Clinical reviews in allergy and immunology

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Management of chronic obstructive pulmonary disease: Moving beyond the asthma algorithm

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Activity Objectives

1. To identify therapeutic options for chronic obstructive pulmonary disease (COPD): evidence based on prospective controlled trials.
2. To describe specific benefits of pharmacologic agents (inhaled corticosteroids [ICSs], long-acting β-agonists, and anticholinergics) in patients with COPD.
3. To describe the benefits of nonpharmacologic therapies in patients with COPD.
4. To name the recommended vaccinations for patients with COPD.

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For many years, chronic obstructive pulmonary disease (COPD) was considered a disease of fixed airflow obstruction for which there was no good treatment. Out of desperation and frustration, health care providers extrapolated from asthma to COPD, and standard asthma therapy was adopted without evidence for efficacy. In recent years, we have gained a better understanding of the pathophysiologic differences between asthma and COPD, and prospective controlled trials have provided a rationale for therapy. Smoking cessation is critically important, both as primary prevention and as an effective way to slow the decrease in lung function in patients with established disease. β_2-Adrenergic and anticholinergic agonists improve lung function and relieve symptoms in most patients. Tiotropium improves exercise tolerance and quality of life and reduces exacerbations and hospitalizations. The increase in lung function seen with tiotropium is sustained with continued use over at least 3 to 4 years. Inhaled corticosteroids decrease exacerbations and improve quality of life, and their effect seems greatest in patients with lower lung function and in exacerbation-prone patients. There is no evidence that inhaled corticosteroids alone affect mortality, despite the reduction in exacerbations and increased risk of pneumonia. In some patient populations, inhaled fluticasone, salmeterol, or the combination might slow the rate of loss of lung function. Rather than reflexively using effective asthma therapy in the patient with COPD, current and future therapy for COPD is increasingly evidence based and targeted to specific inflammatory pathways that are important in patients with COPD. (J Allergy Clin Immunol 2009;124:873-80.)

Key words: *Chronic obstructive pulmonary disease, asthma, airflow obstruction, inhaled corticosteroids, oral corticosteroids, bronchodilators, long-acting bronchodilators, β_2-agonists, anticholinergics, mucolytics, antioxidants, pulmonary rehabilitation, home oxygen, smoking cessation, immunization*

Chronic obstructive pulmonary disease (COPD) and asthma are chronic lung diseases characterized by airway inflammation and airflow limitation, which is variably reversible. Both are associated with high morbidity and cost to the community.[1] The pathogenesis of both diseases depends on the critical interaction between environmental stimuli and a genetically predisposed host. Aeroallergens, air pollutants, and infections are key triggers

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Abbreviations used
COPD: Chronic obstructive pulmonary disease
FVC: Forced vital capacity
ISOLDE: Inhaled Steroids in Obstructive Lung Disease
OR: Odds ratio
TORCH: Towards a Revolution in COPD Health

of asthma exacerbations.[2] In the United States and most of the developed world, cigarette smoking is the single most important cause of COPD[3]; in undeveloped countries biomass fuel has been implicated.[4] Inhaled corticosteroids improve asthma control, decrease exacerbations, and help to maintain lung function over time.[5] Until recently, smoking cessation was believed to be the only intervention that reduced the accelerated rate of decrease of lung function that characterizes COPD.[6] More recently, pharmacologic therapy has been shown to be effective. Unlike asthma, which is characterized predominantly by airway inflammation without structural changes, COPD encompasses the 2 distinct but often related processes of chronic bronchitis and emphysema, both of which result in structural changes that limit airflow. Chronic bronchitis is an inflammatory condition of the large and small airways that results in enlargement of mucus glands, increased numbers of goblet cells, and mucus hypersecretion. Emphysema involves destruction of the lung parenchyma with dilation and destruction of the respiratory bronchioles. The inflammatory patterns seen in patients with asthma and COPD are distinct, with eosinophils and T_H2 cells predominating in those with asthma, and macrophages, neutrophils, and $CD8^+$ lymphocytes playing key roles in COPD.[7] These cellular patterns are mediated by overlapping but distinct networks of proinflammatory cytokines, chemokines, and growth factors. Although T_H2 cytokines, such as IL-13, IL-4, and IL-5, as well as chemokines, such as stem cell factor and thymic stromal lymphopoietin, play an important role in asthma, COPD pathogenesis appears to be dominated by TGF-β, TNF-α, fibroblast growth factor, IL-1β, and IL-6.[7] Inhaled and systemic corticosteroids, respectively, are the mainstay of therapy for stable asthma and for acute exacerbations of asthma and COPD and are aimed at decreasing airway inflammation. However, the elucidation of distinct inflammatory networks involved in COPD and asthma promises the development of novel, targeted immunologic therapies. Although asthma is a disease of reversible airflow obstruction that can become fixed in some patients, COPD has been characterized classically by a lack of major reversibility of airflow obstruction. However, like asthmatic subjects, patients with COPD often experience symptomatic and objective improvement with β_2-agonists and anticholinergic bronchodilator medications. Thus these agents are widely used and recommended in the management of both asthma and COPD.

CORTICOSTEROIDS

Inhaled corticosteroids

Although the inflammatory process differs in asthma and COPD, inhaled corticosteroids, which are aimed at decreasing airway inflammation, form the basis for management of symptoms of stable disease. In patients with asthma, inhaled corticosteroids decrease airway inflammation, improve lung function, reduce symptoms and airway hyperresponsiveness, and prevent exacerbations and mortality.[8-14] Until recently, a role for inhaled corticosteroids in the treatment of COPD has been less clear. A number of studies have suggested that inhaled corticosteroid therapy reduces both local and systemic inflammation in patients with COPD. In a double-blind, randomized, placebo-controlled study of 30 patients comparing 500 μg of fluticasone inhaled twice daily with placebo, airway biopsy confirmed that the predominant inflammatory cell types in the airways of patients with COPD include $CD8^+$ T cells, macrophages, and neutrophils and that fluticasone reduced subepithelial mast cell numbers and the ratio of CD8/CD4 T cells in the epithelium.[15] These results were not replicated in a study of fluticasone versus placebo over 6 months in 23 patients with COPD.[16] Additionally, a number of studies have examined the effects of inhaled corticosteroid therapy on inflammatory indices in the sputum of patients with COPD and have demonstrated little effect.[17-19] However, similar studies analyzing inflammatory indices in bronchoalveolar lavage fluid have shown that inhaled corticosteroid therapy reduces cellularity, as well as levels of albumin, lactoferrin, lysozyme, and IL-8.[20,21] Finally, Sin et al[22] demonstrated that the use of inhaled corticosteroid therapy in patients with mild-to-moderate COPD reduced plasma levels of C-reactive protein; however, other investigators have been unable to demonstrate effects on cytokine production from PBMCs studied *ex vivo*.[23]

Unlike asthma, it has been difficult to demonstrate convincing clinical benefits from the daily use of inhaled corticosteroids in patients with COPD, despite clear evidence of both systemic and airway inflammation. In a recent meta-analysis performed by Drummond et al,[24] 11 randomized controlled trials including more than 14,000 patients were systematically reviewed comparing inhaled corticosteroid therapy with nonsteroid inhaled therapy for 6 months or more. In 5 studies with more than 9,000 patients, all-cause mortality at 1 year was reported. There were 128 deaths in the treatment group and 148 deaths in the control group and no survival difference associated with inhaled corticosteroid use at 1 year. Seven studies including more than 10,000 patients reported pneumonia outcomes. These studies included 777 and 561 events in the inhaled corticosteroid treatment group and non–inhaled corticosteroid group, respectively. Patients receiving inhaled corticosteroid therapy had a higher incidence of pneumonia (relative risk, 1.34; $P = .03$). Only 3 studies reported fracture events, with 195 and 178 events, respectively; there was no difference in the risk of fracture between patients receiving inhaled corticosteroid therapy and those receiving non–inhaled corticosteroid therapy.

Within the last decade, 4 large studies have examined the effect of long-term inhaled corticosteroids on outcomes in patients with COPD. To the disappointment of many, the Copenhagen City Heart Study, European Respiratory Society Study on Chronic Obstructive Pulmonary Disease, Inhaled Steroids in Obstructive Lung Disease (ISOLDE), and Lung Health Study II all failed to demonstrate an effect of inhaled corticosteroids on lung function over time.[25-28] The observations from these individual studies are bolstered by data from a 2007 meta-analysis performed by the Cochrane Collaboration assessing the effect of inhaled corticosteroid therapy on lung function in patients with stable COPD.[29] In this analysis of 47 randomized, placebo-controlled trials of long-term use of inhaled corticosteroids including more than 13,000 patients with stable COPD, there was no reduction in the decrease of FEV_1 nor was there a reduction in overall mortality. Inhaled corticosteroids might, however, slow disease progression in patients with more severe COPD. For example,