Chronic Obstructive Pulmonary Disease (COPD)

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health issue. It is one of the most common causes of morbidity and mortality in the world, and is increasing in prevalence. COPD is characterized by a slow, progressive airflow limitation that is mostly irreversible. Chronic inflammation, most often caused by **cigarette smoking**, leads to fixed narrowing of the small **airways** and alveolar wall destruction. Current therapies are ineffective in preventing the continual progression of airflow limitation that characterizes the disease.

Definition

Chronic obstructive pulmonary disease has been defined by the Global Initiative on Obstructive Lung Disease (GOLD) as a disease state characterized by airflow limitation that is not fully reversible Pauwels et al (2001). The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the **lungs** to noxious particles and gases.

Classification

Chronic obstructive pulmonary disease (COPD) is classified as a chronic inflammatory lung disease. Most patients with COPD present with three pathological characteristics: (a) chronic obstructive **bronchitis**, (b) emphysema, and (c) mucus plugging Barnes (2002).

Consequences

Chronic obstruction of the small airways associated with chronic obstructive pulmonary disease (COPD) can lead to a significant reduction in **lung function** and gas exchange. This may lead to oxygen deprivation in cells and tissues throughout the body. Death may result from severe cases of COPD.

Associated Disorders

Chronic obstructive pulmonary disease (COPD) includes (a) chronic **bronchitis** with fibrosis and obstruction of small **airways** and (b) emphysema with enlargement of airspaces and destruction of lung parenchyma, loss of lung elasticity, and closure of small airways Barnes (2003a). Emphysema is defined as a chronic pulmonary disease characterized by an increase in the normal size of air spaces distal to the terminal bronchioles, with destructive changes in their walls. Chronic bronchitis is defined by a productive **cough** of more than three months duration for more than two successive years caused by mucus

hypersecretion. However, unlike COPD, chronic bronchitis is not usually associated with airflow limitation. COPD differs from **asthma** in that airflow limitation is mostly irreversible, whereas the airflow obstruction associated with asthma is usually reversible in early stages, either spontaneously or with treatment.

Etiology

Long-term **cigarette smoking** is the most frequent cause of chronic obstructive pulmonary disease (COPD), accounting for 80–90% of all cases (www.lungusa.org/press/lung_dis/asn_copdback.html). Although smoking is the major risk factor for the development of COPD, only a small percentage of smokers (10–20 %) develop the disease Weiss et al (2003). This variable response to cigarette smoking clearly suggests genetic susceptibility. Other **environmental** factors may include air pollution and exposure to cooking fumes in developing countries Barnes (2003b).

Epidemiology

The exact prevalence of COPD is not known. In 1994, it was estimated that 16 million individuals were diagnosed with chronic obstructive pulmonary disease (COPD) in the United States, whereas another 16 million were undiagnosed Petty (1997). It was the fourth leading cause of death in the United States in 1998, accounting for 112,584 deaths National Center for Health Statistics (1999). It is the most steeply rising cause of death in individuals over 65 years of age, which represents the most rapidly growing segment of the population in the United States Weiss et al (2003). COPD accounted for 13.2 million doctor visits in 1997 National Center for Health Statistics (1999). There were 668,362 hospitalizations for which COPD was the first-listed discharge diagnosis in 1998 National Center for Health Statistics (2000a), National Center for Health Statistics (2000b). COPD costs the United States economy an estimated 31.9 billion dollars a year (www.lungusa.org/press/lung_dis/asn_copdback.html). The World Health Organization-World Bank predictions for the increase in the global burden of common diseases worldwide indicate that COPD will rise from sixth to third ranking, and in morbidity from twelfth to fifth by 2020 Lopez and Murray (1998).

Pathophysiology

COPD is characterized by acceleration in the normal decline of **lung function** with age. The pathological cellular and molecular mechanisms of COPD have been, for the most part, largely undefined. Recent evidence indicates that chronic inflammation of the small airways and lung parenchyma develops in response to inhalation exposure to **cigarette smoke** or other **environmental** stimuli, such as air pollution or cooking fumes, in susceptible individuals. The resulting inflammation develops into fibrosis with narrowing of the small airways (chronic obstructive **bronchitis**) and lung parenchymal destruction due to the action of various inflammatory cell-mediated proteases Barnes (2002). A variety of immune cells, including neutrophils, macrophages, and cytotoxic ($CD8^+$) T-lymphocytes, are recruited into the lungs and become activated. Increased numbers of neutrophils are found in the sputum and recovered bronchoalveolar lavage fluid (BALF) of COPD patients. Neutrophils secrete serine proteases, such as neutrophil elastase, **cathepsin G**, proteinase-3, which may contribute to alveolar destruction. A marked increase in macrophage number has been observed in the airways, lung parenchyma, BALF, and sputum of

COPD patients. There is a correlation between macrophage number and severity of COPD Di Stefano et al (1998). Macrophages may be activated by cigarette smoke to release inflammatory mediators, such as **tumor necrosis factor-alpha** and **interleukin-8**, initiating the development of cellular inflammation. Mounting evidence suggests involvement of matrix metalloproteinases (MMPs) in COPD Barnes (2003a). Expression of MMPs has been elevated in the BALF, and macrophages of COPD patients are likely involved in the destruction of exposed lung tissue. In addition, increased oxidative stress is implicated as a possible mechanism by which the lungs become damaged in COP D. Cigarette smoke, as well as activated neutrophils and macrophages, expose lung cells and tissues to high concentrations of damaging reactive oxygen species.

Signs and Symptoms

The development of chronic obstructive pulmonary disease (COPD) can be described in three stages (www.lungusa.org/press/lung_dis/asn_copdback.html): (a) Stage 1: **Lung function**, as measured by forced expiratory volume in one second (FEV_1), is greater than or equal to 50% of predicted normal lung function with a minimal impact on health-related quality of life. Symptoms may progress during this stage as patients begin to experience severe breathlessness (b) Stage 2: FEV_1 is 35–49% of predicted normal lung function with a significant impact on health-related quality of life (c) Stage 3: FEV_1 is less than 35% of predicted normal lung function with a profound impact on health-related quality of life. Respiratory symptoms of COPD include chronic **cough**, chest tightness, shortness of breath, an increased effort to breathe, increased mucus production and frequent clearing of the throat. In addition, systemic symptoms have been observed with COPD and are likely the result of oxygen deprivation and exposure to circulating pro-inflammatory mediators Agusti et al (2003), Wouters (2002). Systemic effects associated with COPD include weight loss, skeletal muscle dysfunction, **depression**, **headache**, sleeplessness, impaired mental ability and irritability.

Standard Therapies

Treatment of chronic obstructive pulmonary disease (COPD) is mostly symptomatic. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has developed guidelines for the treatment of this condition Pauwels et al (2001). The steps include: a) establish diagnosis and assess symptoms b) stop **smoking**, change unhealthy lifestyle habits, immunization against **influenza** c) treat obstruction with bronchodilators d) assess hypoxia, possibly treat with long-term oxygen therapy e) establish pulmonary rehabilitation program.

Smoking cessation is the only therapeutic intervention that has been shown to reduce disease progression Barnes (2002). **Nicotine**-replacement therapy may be required. Bronchodilators are the mainstay of drug therapy and may improve shortness of breath. The choice of bronchodilators includes anticholinergics, beta-2 adrenoceptor agonists, and **theophylline**. Often, a combination of bronchodilators from different drug classes is given to treat the symptoms of COP D. Combining bronchodilators may improve efficacy in the treatment of COPD and decrease side effects as compared with increasing the dose of a single bronchodilator MacNee and Calverley (2003). Inhaled corticosteroids are commonly prescribed for COPD, but their use is controversial. Long-term studies indicate that corticosteroids do not reduce the inflammatory response in COPD or prevent the progression of the disease Barnes (2002). Because poor oxygenation is one of the fundamental problems associated with COPD, supplemental oxygen is an important

part of therapy for those with severe disease Barnes (2003b). Long-term oxygen therapy (>15 hrs/day) has been shown to prolong survival (~30 %) of these patients.

Agent Name	Discussion
Anticholinergics	Anticholinergics, such as **ipratropium** bromide and tiotropium bromide, are the most effective group of bronchodilators in the treatment of chronic obstructive pulmonary disease (COPD). By blocking **cholinergic muscarinic receptors**, these drugs inhibit the vagal cholinergic tone that is responsible for airflow obstruction associated with this condition Barnes (2003b). In addition, anticholinergics reduce mucus hypersecretion. Ipratropium bromide is usually given 3–4 times daily by **inhalation or nebulizer**. Systemic absorption of ipratropium is minimal, and side effects are uncommon. Tiotropium bromide is a newer anticholinergic that can be given once daily. It is well-tolerated and highly effective in the treatment of COP D. Its systemic side effects are minimal.
Beta-2 Adrenoceptor agonists	Short-acting beta-2 adrenoceptor agonists, such as **albuterol** and **terbutaline**, are given by nebulizer on an ''as required'' basis for symptomatic relief of breathing difficulties associated with COP D. Long-acting beta-2 agonists, such as **salmeterol** and **formoterol**, have a duration of action of 12 hours and significantly improve the respiratory symptoms, exercise capacity, and health status of those with chronic obstructive pulmonary disease MacNee and Calverley (2003).
Theophylline	Theophylline is the third choice of pharmacotherapy behind anticholinergics and beta-2 adrenoceptor agonists in the management of chronic obstructive pulmonary disease. It is a non-selective inhibitor of **cyclic nucleotide phosphodiesterase**. A bronchodilator, theophylline improves symptoms of COPD by deflating the lungs, most likely through an action on **peripheral airways**Barnes (2003b). Theophylline has a narrow therapeutic index, limiting its use. Plasma drug levels of theophylline should be monitored, especially in elderly patients. Cigarette smoking, age, cardiac failure, liver disease, **pneumonia** and drugs, such as **macrolide antibiotics**, **ciprofloxacin**, **allopurinol** and **cimetidine**, interfere with **hepatic metabolism** of theophylline and therefore, may affect its plasma concentration.

Experimental Therapies

Potential new strategies for the treatment of COPD have focused on reducing **pulmonary** inflammation. Thus, therapeutic intervention has been directed toward mediators involved in the recruitment and activation of neutrophils as well as the production of reactive oxygen species and inflammatory mediators associated with the increased oxidative stress Barnes (2002). Additionally, there is compelling evidence for an imbalance between proteases and antiproteases that control the digestion of lung elastin in COP D. It has been hypothesized that the inhibition of these proteolytic enzymes, or the elevation in endogenous antiproteases, may prevent the progression of airflow obstruction in COPD Barnes (2002). New therapeutic approaches in the treatment of COPD are being developed to control elastin digestion in emphysema by inhibiting proteases.

Agent Name	Discussion
Leukotriene-B-4 (LTB-4) inhibitors	**Leukotriene-B-4 (LTB-4)** is a potent chemoattractant of neutrophils and is increased in the sputum of patients with chronic obstructive pulmonary disease Barnes (2002). Selective LTB-4-receptor antagonists, such as **LY29311**, SC53228, CP105696, SB201146, and BIIL284, are in clinical development.

Chemokine inhibitors	Chemokines of the CXC family, such as **interleukin-8 (IL-8)**, are involved in neutrophil chemotaxis. A human monoclonal antibody specific for IL-8 blocks neutrophil chemotaxis and is currently in clinical trials Barnes (2002). Inhibitors of **CXC chemokine receptors**, such as **CXCR1**, **CXCR2**, have also been developed and are in clinical trials.
Tumor necrosis factor-alpha (TNF-alpha) inhibitors	Tumor necrosis factor-alpha (TNF-alpha) levels are increased in the sputum of COPD patients Barnes (2002). Infliximab, a monoclonal anti-TNF-alpha antibody, and **etanercept**, a **TNF-alpha receptor** inhibitor, are effective in other chronic inflammatory diseases and may be useful in the management of COPD.
Antioxidants	Oxidative stress is elevated in patients with COPD Barnes (2002). Accordingly, antioxidants, such as **N-acetyl cysteine**, have been used in the treatment of this condition. A small, but significant, reduction in exacerbations of COPD has been observed with oral N-acetyl cysteine treatment. Other antioxidants, such as glutathione compounds, superoxide dismutase analogues, and selenium-based drugs, are in development as pharmacotherapies for COPD.
Phosphodiesterase-4 (PDE-4) inhibitors	Phosphodiesterase-4 (PDE-4) is expressed in neutrophils, CD8+ T-cells and macrophages. Cilomilast and roflumilast, selective PDE-4 inhibitors, are effective in controlling neutrophil inflammation in animals and have been found to display some beneficial effects in patients with chronic obstructive pulmonary disease Barnes (2002).
Protease inhibitors	Small-molecule inhibitors of proteases, such as ONO5046 and FR901277, have been developed. These agents inhibit neutrophil elastase, **cathepsin G** and proteinase 3 Barnes (2002). These inhibitors have entered clinical trials. Matrix metalloproteinases (MMPs) also have been proposed to be a target for drug therapy. MMPs inhibitors, such as **marimastat**, are currently being developed.
Remodeling agents	Loss of elastic recoil and the proteolytic destruction of the lung parenchyma are hallmarks of COP D. New drug therapy strategies are directed towards preventing the enzymatic disease process associated with COP D. Retinoic acid has been observed to increase the number of alveoli in developing rats as well as reverse the histological and physiological changes induced by elastase treatment of adult rats Barnes (2002). Agonists of retinoic acid receptor subtypes have been developed and are currently being examined in clinical trials as a treatment for emphysema.

Animal Models

A single intratracheal instillation of elastase induces emphysema in laboratory animals. The response is characterized by a rapid neutrophil influx in the **lungs**, release of extracellular matrix fragments in to the airspaces, and destruction of the alveolar walls Snider (1992). After resolution of the initial acute inflammatory response there is considerable alveolar remodeling of damaged alveolar structures with loss of compliance and airflow obstruction comparable to what is seen in humans with advanced emphysema. Elastase-induced emphysema remains a useful model because it is relatively simple to perform, replicates many aspects of the disease and has been of value in assessing the efficacy of new therapeutic agents Shapiro (2000). However, exposure to **cigarette smoke** may cause a variety of other abnormalities not observed in this model. While smoke-induced animal models of emphysema have been

developed, they have yielded inconsistent results regarding chronic mucus hypersecretion and inflammation Costa and Kodavanti (2003). Because there is considerable species-to-species variation in the degree and/or presence of the different abnormalities associated with smoke-induced emphysema, care must be exercised in the interpretation of the results from animal studies Wright and Churg (2002). In addition, very little information is available on the biochemical and molecular changes induced by cigarette smoke in animal models. The use of transgenic animal models should provide a new methodology to study cigarette smoke-induced emphysema in the future. Studies are ongoing using strains of mice deficient in individual candidate proteinases, such as MMP-12, which may be involved in the pathogenesis of cigarette smoke-induced emphysema Shapiro (2000).

Other Information – Web Sites

This is a freely accessible website maintained by the American Lung Association that gives a brief but informative background of COPD: www.lungusa.org/press/lung_dis/asn_copdback.html
COPD international is a free website that provides information and interactive support for COPD patients and caregivers: www.copd-international.com
This is a free website maintained by the Global Initiative for Chronic Obstructive Lung Disease that provides up-to-date information on COPD treatment and management strategies: www.goldcopd.com

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Further Reading

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