cough, sputum production) |

| | |
|----------------------|---|
| II: Moderate COPD | <ul style="list-style-type: none"> • $FEV_1/FVC < 70\%$ • $50\% \leq FEV_1 < 80\%$ predicted • With or without chronic symptoms (cough, sputum production) |
| III: Severe COPD | <ul style="list-style-type: none"> • $FEV_1/FVC < 70\%$ • $30\% \leq FEV_1 < 50\%$ predicted • With or without chronic symptoms (cough, sputum production) |
| IV: Very Severe COPD | <ul style="list-style-type: none"> • $FEV_1/FVC < 70\%$ • $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure |

For those patients with Stage II COPD or greater, additional diagnostic tests may be warranted. Unless bullous disease is present, a chest X-ray is rarely diagnostic, but may be helpful in ruling out other diagnoses. When there is a doubt in the diagnosis, high resolution computed tomography may assist in the differential diagnosis. In patients with an $FEV_1 < 40\%$ predicted or signs of respiratory or right sided heart failure, arterial blood gas measurements should be performed by arterial puncture. For patients who present with COPD at less than 45 years of age, it may be appropriate to test for a coexisting α_1 -antitrypsin deficiency.

Because COPD is a progressive disease, symptoms and pulmonary function should be monitored for complications and to determine when to adjust therapy. Follow-up office visits should include:

- A discussion of new or worsening symptoms
- Spirometry if there is substantial increases in symptoms
- Arterial blood gas measurements in patients with an $FEV_1 < 40\%$ or signs of respiratory failure or right sided heart failure.
- A discussion of the current therapeutic regimen including drug dosages, inhaler technique, adverse effects and the effectiveness of the current regimen.

In addition, the frequency, severity and likely causes of exacerbations should be monitored and any increase in sputum volume or worsening dyspnea should be noted. Coexisting conditions such bronchial carcinoma, tuberculosis, sleep apnea, and left heart failure should be considered when symptoms are suggestive.

Component 2: Reduce Risk Factors

Smoking is the primary risk factor for the development of COPD. Smoking

cessation is the most effective intervention to prevent COPD, and the only intervention shown to slow the accelerated decline in pulmonary function. Every smoker should be offered the opportunity to quit smoking at every visit to a health care provider. Table 3 outlines the 2000 Public Health Service Report entitled "Treating Tobacco Use and Dependence: A Clinical Practice Guideline." The provider is referred to this report for more in-depth information. In addition to the effectiveness of certain pharmacotherapeutic interventions, three types of counseling have been shown to be particularly effective: 1) practical counseling, 2) social support as a part of treatment, and 3) social support arranged outside of treatment. Pharmacotherapy should be recommended when counseling is not sufficient to help patients stop smoking.

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| 1. Ask | Systematically identify all tobacco users at every visit. Tobacco use for every patient at every clinic visit should be asked about and documented |
| 2. Advise | Strongly urge all tobacco users to quit using a clear, strong and personalized manner |
| 3. Assess | Determine the patient's willingness to make an attempt to quit smoking by asking them if they are willing to quit smoking at this time (e.g. within the next 30 days) |
| 4. Assist | Assist the patient in quitting by helping them to develop a quit plan, providing practical counseling, providing intra-treatment social support, providing extra-treatment social support, recommending the use of approved pharmacotherapy except in special circumstances and providing supplementary materials |
| 5. Arrange | Schedule follow-up contact either in person or on the phone |

| Product | Dose | Duration |
|--|---|-----------------|
| <u>Nicotine Gum</u> <i>Nicorette</i> ®, Generic 2mg, 4mg | Highly addicted: 4mg Less addicted: 2mg 1-2 pieces every 1-2 hours for 1-6 weeks, then 1 piece every 2-4 hours for weeks 7-9, then 1 piece every 4-8 hours weeks 10-12. | Up to 12 weeks |
| <u>Nicotine Lozenge</u> <i>Commit</i> ® 2mg, 4mg | Highly addicted: 4mg Less addicted: 2mg 1 lozenge every 1-2 hours for 1-6 weeks, then 1 lozenge every 2-4 hours for weeks 7-9, then 1 lozenge every 4-8 hours | Up to 12 weeks |

| | | |
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| | weeks 10-12. | |
| <u>Nicotine Transdermal Patch</u> | | |
| <i>Nicotrol</i> ® 5, 10, and 15mg 16 hour release | > 10 cigarettes/day: 15mg patch X 6 weeks, then 10mg patch X 2 weeks, then 5mg patch X 2 weeks. Not recommended for those that smoke ≤ 10 cigarettes/day | 10 weeks |
| <i>Nicoderm CQ</i> ® 7, 14, and 21mg 24 hour release | > 10 Cigarettes/day 21mg patch X 6 weeks, then 14mg patch X 2 weeks, then 7mg patch X 2 weeks ≤10 Cigarettes/day 14mg patch X 6 weeks, then 7mg patch X 2 weeks | 10 Weeks 8 Weeks |
| <i>Generic 1</i> 7, 14, and 21mg 24 hour release | > 10 Cigarettes/day 21mg patch X 4 weeks, then 14mg patch X 2 weeks, then 7mg patch X 2 weeks ≤10 Cigarettes/day 14mg patch X 6 weeks, then 7mg patch X 2 weeks | 8 Weeks 8 Weeks |
| <i>Generic 2</i> 11 and 22mg 24 hour release | > 15 Cigarettes/day 22mg patch X 6 weeks ≤15 Cigarettes/day 11mg patch X 6 | 6 Weeks 6 Weeks |
| <u>Nicotine Nasal Spray</u> | | |
| <i>Nicotrol NS</i> ® 0.5mg nicotine in 50mcL spray | 1-2 doses per hour (2 sprays = 1 dose, Initially use at least 8 doses/day, do not use more than 5 doses/hour or 40 doses/day) Gradually decrease dosage over 3-6 months. | 3-6 months |
| <u>Nicotine Oral Inhaler</u> | | Up to 6 months |

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| <i>Nicotrol Inhaler</i> ® 10mg cartridge delivers 4mg dose of nicotine | Usual dose is 6-16 cartridges/day. Cartridge is depleted after 20 minutes of puffing. Patient should initially use at least 6 cartridges/day | |
| <u>Bupropion SR</u> <i>Zyban</i> ® 150mg sustained release tablet | 150mg every morning for 3 days, then increase to 150mg twice a day allowing at least 8 hours between doses. Patient should quit smoking 1-2 weeks after starting therapy. | 8-12 weeks, up to 6 months for maintenance |

If occupational exposure to noxious substances is being considered as a contributing factor, the contributing substance should be eliminated or exposure to the substance limited. If a patient is susceptible to indoor and/or outdoor pollution, exposure should also be limited.

| Figure 1. Summary of COPD Stage Characteristics and Treatment | | | | | |
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| Category | 0: At Risk | I: Mild | II: Moderate | III: Severe | IV: Very Severe |
| Characteristics | <ul style="list-style-type: none"> • Chronic Symptoms • Exposure to Risk Factors • Normal Spirometry | <ul style="list-style-type: none"> • FEV₁/FVC < 70% • FEV₁ ≥ 80% predicted • With or without chronic symptoms (cough, sputum production) | <ul style="list-style-type: none"> • FEV₁/FVC < 70% • 50% ≤ FEV₁ < 80% predicted • With or without chronic symptoms (cough, sputum production) | <ul style="list-style-type: none"> • FEV₁/FVC < 70% • 30% ≤ FEV₁ < 50% predicted • With or without chronic symptoms (cough, sputum production) | <ul style="list-style-type: none"> • FEV₁/FVC < 70% • FEV₁ < 30% predicted or chronic respiratory failure or right heart failure |
| | Avoidance of risk factors; influenza vaccine | | | | |
| | Add short-acting bronchodilator when needed ¹ | | | | |
| | Add regular treatment with one or more long acting bronchodilators ² | | | | |
| | Add rehabilitation | | | | |
| | Add inhaled corticosteroids if repeated exacerbations | | | | |
| | Add long-term | | | | |

All patients should be vaccinated against the influenza virus on a yearly basis. Routine use of the polyvalent pneumococcal vaccine in all patients is not recommended; however, the vaccine should be given to those patients that have other indications (e.g., age > 65, immunosuppression).

None of the current pharmacologic agents have demonstrated the ability to slow the decline in lung function that characterizes the disease; however, medications are useful to prevent and control symptoms, decrease the frequency and severity of exacerbations, and improve health status and exercise tolerance.

Bronchodilators are the primary agents used in the symptomatic management of COPD and should be administered by inhalation. Bronchodilators may be given on an as needed or on a regular basis to prevent or decrease symptoms. In addition, all bronchodilators will increase exercise capacity even if they do not produce a significant increase in FEV₁. Because individual responses often vary, there is no clear advantage of one bronchodilator over another; however, long-acting inhaled bronchodilators are more convenient than short-acting bronchodilators, and they are recommended for patients who require regular bronchodilator therapy. Until recently, anticholinergic bronchodilators were only available in a short acting form (ipratropium), but recently, tiotropium, a long acting anticholinergic with a duration of action that exceeds 24 hours and an adverse effect profile similar to ipratropium, is available. Combining bronchodilators with different mechanisms and duration of action may increase the degree of bronchodilation and health status with the same or lesser risk of adverse effects; however increasing the dose of a single bronchodilator may provide similar benefit. The approach of combining bronchodilators tends to increase the cost of therapy, and if side effects are not a limiting factor, increasing the dose of a single agent may be preferred.

Regular treatment with inhaled corticosteroids does not decrease the disease related decline in pulmonary function. For symptomatic patients with an FEV₁ <50% predicted (stage III and IV) and frequent exacerbations, regular use of inhaled corticosteroids has been demonstrated to decrease frequency of exacerbations. Despite the common practice of using a short course of oral corticosteroids to identify patients who might benefit from long-term corticosteroid therapy, current evidence indicates that response to a short course of oral corticosteroids is not predictive of the long-term response to inhaled corticosteroids.

In young patients with severe α 1-antitrypsin deficiency and established emphysema, α 1-antitrypsin augmentation therapy may be an option. This therapy is extremely expensive and is not recommended for patients with COPD that is not related to this hereditary defect. Other agents that are not generally recommended for the management of stable COPD include mucolytics, antioxidants, immunoregulators, vasodilators, respiratory stimulants and narcotics. Due to the protective role of cough, regular use of antitussives is not recommended. Chronic use of antibiotics is also not effective.

| Table 6. Indications for Hospital Assessment or Admission for Exacerbations of COPD |
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| <ul style="list-style-type: none">• Marked increase in intensity of symptoms, such as sudden development of resting dyspnea.• Severe background COPD.• Onset of new physical signs (e.g. cyanosis, peripheral edema).• Failure of exacerbations to respond to initial medical management.• Significant comorbidities.• Newly occurring arrhythmias.• Diagnostic uncertainty.• Older age.• Insufficient home support. |
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| Table 7. Discharge Criteria for Patients with Exacerbations of COPD |
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| <ul style="list-style-type: none">• Inhaled β_2-agonists therapy is required no more frequently than every 4 hours.• Patient, if previously ambulatory, is able to walk across the room.• Patient is able to eat and sleep without frequent awakening by dyspnea.• Patient has been clinically stable for 12-24 hours.• Arterial blood gasses have been stable for 12-24 hours.• Patient (or home care giver) fully understands correct use of medications• Follow-up and home care arrangements have been completed (e.g., visiting nurse, oxygen delivery, meal provisions).• Patient family and physician are confident patient can manage successfully. |
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A comprehensive pulmonary rehabilitation program including exercise training, nutrition counseling, and education are effective when conducted in inpatient, outpatient, and home settings. The minimum duration of a successful program is two months, and it appears that the longer the program, the more effective the

results.

The long-term administration of oxygen (> 15 hours a day) is the only therapy that has been shown to reduce mortality. Oxygen therapy is indicated in patients with stage IV COPD and a PaO₂ < 55mm Hg or a PaO₂ < 60 mm hg with evidence of pulmonary hypertension, congestive heart failure, or polycythemia. The goal of therapy should be to increase baseline PaO₂ to at least 60mm Hg at rest. Routine mechanical ventilation does not appear to be beneficial.

Component 4: Manage Exacerbations

Exacerbation of symptoms in COPD often requires medical intervention and the mortality of patients requiring hospitalization is high. The most common causes are infection and air pollution, but often the cause is not readily apparent. The primary symptom of an exacerbation is increased breathlessness, which may be accompanied by wheezing, chest tightness, increased cough and sputum production, changes in the color and/or tenacity of the sputum, and fever. The severity of the exacerbation should be assessed using a complete medical history, lung function tests, arterial blood gas measurements, and other laboratory tests. A peak expiratory flow of < 100 L/minute or and FEV₁ < 1.00 L indicates a severe exacerbation. A paO₂ < 60 mm Hg and/or a SaO₂ < 90% indicates respiratory failure, and an arterial pH < 7.30 indicates a life-threatening episode. Chest X-rays and ECGs may be beneficial in identifying alternative diagnoses that may mimic the symptoms of an acute exacerbation. White blood cell counts are usually not helpful, and because COPD patients are chronically colonized with bacteria, sputum gram-stains are often not informative.

The primary strategies for the treatment of acute exacerbations are the intensification of bronchodilator therapy, systemic corticosteroids, and antimicrobial therapy. In more severe exacerbations, supplemental oxygen therapy or mechanical ventilation are necessary. If there is no indication for hospitalization (Table 6), patients may be treated at home. Frequency and/or doses of inhaled bronchodilators should be increased, and if a patient is not already on an inhaled anticholinergic, one may be added. High dose nebulized bronchodilators may be used for short-term treatment of the exacerbation; however, nebulized therapy should not be continued for the management of stable COPD. If the patient's FEV₁ is < 50% predicted, systemic corticosteroids should be considered. The recommended dose of prednisone is 40mf by mouth daily for 10 days. The role of bacterial infection as a cause of COPD exacerbation is controversial. It is suspected that approximately 50% of exacerbations are caused by infection with approximately half of these of bacterial origin. Antibiotics should be considered when patients with worsening dyspnea and cough also have increased sputum volume and purulence. The antibiotic chosen should reflect local resistance and sensitivity patterns for *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Ampicillin, amoxicillin, doxycycline, and sulfamethoxazole/trimethoprim are often effective, and there is no evidence to indicate that new, more expensive antibiotics are more effective.

Oxygen therapy is the cornerstone for the treatment of hospitalized patients. The goal is to achieve a PaO₂ > 60mm Hg or SaO₂ > 90%. Arterial blood gases should be evaluated approximately 30 minutes after oxygen therapy is initiated to insure appropriate oxygenation without CO₂ retention or acidosis. As with home treatment, bronchodilator therapy should be maximized. Although the role of aminophylline in the treatment of COPD exacerbations is controversial, the addition of oral theophylline or intravenous aminophylline may be considered. If these agents are used, close monitoring of serum theophylline concentrations is warranted to avoid adverse effects. The addition of oral or intravenous corticosteroids is recommended. Doses of 30-40mg of prednisone for 10-14 days are recommended. Therapy for longer than 2 weeks is not beneficial, and higher doses have a significant risk for adverse effects. As with home treatment, antibiotics should be used when patients with worsening dyspnea and cough also have increased sputum volume and purulence. Ventilatory support may also be necessary in severe cases.

Criteria for discharge from the hospital are shown in Table 7. A follow-up assessment should be scheduled for 4-6 weeks after hospital discharge. The assessment should include the patient's ability to cope in their usual environment, measurement of FEV₁, reassessment of inhaler technique, understanding of the recommended treatment option, and the need for long-term oxygen therapy and/or home nebulizer for patients with very severe COPD.

Summary

COPD can be a severe and debilitating disease. Smoking cessation is the only intervention known to slow the progression of the disease, and therapy is directed at the treatment of symptoms and the improvement of quality of life. Bronchodilators are the cornerstone of the management of stable disease, and therapy should be intensified in a step-wise fashion. Exacerbations are common, and are treated with increased bronchodilator therapy and corticosteroids. Antibiotics are only effective in patients with increased sputum volume and purulence.