
COPD : STATE OF THE ART

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most common diseases that affect many people around the world, including the Chinese in North America. Precise prevalence, mortality and morbidity figures are not available. But, whatever figures available are most likely underestimated because the disease is often not recognized until it is moderately advanced. In the U.S., the prevalence has been increasing. An estimated 17 million peoples in the U.S. are diagnosed with COPD, and probably similar number are undiagnosed. COPD is now the fourth leading cause of death in the U.S. It is the only major chronic disease that is currently on the rise in prevalence and mortality. The WHO predicts that by 2020, COPD will rise from its current ranking as the 12th most prevalent disease worldwide to the 5th, and from the 6th most common cause of death to the 3rd. Health care costs due to COPD are staggering. In 1993, COPD accounted for \$ 14.7 billion in U.S. health care direct costs, plus an additional \$9.2 billion in indirect costs. Therapy for COPD patients, in particular those with advanced stage, is generally disappointing, and frustrated for both the doctors and patients. The relentless progression of the disease leaves the patient short of breath and debilitated. However, with the rapid advances in medical research and discovery in recent years, we now have a better understanding of the disease, leading to a more refined new definition of the disease and a few new treatment options. Today's discussion will focus on these recent advances about COPD.

DEFINITION

For many years, there have been different definitions of COPD. These make comparisons studies, such as prevalence, treatment success, and health care costs very difficult. To help clarify its diagnosis and recognition, The committee of the recently formed The Global Initiative for Chronic Obstructive Lung Disease (GOLD) developed a working consensus definition of COPD: "COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases". It encompasses chronic bronchitis and emphysema. Most patients with COPD have both chronic bronchitis and emphysema, but to different extent.

PATHOGENESIS

- Chronic inflammation – It is now clear that COPD is characterized by chronic inflammation throughout the airway, parenchyma and pulmonary vasculature. This inflammation is caused by exposure to inhaled noxious particles and gases from the various environmental risk factors. This inflammatory process is markedly different from that in asthma. Macrophages, T-lymphocytes (predominantly CD8+), and neutrophils are the inflammatory cells that are increased in COPD. Mediators involved in COPD include leukotriene B4 (LTB4), interleukin 8 (IL-8), and tumor necrosis factor-*a* (TNF-*a*). There is probably complex interaction between cells and mediators,

resulting in progressive obstructive changes in small airways and destruction of lung parenchyma in COPD.

- Protease-antiprotease imbalance – Proteases thought to cause emphysema, are normally counteracted by antiproteases. When there is an imbalance, e.g. in alpha-1 antitrypsin deficiency, emphysema develops.
- Oxidative stress – Oxidative stress may exacerbate COPD through several mechanisms, including the activation of the transcription factor nuclear factor- κ B (NF- κ B), which switches on the genes for TNF- α , interleukin-8, and other inflammatory proteins, and oxidative damage of antiproteases, such as alpha-1-antitrypsin and secretory leukoprotease inhibitor, thus enhancing inflammation and proteolytic injury.

DIAGNOSIS

A diagnosis of COPD should be considered in any patient who has the characteristic symptoms of chronic cough, chronic sputum production or dyspnea, and/or a history of exposure to risk factors for the disease, especially cigarette smoking. Physical examination is rarely diagnostic in COPD. Signs of airflow limitation are rarely present until the disease is at its advanced stages. Diagnosis of COPD is established by the presence of airflow limitation on spirometry measurement. Patients with COPD typically show a decrease in both FEV₁ (forced expiratory volume in one second) and FVC (forced vital capacity), but FEV₁ is more affected. A post-bronchodilator FEV₁ < 80% of the predicted value with a FEV₁/FVC < 70% confirms the presence of airflow limitation that is not fully reversible, and thus establish the diagnosis of COPD. The FEV₁/FVC is a more sensitive measure of airflow limitation, and a FEV₁/FVC < 70% is considered an early sign of airflow limitation in patient whose FEV₁ remains normal (> or = 80% of predicted).

Classification of COPD by Severity

The degree of spirometric abnormality generally reflects the severity of COPD. But the relationship between symptoms and the degree of airflow limitation is not perfect. Therefore, to assess the severity of the disease and develop a management plan for individual patient, both symptom and spirometry value should be considered. GOLD proposed the classification of COPD severity into four stages as shown in Table 1.

Table 1: Classification of COPD by Severity

STAGE	CHARACTERISTICS
0: At Risk	<ul style="list-style-type: none"> • Normal spirometry • Chronic symptoms (cough, sputum production)
I: Mild COPD	<ul style="list-style-type: none"> • FEV₁/FVC < 70% • FEV₁ > or = 80% predicted • With or without chronic symptoms (cough, sputum production)
II: Moderate COPD	<ul style="list-style-type: none"> • FEV₁/FVC < 70% • 30% < or = FEV₁ < 80% predicted (IIA: 50% < or = FEV₁ < 80%) (IIB: 30% < or = FEV₁ < 50%) • With or without chronic symptoms (cough, sputum, dyspnea)

STAGE	CHARACTERISTICS
III: Severe COPD	<ul style="list-style-type: none"> • FEV1/FVC < 70% • FEV1 < 30% predicted or FEV1 < 50% predicted <u>plus</u> respiratory failure or clinical signs of right heart failure

SELECTED TREATMENT MODALITIES

Risk Reduction

Reducing the risk factors that cause COPD, in particular the environmental factors, is important in preventing the onset and progression of COPD. Smoking cessation is the single most important, effective, and cost-effective therapeutic intervention to reduce the risk of developing COPD and to slow its progression. It is the only therapeutic intervention that can lessen or stop the rate of progression of COPD. Smoking cessation is crucial in the management of all stages of COPD, and patients should be encouraged to quit as soon as possible. It has been documented that mild pulmonary function abnormalities are completely reversible in smokers who have been smoking for a relatively short duration.

Bronchodilators

Bronchodilator medications are central to the management of COPD. These agents include sympathomimetic drugs (*B*-agonists), anticholinergic agents, and theophylline. There is ample evidence supporting the usefulness of these agents in relieving symptoms associated with COPD. Failure to respond to a single dose of bronchodilator on initial spirometric testing does not signify fixed airway obstruction. All these bronchodilators have been shown to increase exercise capacity in COPD, without necessarily producing significant changes in FEV1.

- Sympathomimetic Drugs – These agents have been the mainstays of treatment for COPD. *B*-2 agonists, with fewer cardiac side effects, are the drugs of choice. Because of their rapid onset of action, they are preferred in treating acute bronchospasm. The inhaled route of administration is preferred in order to maximize beneficial effects and minimize systemic adverse effects. Obtaining the maximal benefit from an aerosol MDI (meter-dose inhaler) requires the proper use of the device. It is imperative that proper techniques be demonstrated to the patient. If necessary, a spacer can be employed. The new dry powder inhaler is breath-activated, and therefore, no hand-breath coordination is required for its use. It is more user friendly. The long acting preparations, salmeterol and formoterol, have recently been shown to be effective bronchodilators in COPD. They have the advantage of twice daily dosing. Tachyphylaxis has not been shown.
- Anticholinergic Agents – These agents are effective bronchodilators in the treatment of COPD. Ipratropium bromide is a synthetic derivative of atropine given by inhalation. It has a slower onset and longer duration of action when compared to short-acting *B*-2-agonists. A long-acting anticholinergic agent, tiotropium bromide, was recently released, but not yet available in the U.S. Tiotropium is very long acting due to its affinity to M3 receptors. Studies have demonstrated that FEV1 is significantly better in patients on tiotropium when compared with placebo.

- Theophylline – Although the use of theophylline in the treatment of COPD is controversial, mainly because of its narrow therapeutic index, several studies have shown that theophylline provides clear benefits to patients with COPD. When used appropriately, theophylline remains a useful drug in the management of COPD. Recognizing its potential toxicity, patients should be treated with lower dosage, aiming for serum levels of 8-12 $\mu\text{g/ml}$.

Combination therapy of bronchodilators with different mechanisms of action produces more bronchodilation than single drug alone. It can also be used to lessen side effects of medications. Therefore, combination of a *B*-2 agonist, an anticholinergic, and/or theophylline can be employed to achieve additional improvements in lung function and quality of life.

Corticosteroids

Both systemic and inhaled corticosteroids have been proven to be effective and beneficial in the treatment of bronchial asthma. However, their efficacy in COPD is not as clear-cut. There are studies that have shown objective improvement in airway obstruction in some patients receiving systemic corticosteroids. Similarly, there are reports showing definitive improvement in airflow obstruction, airway inflammation, and symptoms with inhaled corticosteroids in COPD. But they do not slow the rate of decline in FEV1 in these patients. Many existing COPD guidelines recommend the use of a short course (2-3 weeks) of systemic corticosteroids to identify COPD patients who might benefit from long-term treatment with systemic or inhaled corticosteroids. But there is increasing evidence that it is a poor predictor of the long-term response to inhaled corticosteroids. Instead, the present guidelines recommend a trial of 6 weeks to 3 months with inhaled corticosteroids to identify such patients. Regular treatment with inhaled corticosteroid is only appropriate for symptomatic COPD patient with a documented spirometric response, or in those with a FEV1 < 50% of predicted (stage IIB and stage III COPD) and repeated exacerbations requiring treatment with antibiotics or systemic corticosteroids. Systemic corticosteroids are mainly used during acute exacerbations of COPD. Long-term treatment with oral systemic corticosteroids is not recommended in COPD.

Long-term Supplemental Oxygen Therapy

Studies have repeatedly confirmed the benefits of long-term oxygen therapy in the management of patient with severe COPD. It is the only therapy that increases the survival in hypoxemic patients with COPD, in addition to improving their symptoms and quality of life. The goal is to maintain a PaO₂ of at least 60 mmHg (SaO₂ of 90%). Indications for long-term oxygen therapy are listed in Table 2.

Table 2: Indications for Long-term Oxygen Therapy in COPD

At Rest (room air)	PaO ₂ = or < 55 mmHg; or SaO ₂ = or < 88% PaO ₂ = 56-59 mmHg; or SaO ₂ = 89%; with: hematocrit >56%, or cor pulmonale, or right heart failure
During Exercise (room air)	PaO ₂ = or < 55 mmHg; or SaO ₂ = or < 88%
During Sleep (room air)	PaO ₂ = or < 55 mmHg; or SaO ₂ = or < 88% PaO ₂ drop > 10 mmHg; or SaO ₂ drop > 5%; with symptoms and signs of hypoxemia

Pulmonary Rehabilitation

Pulmonary rehabilitation attempts to get patients back to their best possible functional capacity. Many studies have confirmed the overall usefulness of a comprehensive pulmonary rehabilitation program. The benefits include improvement in dyspnea, exercise endurance, and quality of life. It may also decrease the rate of repeated hospitalization and total hospital days. However, pulmonary rehabilitation does not usually improve lung function. For many years, pulmonary rehabilitation was not covered by medical insurance. But starting November 2001, it is now covered by Medicare in New York State.

Surgical Treatments

There is no pharmacological treatment for emphysema and the component of airway obstruction resulting from loss of elastic recoil in emphysema. The disease process is irreversible. Therefore, it is logical to explore surgical approach.

Bullectomy

Bullectomy has been proven effective in patient with bullous emphysema, who has a giant bulla or bilateral bullae, with dyspnea and obstructive airway dysfunction. Giant bulla is defined as bulla that occupies at least one-third of the hemithorax. Bullectomy can be done via standard thoracotomy or VATS (video-assisted thoracic surgery). The improvement in lung function and dyspnea tends to correlate with the size of the bullae, that is, the larger the bulla(e), the better the improvement after surgery.

Lung Volume Reduction Surgery (LVRS)

LVRS is a surgical procedure, specifically designed for patients with severe emphysema. Dr. Otto Brantigan pioneered the surgery in the 1950's. Despite symptomatic improvement, the operation was abandoned due to high post-operative mortality rate. With recent advances in surgical technique, Dr. Joel Cooper in St. Louis reintroduced LVRS in 1993. Surgery involves removing 20-30% of the most diseased part of the emphysema lungs. Data from several studies, including our own at Columbia-Presbyterian Medical Center, showed that carefully selected patients with emphysema do benefit from LVRS. In successful cases, following LVRS, there is objective improvement in pulmonary function (including arterial oxygenation), dyspnea, exercise capacity, and quality of life indices. Patients with localized upper lobe emphysema appear to do the best. Data from several studies have shown that the improvement seems to last for 3-4 years. Most patients started to have deteriorating pulmonary function after 3-4 years post-LVRS. But symptomatically and objectively, they are still better than prior to LVRS.

Probable mechanisms of improvement with LVRS include:

- Improved lung and chest wall mechanics
- Improved respiratory muscle function
- Decompression of relatively more normal lung

Because of the uncertainty of the risk of LVRS, the magnitude and duration of its benefit, and the selection of optimal candidate, as well as many other unanswered questions and cost, Medicare stopped paying for the procedure in 12/95. HCFA and NIH began a multi-center, randomized trial to evaluate this surgery, the National Emphysema Treatment Trial (NETT). In this trial, patients are

randomized to best medical treatment for 5 years, or best medical treatment plus LVRS. The study is still ongoing. But the safety monitoring board of NETT released a preliminary finding a few months ago. It reported a subgroup of patients in the trial who are at substantial increased risk for death if they undergo LVRS. The article is somewhat misleadingly entitled, "Patients at High Risk of Death after LVRS". The characteristics of patients at high risk were FEV1 < or = 20% of predicted, and either DLco < or = 20% of predicted, or homogeneous distribution of emphysema on high resolution CT scan. The 30-day mortality for the patients treated surgically in the small group was 16%, while that of the medically treated group was zero. It is important not to assume the result of the majority of patients enter into the NETT trial. The final results of the NETT are not yet available. But for now, NETT has clearly shown that patients with FEV1 of < or = 20% of predicted who has either homogeneous pattern of emphysema on HRCT, or DLco of < or = 20% of predicted should not be operated on.

Lung Transplantation

Lung transplantation is now considered a very viable therapeutic modality in patients with very advanced COPD. In appropriately selected patients, lung transplantation has been shown to improve quality of life and functional capacity. Single lung transplantation is the most common procedure for COPD (emphysema).

GENERAL APPROACH TO CURRENT MANAGEMENT OF COPD

With the new understanding of the disease process, a new approach of management should be adopted. Treatment regimen should be initiated according to the severity of the disease, using the new proposed staging system as a guide. After the diagnosis of COPD is established, education about the disease should be undertaken, so that the patient has a better understanding of the illness and can take an active role in its management. Avoidance of risk factors should be instituted. Smoking cessation should be emphasized and demanded. Influenza and pneumococcal vaccine should be given routinely to COPD patients of all stages. Pharmacotherapy is recommended in patients who are symptomatic. It should be instituted in a stepwise fashion according to the severity of symptoms and stage of the disease. Recommended treatment at each stage of COPD according to the GOLD guideline is shown in Table 3. In mild stage I disease, short-acting bronchodilator, such as a *B*-2-agonist, can be given on an as needed basis for intermittent symptoms. When symptoms are more persistent, or in stage II disease, regular treatment with one or more bronchodilators can be used. Inhaled corticosteroids can be tried when symptoms are significant. If there is positive response in symptoms or lung function, inhaled corticosteroids can be continued on a regular basis. In stage IIB or stage III disease, when there are repeated exacerbations, inhaled corticosteroids should be part of the regular regimen in an attempt to reduce the frequency of exacerbations. Pulmonary rehabilitation should be part of the treatment program in patients at all stages of disease, particularly those who remain symptomatic and are restricted in their daily activities despite maximal pharmacotherapy. When excessive secretions are present, measures to mobilize them, such as chest physiotherapy, can be instituted. Long-term oxygen therapy is indicated in patients with hypoxemia. For appropriate candidates, surgical treatment with bullectomy, lung volume reduction surgery, or lung transplantation should be considered. Close attention to psychosocial problems and their appropriate treatment is also important in the overall management of patients with COPD.

Table 3: Therapy of COPD

STAGE	RECOMMENDED TREATMENT
All	<ul style="list-style-type: none"> • Avoidance of risk factors • Influenza and pneumococcal vaccination
0: At risk	
I: Mild COPD	<ul style="list-style-type: none"> • Short-acting bronchodilator when needed
IIA: Moderate COPD	<ul style="list-style-type: none"> • Regular treatment with one or more bronchodilators • Inhaled corticosteroids if significant symptoms and lung function response • Pulmonary rehabilitation
IIB: Moderate COPD	<ul style="list-style-type: none"> • Regular treatment with one or more bronchodilators • Inhaled corticosteroids if significant symptoms and lung function response or if repeated exacerbations • Pulmonary rehabilitation
III: Severe COPD	<ul style="list-style-type: none"> • Regular treatment with one or more bronchodilators • Inhaled corticosteroids if significant symptoms and lung function response or if repeated exacerbations • Pulmonary rehabilitation • Long-term oxygen therapy if respiratory failure • Consider surgical treatments

THE FUTURE – POTENTIAL NEW TREATMENT

With a better understanding of the cellular and molecular mechanisms involved in COPD, new molecular targets become available for the development of drugs. There are several classes of new drugs that are being developed, and could potentially be the new treatment for COPD in the near future.

- Mediator Antagonists – 5-lipoxygenase inhibitors, specific leukotriene B₄ antagonists, specific antagonists of CXCR2 (one of the receptors on neutrophils that are activated by interleukin-8), humanized antibodies and soluble receptors that block TNF- α , and antioxidants
- Protease Inhibitors – Inhibitors of neutrophil elastase, matrix metalloproteinase inhibitors, human recombinant protease inhibitors, and gene therapy
- New Antiinflammatory Drugs – phosphodiesterase 4 inhibitors, inhibitors of NF- κ B, inhibitors of p38 mitogen-activated protein kinase, and interleukin-10

CONCLUSION

The state of the art of COPD is such that the disease continues to have a high prevalence, morbidity, mortality, and health care costs throughout the world. We should focus on prevention and detection with subsequent appropriate treatment of the disease. COPD remains very much under diagnosed. It is extremely important to detect the disease at an early stage before symptoms begin. So that we can prevent the disease from progressing to the point at which the patients suffer severely, and large amount of medical resources are spent. Although smoking cessation is the only strategy that may abate the relentless progression of airflow limitation, as discussed earlier, several treatment measures

are currently available that can reduce the symptoms of COPD. The view of COPD as an untreatable disease should be abandoned, and replaced by a positive approach to management with combination of these measures to improve the quality of life in symptomatic patients. With the recent advances in research and better understanding of the disease, it is a matter of time that more effective drugs and therapies will become available to relieve the sufferings of patients with COPD.

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