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Hospitalist Update:

Treatment of Stable COPD: Recent Guidelines and Medication Update

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Chronic Obstructive Pulmonary Disease (COPD) is a preventable cause of morbidity and mortality that poses a significant public health burden. The disease is characterized by progressively worsening airflow limitation and chronic airway inflammation with hyperresponsiveness to noxious particles and gases. The airflow limitation seen in COPD is caused by disease of the small airways and parenchymal destruction (obstructive bronchiolitis and emphysema, respectively). The associated chronic inflammation can lead to structural changes with narrowing of the small airways, loss of lung elastic recoil, and diminished ability of the lungs to remain open during the expiratory phase. Previously used terminology to describe COPD may have failed to include the hallmark of the diagnosis, airflow limitation. The term emphysema refers to the destruction of gas exchanging surfaces of the lung, and is a pathological description of one characteristic of COPD. Another term, chronic bronchitis, defined as cough with sputum production for at least 3 months in each of 2 consecutive years, may be associated with normal spirometry.

Treatment options for COPD include both pharmacologic and non-pharmacologic varieties, typically added in a stepwise fashion with the goals of controlling symptoms, improving quality of life, and decreasing the frequency and severity of exacerbations. The goal of this review is to provide a guide for treatment of stable COPD, and has been taken from the most recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, last updated in April of 2011.

Severity classifications set forth by the GOLD guidelines are often used to assist with guiding therapy. In stage I disease, short-acting bronchodilators alone are typically adequate, with long-acting beta agonists (LABA) and inhaled corticosteroids (ICS) typically being added in a stepwise fashion in stage II disease. Classification of disease severity by gold criteria is as follows:

Stage I	Mild COPD	FEV1/FVC<0.70	$FEV_1 \geq 80\%$ normal
Stage II	Moderate COPD	FEV1/FVC<0.70	FEV_1 50-79% normal
Stage III	Severe COPD	FEV1/FVC<0.70	FEV_1 30-49% normal
Stage IV	Very Severe COPD	FEV1/FVC<0.70	FEV_1 <30% normal, or <50% normal with chronic respiratory failure present

Smoking cessation

In patients who smoke, cessation can influence progression of disease greater than any other intervention. Long-term quit rates as high as 25% have been reported with effective use of resources. Pharmacologic interventions to assist with cessation include nicotine replacement as well as multiple other pharmacologic therapies. When compared to placebo, nicotine replacement products are more effective and increase long-term smoking abstinence rates. Contraindications to this form of therapy include unstable coronary artery disease, untreated peptic ulcer disease, recent MI, and recent stroke. Medications available to assist with cessation include Varenicline, bupropion, and nortriptyline, all of which have shown an increase in long-term quit rates compared to placebo. In addition, counseling by healthcare providers for as little as 3 minutes regarding need for cessation creates quit rates of 5-10%. When all available modalities for cessation are combined quit rates have been shown to increase to 35% at one year.

Pharmacologic Therapy for Stable COPD

Again, the goal of therapy is to reduce symptoms, reduce the frequency and severity of exacerbations, and improve quality of life. Commonly used medications in the treatment of stable COPD include beta 2 agonists, anti-cholinergics, and inhaled corticosteroids in combination with long-acting beta agonists. The choice of a medication regimen is typically tailored based on patient response to therapy and cost. None of the available medications have shown to improve the long-term decline in lung function seen in COPD. For a list of commonly used medications, see table 3.3 in the most recent edition of the GOLD guidelines.

Bronchodilators:

Bronchodilators increase the FEV1 by decreasing airway smooth muscle tone and can be given on an as-needed or scheduled basis. Effective bronchodilation results in improved emptying of the lungs, reduction in hyperinflation, and increased exercise tolerance. Medications included in this class include beta-2 agonists, anti-cholinergics, and methylxanthines. Commonly used short-acting bronchodilators include albuterol, levalbuterol, and ipratropium bromide. Single or combination therapy is acceptable, but combination therapy with a short-acting beta-2 agonist and anti-cholinergic provides greater and more sustained improvements in FEV_1 compared to either class alone.

Methylxanthines provide modest bronchodilation, but their use is limited by interactions with other medications and potential toxicity. Routine use of methyl-xanthines is not recommended unless

other bronchodilators are not available or are unaffordable for long-term treatment. Long acting beta agonists (LABA), such as formoterol and salmeterol, improve FEV_1, lung volumes, dyspnea, quality of life, and exacerbation rates. Duration of action is 12 hours or more, although a long-acting beta-agonist with duration of action lasting 24 hours, Indacaterol, has recently become available.

Tiotropium is a long-acting anti-cholinergic bronchodilator that has a duration of action > 24 hours. It has been shown to reduce exacerbations and related hospitalizations, improve symptoms, and also to improve the effectiveness of pulmonary rehabilitation.

Corticosteroids, Inhaled:

Inhaled corticosteroids (ICS) can improve symptoms, lung function, quality of life, and reduce the frequency of exacerbations if used regularly in patients with an FEV_1 < 60% predicted. ICS are recommended for patients with severe and very severe airflow limitation and for patients with frequent exacerbations that are not controlled by LABA. There is no effect on long-term decline in FEV_1 or mortality, but it should be noted that withdrawal from treatment with ICS may lead to exacerbations of COPD.

Combination therapy with ICS and LABA is more effective than either class alone, and has been shown to reduce exacerbations and improve lung function and health status in patients with moderate to very severe COPD. One large prospective clinical trial showed no statistically significant effect of combination therapy on mortality, but meta-analysis indicated that combination therapy may reduce mortality. Combination of ICS/LABA with tiotropium has not been well studied, but has been shown to improve lung function and quality of life, and may lead to a reduction in the number of exacerbations.

Corticosteroids, systemic:

The numerous side effects associated with long-term treatment with corticosteroids limit their use clinically. Of particular importance is steroid-induced myopathy, which can lead to weakness, decreased functional ability, and respiratory failure. Routine use is not recommended.

Phosphodiesterase-4 Inhibitors:

These reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP. Roflumilast is a once daily oral medication of this class. It has no bronchodilator activity, but has been shown to improve FEV1 in patients treated with salmeterol or tiotropium. Roflumilast has been shown to reduce exacerbations that require corticosteroids by 15-20% in patients with chronic bronchitis, severe to very severe COPD, and a history of previous exacerbations. Use should be limited to this subset of patients.

Other Pharmacologic Treatments

Vaccines

The influenza vaccine can reduce serious illness and even death in COPD patients. Yearly vaccination is recommended. Pneumococcal vaccination is suggested for patients 65 years and older and ,

younger patients with comorbid conditions, and has also reduced the incidence of community-acquired pneumonia in COPD patients < 65 years of age with an FEV_1 < 40% predicted.

Alpha-1 Antitrypsin Augmentation Therapy

This therapy is reserved for young patients with severe hereditary alpha-1 antitrypsin deficiency and emphysema. Therapy is only available in select countries and is very expensive.

Antibiotics

Older studies have shown both continuous prophylactic antibiotics and antibiotic prophylaxis during winter months have no benefit in reducing the frequency of exacerbations. More recent studies have shown some beneficial effects of antibiotics on exacerbation rate, including a recent trial of daily azithromycin, but further studies are needed before this type of treatment can be recommended due to concern for antibiotic resistance. Hence at this time, antibiotics should be reserved for infection-induced exacerbations and other bacterial infections.

Mucolytic and Antioxidant Agents

Use of these agents has been investigated in multiple studies with differing results. The overall benefits are small, and routine use is not recommended.

Antitussives

Inhibition of cough in COPD is not recommended as this is an important protective mechanism for mucus clearance. Routine use of antitussives is not recommended.

Vasodilators

Pulmonary hypertension is believed to be associated with a worsened prognosis in COPD. While it would seem beneficial to reduce right ventricular afterload and improve oxygen delivery to the tissues, results of studies have been disappointing. Nitric oxide has been shown to worsen gas exchange by altering hypoxic vasoconstriction, creating increased blood flow to poorly ventilated lung units. This drug is contraindicated in stable COPD, and the use of endothelium-modulating agents as treatment for pulmonary hypertension in COPD patients is not recommended pending further studies.

Narcotics

In patients with very severe disease, dyspnea is effectively treated using oral or parenteral narcotics. Nebulized opiates may be effective, but definitive data is still lacking. Serious side effects can occur, and patients must be made aware of potential consequences of overuse.

Non-Pharmacologic Therapies

Pulmonary Rehabilitation:

Pulmonary rehabilitation focuses on problems that may not be addressed with normal medical management of COPD, including deconditioning, social isolation, depression, muscle wasting, and weight loss. Goals of pulmonary rehab include reducing symptoms, improving quality of life, and increasing physical and emotional participation in activities of daily life. Increases in peak workload, peak oxygen consumption, and endurance have been well documented as a result of pulmonary rehabilitation. The minimum duration of an effective program is six weeks, and the benefits continue to increase

with further increases in the duration of program. If a formal program is unavailable it is to advise graded increases in physical activity with a goal of 20 minutes per day. Most programs include exercise training, smoking cessation assistance, nutrition counseling, and education regarding COPD and medical therapy for the disease.

Other Treatments

Oxygen Therapy:

Administration of oxygen therapy for > 15 hours per day in patients with severe resting hypoxemia has been shown to increase their survival. Long-term oxygen therapy is indicated for those with:

- A PaO2 at or below 55 mmHg or SaO2 at or below 88% confirmed on two occasions over a three week period. This can be with or without hypercapnia.

(Or)

- A PaO2 between 55 and 60 mmHg, or SaO2 of 88% in the setting of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (Hct > 55%).
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Ventilatory Support:

Non-invasive ventilation (NIV) is being used more frequently in patients with stable, very severe COPD. There may be a survival benefit associated with NIV use, but quality of life remains unaffected. In those patients with both COPD and obstructive sleep apnea there are benefits in both survival and hospital admission rates with use of NIV.

Surgical Treatments

Multiple surgical interventions exist as potential treatment for very severe COPD, including Lung Volume Reduction Surgery, Bronchoscopic Lung Volume Reduction, Lung Transplantation, and Bullectomy. All carry significant operative and post-operative risks, and are typically associated with a higher health care cost when compared to medical management of COPD. Strict patient selection is required to optimize outcomes.

Summary

This review was intended to give general guidelines regarding medical management of stable COPD. The goal of therapy is to reduce symptoms, increase exercise tolerance, improve health status, reduce the frequency of exacerbations, prevent disease progression and reduce mortality. These goals should be reached with the fewest possible side effects from medications, which is often difficult given the number of comorbidities seen in COPD patients. The medications used for each particular patient are determined by patient response to therapy and cost of therapy. For full details, see the most recent set of GOLD guidelines, from which this material was obtained.

Useful References:

- *Global Initiative for Chronic Obstructive Lung Disease, Updated April 2011. www.goldcopd.org*
- *COPD: overview of definitions, epidemiology, and factors influencing its development. Rennard SI. Chest. 1998: 113 (4 Suppl): 235S*
- *Murray and Nadel's Textbook of Respiratory Medicine, 5th ed. Vol 3, Chapter39, pg 919-956.*