

## 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  $\beta$ -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.  $\beta_2$ -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,  $\beta_2$ -agonists, anticholinergics, mucolytics, antioxidants, pulmonary rehabilitation, home oxygen, smoking cessation, immunization

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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.<sup>1</sup> 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

**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.<sup>2</sup> In the United States and most of the developed world, cigarette smoking is the single most important cause of COPD<sup>3</sup>; in undeveloped countries biomass fuel has been implicated.<sup>4</sup> Inhaled corticosteroids improve asthma control, decrease exacerbations, and help to maintain lung function over time.<sup>5</sup> Until recently, smoking cessation was believed to be the only intervention that reduced the accelerated rate of decrease of lung function that characterizes COPD.<sup>6</sup> 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<sub>H</sub>2 cells predominating in those with asthma, and macrophages, neutrophils, and CD8<sup>+</sup> lymphocytes playing key roles in COPD.<sup>7</sup> These cellular patterns are mediated by overlapping but distinct networks of proinflammatory cytokines, chemokines, and growth factors. Although T<sub>H</sub>2 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- $\beta$ , TNF- $\alpha$ , fibroblast growth factor, IL-1 $\beta$ , and IL-6.<sup>7</sup> 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  $\beta_2$ -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.<sup>8-14</sup> 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  $\mu$ g 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<sup>+</sup> T cells, macrophages, and neutrophils and that fluticasone reduced subepithelial mast cell numbers and the ratio of CD8/CD4 T cells in the epithelium.<sup>15</sup> These results were not replicated in a study of fluticasone versus placebo over 6 months in 23 patients with COPD.<sup>16</sup> 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.<sup>17-19</sup> 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.<sup>20,21</sup> Finally, Sin et al<sup>22</sup> 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*.<sup>23</sup>

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,<sup>24</sup> 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.<sup>25-28</sup> 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.<sup>29</sup> 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<sub>1</sub> nor was there a reduction in overall mortality. Inhaled corticosteroids might, however, slow disease progression in patients with more severe COPD. For example,

Celli et al<sup>30</sup> reported that in subjects in the Towards a Revolution in COPD Health (TORCH) study with moderate-to-severe COPD (mean postbronchodilator FEV<sub>1</sub> of approximately 45% of predicted value), treatment with fluticasone propionate for 3 years reduced the rate of decrease in FEV<sub>1</sub> compared with placebo (42 vs 55 mL/y,  $P < .003$ ). Similar reductions were observed with salmeterol alone and with the salmeterol/fluticasone combination.

Despite the lack of survival benefit associated with the daily use of inhaled corticosteroid therapy, a number of randomized controlled trials have demonstrated a reduction in the frequency of exacerbations, as well as the improvement in quality-of-life scores. The Cochrane meta-analysis demonstrated that the long-term use of inhaled corticosteroids reduced the mean rate of exacerbation and slowed the rate of decrease in quality of life, as measured with the St George's Respiratory Questionnaire.<sup>29</sup> Inhaled triamcinolone reduced exacerbations in the Lung Health Study II from 28.2 per 100 person-years to 21.1 per 100 person-years ( $P = .005$ ).<sup>28</sup> In the ISOLDE study fluticasone significantly reduced exacerbations, and its effect was greatest in subjects with low lung function.<sup>27</sup> Two different meta-analyses confirmed this effect of inhaled corticosteroids on exacerbations of COPD.<sup>29,31</sup> Based on these studies, the Global Initiative for Chronic Obstructive Lung Disease guidelines recommend inhaled corticosteroid therapy for symptomatic patients with a FEV<sub>1</sub> of less than 50% of predicted value and repeated exacerbations (3 in the last 3 years).<sup>32</sup> Additionally, the American Thoracic Society/European Respiratory Society guidelines recommend therapy with inhaled corticosteroids if FEV<sub>1</sub> is less than 50% of predicted value and there have been exacerbations of COPD requiring a course of oral corticosteroids or antibiotics at least once within the last year.<sup>33</sup>

The exact role of inhaled corticosteroids in patients with COPD remains to be determined because data from the literature are seemingly in conflict. Clinical trials have clearly demonstrated a reduction in exacerbations but no effect on mortality. Recent meta-analyses describe an increased risk of pneumonia in patients with COPD who take inhaled corticosteroids. It is likely that these results reflect, in part, the heterogeneity of COPD, with some subpopulations more likely to benefit from inhaled corticosteroids and others who might be more at risk for pneumonia. For now, inhaled corticosteroids appear warranted in the exacerbation-prone patient, and the potential risk for pneumonia might suggest the use of low doses to minimize the potential risk.

### Oral corticosteroids

Although central to the management of acute exacerbations of both asthma and COPD, oral corticosteroids have been successfully used chronically to treat the patient with severe asthma who is refractory to other treatment. The use of systemic corticosteroids in patients with stable COPD has been more controversial. The literature on the use of oral corticosteroids in patients with COPD has been difficult to interpret because of differences in dose and length of treatment. The long-term use of low-dose corticosteroids is not supported by the literature.<sup>34-37</sup> Data on the long-term (>6 weeks) use of high-dose oral corticosteroids in patients with COPD have been limited. In 13 short-term studies the use of high-dose oral corticosteroids (>30 mg of prednisolone) for 2 weeks was associated with an increase in FEV<sub>1</sub>.<sup>38</sup> However, the effect was not uniform and demonstrated marked individual

variation. A single study of 67 patients with COPD randomized to 30 mg of prednisolone daily or placebo for 2 weeks found that improvements in FEV<sub>1</sub> and quality-of-life scores were greater in those patients with higher baseline sputum eosinophil counts and were associated with a reduction in sputum eosinophil counts, suggesting that this subgroup might benefit from long-term treatment.<sup>39</sup> Unlike FEV<sub>1</sub>, studies of effects on quality-of-life measures, symptom scores, or exacerbation rates either for long- or short-term high-dose corticosteroids are extremely limited and do not show a statistically significant improvement.<sup>38</sup> The improvement in FEV<sub>1</sub> with short-term use of high doses of oral corticosteroids should be weighed against their well-defined adverse effects, including glucose intolerance, decreased bone density, and adrenal suppression.

### BRONCHODILATORS

Treatment of asthma has focused first on the introduction of anti-inflammatory controller medications, with the addition of bronchodilators as adjuvant treatments aimed at relieving episodic symptoms in the case of short-acting medications or controlling daily symptoms in the case of long-acting medications. In contrast, given the unclear benefits and the potential risk associated with inhaled corticosteroids, treatment of stable COPD has focused instead on bronchodilators. Although response to bronchodilators has been used to differentiate asthma from COPD, this distinction is not as absolute as was once believed. Most asthmatic subjects will demonstrate a 15% increase in FEV<sub>1</sub> in response to bronchodilators. Although the response in patients with COPD is less consistent, most of these patients will demonstrate significant bronchodilator responsiveness if studied on more than 1 occasion.<sup>40</sup> Patients often report symptomatic improvement when treated with  $\beta_2$ -agonists and anticholinergic bronchodilator medications. These medications are recommended in the management of symptomatic COPD.

### Anticholinergic bronchodilators

Anticholinergic medications, such as ipratropium and tiotropium, act as bronchodilators by means of competitive inhibition of the neurotransmitter acetylcholine at its receptor sites within the vagus nerve, thus preventing the transmission of parasympathetic stimuli that mediate bronchoconstriction. They are generally considered a safer class of medications than the  $\beta_2$ -agonists. However, it is widely believed that anticholinergics are less effective than  $\beta_2$ -agonists in the symptomatic treatment of chronic asthma, and there is considerable variation in response.<sup>41</sup>

In comparison with asthma, anticholinergic bronchodilator medications play an important first-line role in the management of COPD. At least 1 clinical trial has demonstrated that ipratropium might be more efficacious in the elderly and those with chronic bronchitis.<sup>42</sup> In a meta-analysis of 11 studies containing 3,912 patients, Appleton et al<sup>43</sup> demonstrated a small benefit from the regular long-term use of ipratropium alone or in combination with  $\beta_2$ -agonists compared with  $\beta_2$ -agonist therapy alone in patients with COPD. In 6 studies comparing regular use of ipratropium versus a short-acting  $\beta_2$ -agonist, a small but significant increase in prebronchodilator FEV<sub>1</sub> (0.03 L; 95% CI, 0-0.06 L) and prebronchodilator forced vital capacity (FVC; 0.07 L; 95% CI, 0.01-0.14 L) was associated with ipratropium use at 3 months, but no significant difference was seen in dyspnea scores.

Interestingly, pooled analysis of 4 studies demonstrated that ipratropium was associated with significantly less added or increased use of oral steroids compared with use of a short-acting  $\beta_2$ -agonist alone, yielding a number needed to treat of 15. Meta-analysis of 5 studies comparing combination therapy with a short-acting  $\beta_2$ -agonist alone demonstrated no differences in prebronchodilator FEV<sub>1</sub>, prebronchodilator FVC, or symptom scores; however, there was an increase in postbronchodilator lung function outcomes. Again, combination therapy was associated with a reduction in the need for oral corticosteroids (number needed to treat = 20).

Tiotropium is a newer anticholinergic that differs from ipratropium in its relatively slow dissociation from M1 and M3 muscarinic receptors, resulting in a bronchodilatory effect that lasts more than 24 hours, allowing daily dosing.<sup>44</sup> Furthermore, its relatively rapid dissociation from the M2 receptor, which functions in feedback inhibition, might further decrease acetylcholine release.<sup>45</sup> In clinical trials of COPD lasting up to 12 months, tiotropium has been shown to improve exercise tolerance and health-related quality of life and to reduce exacerbations and hospitalizations.<sup>46-51</sup> The clinical effects of tiotropium have been compared with those of placebo, ipratropium, and long-acting  $\beta_2$ -agonists. In an analysis of 9 studies including 6,584 patients with moderately severe COPD (Global Initiative for Chronic Obstructive Lung Disease stage IIb), tiotropium decreased the odds of COPD exacerbation (odds ratio [OR], 0.74; 95% CI, 0.66-0.83) and hospitalizations (OR, 0.64; 95% CI, 0.51-0.82) compared with placebo or ipratropium but not with salmeterol.<sup>52</sup> When applied to an average risk of exacerbation of 45% over 1 year, as found in 2 trials of 12 months' duration, the number needed to treat with tiotropium compared with placebo to prevent 1 exacerbation was 14 (95% CI, 11-22). There was no statistically significant difference in all-cause mortality between tiotropium and placebo, ipratropium, or salmeterol in this pooled analysis. However, tiotropium demonstrated statistically significant increases in FEV<sub>1</sub> and FVC from baseline compared with placebo, ipratropium, or salmeterol. Furthermore, the decrease in FEV<sub>1</sub> over 1 year was reduced by 30 mL (95% CI, 7-53 mL) in patients treated with tiotropium compared with those receiving placebo or ipratropium. Symptom and quality-of-life scores demonstrated similar patterns. Finally, in the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study of 5,993 patients treated with tiotropium or placebo for 4 years, FEV<sub>1</sub> increased in the tiotropium group, and this increase over that seen with placebo was maintained throughout the study. Tiotropium was also associated with reduced exacerbations, hospitalizations, and respiratory failure and with improved health-related quality of life.<sup>53</sup>

### $\beta_2$ -Adrenergic bronchodilators

Inhaled short-acting  $\beta_2$ -agonists are the major class of bronchodilators used for the symptomatic management of asthma. These agents improve symptoms and airway function in patients with COPD also,<sup>40</sup> and the regular use of short-acting  $\beta_2$ -agonists in the management of stable COPD has been well studied. In a review of 10 randomized controlled trials of regular use of short-acting  $\beta_2$ -agonists versus placebo, Sestini et al<sup>54</sup> demonstrated a slight but significant improvement in postbronchodilator FEV<sub>1</sub> and FVC, morning and evening peak expiratory flows, and dyspnea scores. None of the studies included reported an effect on exacerbations requiring oral corticosteroids or serious side effects during treatment.

The role of long-acting  $\beta$ -agonist therapy in the treatment of asthmatic subjects is as an adjunct to anti-inflammatory therapy. As monotherapy, these drugs are less effective than inhaled corticosteroids alone and have been associated with increased exacerbations<sup>55</sup> and asthma-related deaths.<sup>56,57</sup> As a result, guidelines and the US Food and Drug Administration specifically recommend that long-acting  $\beta$ -agonists not be used alone to treat asthma.<sup>58,59</sup>

The role for long-acting  $\beta$ -agonists in patients with COPD is different, and the safety concerns raised regarding asthma seem not to apply to COPD. Long-acting  $\beta$ -agonists have been increasingly used in the management of stable COPD. In an analysis of 8 published randomized controlled trials comparing 50  $\mu$ g of salmeterol twice daily with placebo for 4 weeks in adults with poorly reversible COPD, Appleton et al<sup>60</sup> demonstrated a significant improvement in FEV<sub>1</sub> (51 mL; 95% CI, 31.93-70.07 mL) and morning peak expiratory flow (15.81 L/min; 95% CI, 11.96-19.67 L/min). Importantly, pooled analysis of 5 studies and 1,741 patients demonstrated reduced risk of exacerbation in patients treated with salmeterol compared with that seen in those receiving placebo (OR, 0.72; 95% CI, 0.57-0.90). Additionally, the combination of long-acting  $\beta$ -agonist and inhaled corticosteroid therapy has shown benefits in patients with stable COPD beyond those seen with inhaled corticosteroid therapy alone. In a pooled analysis of 7 randomized controlled trials including 5,708 participants comparing combination long-acting  $\beta$ -agonist and inhaled corticosteroid therapy with inhaled corticosteroid therapy alone, combination therapy demonstrated a reduced risk of exacerbation (relative risk, 0.91; 95% CI, 0.85-0.97).<sup>61</sup> Furthermore, combination therapy was associated with a reduced risk of death from all causes compared with inhaled corticosteroid therapy alone (0.77; 95% CI, 0.63-0.94). There were no significant differences in adverse events. The TORCH study of more than 6,000 patients, which was specifically designed to compare the effect of salmeterol plus fluticasone with that of salmeterol alone, fluticasone alone, or placebo, did not reach the predetermined level of statistical significance for its primary outcome, death from any cause, in part because results were adjusted for an interim analysis. However, the combination regimen of salmeterol plus fluticasone reduced exacerbations, improved health status, and improved lung function.<sup>62</sup> Over the 3 years of monitoring, salmeterol, fluticasone, and salmeterol plus fluticasone each reduced the rate of decrease in FEV<sub>1</sub> compared with placebo.<sup>30</sup>

### MUCOLYTICS

Both asthma and chronic bronchitis are diseases that are characterized by mucus hypersecretion and plugging of the distal airways. Given the benefits derived from mucolytic therapy in other hypersecretory disorders, such as cystic fibrosis, there has been a good rationale for the treatment of patients with poorly controlled asthma and chronic bronchitis with agents that reduce sputum viscosity and increase the expectoration of sputum. In some European countries, mucolytics are widely prescribed for this purpose, whereas in the United States these are used infrequently because they are considered ineffective. Studies of mucolytics have been limited in patients with chronic asthma but have been examined for long-term use in the treatment of chronic bronchitis in a number of small but randomized, double-blind, placebo-controlled trials. In the pooled analysis of 26 trials of chronic bronchitis comparing daily oral mucolytics with placebo for at least

2 months, mucolytic therapy demonstrated a small but significant reduction in the number of exacerbations per patient ( $-0.05$ ; 95% CI,  $-0.05$  to  $-0.04$ ).<sup>63</sup> However, these benefits seem to be limited to patients not already receiving inhaled corticosteroids. Newer mucolytics, such as recombinant human deoxyribonuclease, that have shown benefit in cystic fibrosis management have been studied in the management of acute asthma without benefit.<sup>64</sup> Further study of new mucolytics in patients with COPD is warranted.

## ANTIOXIDANTS

Oxidative stress is believed to play an important role in the pathogenesis of COPD. Meta-analyses have suggested that N-acetylcysteine reduces exacerbations of chronic bronchitis by 22% to 29%,<sup>65-67</sup> but data from large, prospective, controlled trials are limited. The Bronchitis Randomized on N-acetylcysteine Cost-Utility Study (BRONCUS) followed 523 patients for 3 years, comparing the yearly loss of FEV<sub>1</sub> and the number of exacerbations per year in subjects taking daily N-acetylcysteine compared with those taking placebo. N-acetylcysteine did not prevent deterioration of lung function, nor did it prevent exacerbations.<sup>68</sup> Although subgroup analysis suggested a small effect on exacerbations in subjects who were not taking inhaled corticosteroids, most experts have little enthusiasm for this treatment. Inhaled N-acetylcysteine as a mucolytic agent in the treatment of COPD has not been well studied.

## NOVEL PHARMACOLOGIC THERAPIES

As our understanding of the distinct pathophysiology of COPD increases, novel targeted therapies are being developed and tested. One such class of medications is the phosphodiesterase 4 inhibitors, which have been shown to inhibit chemotaxis, leukocyte activation, and cytokine production *in vitro* and in animal models of COPD.<sup>69</sup> One such phosphodiesterase 4 inhibitor, roflumilast, reduced the number of neutrophils and eosinophils in the sputum of patients with COPD<sup>70</sup> and improved lung function in patients with moderate-to-severe COPD.<sup>71,72</sup> Two recent publications (4 studies) suggest that roflumilast has a beneficial effect on lung function and on COPD exacerbations in selected patients, probably through a specific anti-inflammatory effect.<sup>73,74</sup> The identification of different subsets of patients with different inflammatory pathways involving, for example, TNF- $\alpha$ , CXCL8, IL-17, and neutrophil elastase provides a rationale for testing new anti-inflammatory molecules.

## NONPHARMACOLOGIC THERAPIES

### Oxygen

Despite the importance of pharmacologic therapies for the treatment of chronic asthma and COPD, physicians must also recognize the benefits that nonpharmacologic therapies can provide. Arguably, the most important nonpharmacologic therapy for patients with advanced chronic bronchitis and emphysema who also have chronic hypoxemia is the administration of long-term supplemental oxygen therapy. Two landmark studies performed in the 1970s, the Nocturnal Oxygen Therapy Trial and the Medical Research Council Trial, demonstrated a significant survival benefit in those hypoxemic patients treated with continuous oxygen therapy compared with those receiving no therapy or nocturnal oxygen alone.<sup>75,76</sup> These data are 25 years old, however, and studies included only patients with severe hypoxemia. Survival benefit in patients who experience only mild-to-moderate hypoxemia or who have hypoxemia only with exertion is unknown.<sup>77</sup>

## Smoking cessation

The benefits of smoking cessation on morbidity and mortality in patients with chronic asthma and COPD have been well documented and should be a major focus in the clinical care of patients with lung disease in general. Improvements in pulmonary function parameters have been shown as early as 1 month after smoking cessation, and by 3 months, decreases in sputum neutrophil counts are apparent along with improvement in FEV<sub>1</sub>.<sup>78</sup> The Lung Health Study first reported in 1994 that smoking cessation slowed the rate of loss of lung function in patients with COPD.<sup>79</sup> In a recently published 14.5-year follow-up, Anthonisen et al<sup>80</sup> reported that sustained smoking cessation continued to be associated with a reduced rate of decrease in lung function. Postma et al<sup>81</sup> studied a group of 81 patients with moderate-to-severe COPD followed for 2 to 21 years. Those 22 patients who stopped smoking during the study demonstrated a change in FEV<sub>1</sub> of  $-49 \pm 7$  mL/y, whereas FEV<sub>1</sub> in the sustained smokers decreased at a faster rate ( $-85 \pm 5$  mL/y). Data on the effects of smoking cessation on all-cause mortality in patients with COPD are also robust. A number of studies have demonstrated improved all-cause mortality and death caused by respiratory disease in patients with COPD who quit smoking compared with current smokers.<sup>80,82,83</sup> Similar studies in asthmatic subjects have demonstrated that smokers have worse symptom control,<sup>84,85</sup> accelerated decrease in lung function,<sup>86,87</sup> and an increased mortality rate after a near-fatal asthma attack<sup>88</sup> compared with nonsmokers with asthma. In addition, asthmatic subjects who smoke have a blunted response to corticosteroids.<sup>89</sup> Smoking cessation remains a difficult problem, but newer medications combined with counseling and behavior modification are more effective, with a higher success rate and a lower rate of recidivism than older treatments.<sup>90,91</sup> Unfortunately, bupropion and varenicline have been associated with depression and suicidal ideation in some patients, and the US Food and Drug Administration has now mandated a black box warning that these agents might be associated with serious neuropsychiatric symptoms.

## Pulmonary rehabilitation

The benefits of pulmonary rehabilitation in patients with COPD have recently been reviewed.<sup>92</sup> A number of randomized controlled (although unblinded) trials have demonstrated unequivocal improvements in exercise capacity, severity of dyspnea, and health-related quality of life.<sup>93</sup> In a recent meta-analysis by Lacasse et al<sup>94</sup> of 31 randomized controlled trials of pulmonary rehabilitation, health-related quality of life was significantly improved in addition to functional exercise capacity, as assessed by distance walked in 6 minutes. Data on physical exercise in patients with chronic asthma are more limited, but in a pooled analysis of 13 studies, physical training improved cardiopulmonary fitness, as measured by an increase in maximum oxygen uptake, and did not demonstrate any negative effects on resting lung function or number of days with wheezing.<sup>95</sup>

## IMMUNIZATIONS

### Influenza

Annual influenza vaccination is recommended for all patients with chronic lung diseases; however, those with COPD are at particular risk of clinical deterioration when infected with such respiratory viruses. Observational studies have shown that influenza vaccines can reduce serious illness and death in patients with COPD

by about 50%.<sup>96</sup> Despite the almost universal recommendation that persons with COPD should receive annual influenza vaccinations, very few randomized controlled trials have evaluated their effect in these patient populations. In a meta-analysis published by Poole et al<sup>97</sup> in 2006, 6 randomized controlled trials of influenza vaccination in patients with COPD were analyzed. Inactivated vaccine resulted in a significant reduction in the total number of exacerbations per subject compared with those receiving placebo ( $-0.37$ ; 95% CI,  $-0.61$  to  $-0.11$ ). In patients with COPD, as well as other elderly patients without COPD, there was a significant increase in the occurrence of local adverse reactions, but these were generally mild and transient. The benefit of annual influenza vaccination in patients with chronic asthma has been more controversial. In 2001, the American Lung Association's Asthma Clinical Research Centers demonstrated that inactivated influenza vaccine was safe in adults and children with asthma, including severe asthma.<sup>98</sup> However, the recommendation to administer the influenza vaccine to asthmatic subjects is not supported by evidence from any randomized controlled trials. In a systematic review of the literature published by Cates et al<sup>99</sup> in 2008, pooled analysis of 2 trials involving 2,306 subjects with asthma did not demonstrate an increase in asthma symptoms in the 2 weeks after administration of the vaccine, suggesting that it is a relatively safe intervention. However, in a randomized controlled trial of 696 children with asthma, Bueving et al<sup>100</sup> did not demonstrate a significant reduction in the number, severity, or duration of asthma exacerbations caused by influenza, raising doubts about its role in adult patients with asthma. Based on such evidence, it seems prudent to administer an annual influenza vaccine to patients with COPD and those with asthma who are elderly or have comorbid conditions in the absence of a contraindication.

### Pneumococcal vaccine

Two case-control studies have shown that asthma is an independent risk factor for invasive pneumococcal disease,<sup>101,102</sup> and the Centers for Disease Control and Prevention now recommend that the pneumococcal polysaccharide vaccine be given to all adults 19 to 64 years of age who have asthma.<sup>103</sup> Data supporting the use of pneumococcal vaccines in patients with COPD are limited, but a recent study by the National Heart, Lung, and Blood Institute's COPD Clinical Research Network demonstrated that 2 different pneumococcal vaccines induced immunoglobulin and opsonization responses in patients with COPD.<sup>104</sup> Whether this immunologic response translates into protection against serious pneumococcal disease remains to be determined. Included in the 2009 Centers for Disease Control and Prevention guidelines is the recommendation that pneumococcal vaccine be administered to all subjects who smoke.

### SUMMARY

In summary, over the past decade, there have been significant advances in the treatment of COPD that contribute to better control of this disease over time. Although COPD was once defined by lack of reversibility, it is now clear that short-acting  $\beta_2$ -agonists and short-acting anticholinergics improve lung function and relieve symptoms. Tiotropium increases exercise tolerance and health-related quality of life and decreases exacerbations and hospitalizations. Tiotropium has not been shown to change the rate of decrease in lung function over time, but it increases FEV<sub>1</sub>, and this increase is maintained over at least

3 to 4 years, resulting in better lung function over time compared with that seen in placebo-treated patients. Inhaled corticosteroids reduce the rate of COPD exacerbations and improve quality of life, perhaps at the risk of increased pneumonia. An effect of inhaled corticosteroids on mortality has not been demonstrated.

Although results have been variable, data are now beginning to emerge suggesting that pharmacotherapy can change the natural history of COPD. Thus although the Lung Health Study II, the ISOLDE study, the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease, and the Copenhagen City Heart Study all failed to provide evidence for a reduction in the rate of decrease in FEV<sub>1</sub> with inhaled corticosteroids, the TORCH study demonstrated that salmeterol plus fluticasone, fluticasone alone, and salmeterol alone each slowed the rate of progression. Whether this protective effect is greater in a subset of patients remains to be determined. Similarly, although no pharmacologic therapy has been shown to affect mortality, a number clearly decrease exacerbations and hospitalizations, which one would expect might contribute to mortality. It is possible that the heterogeneity of COPD populations makes it difficult to identify a survival benefit in studies of diverse populations. Another confounder is the apparent risk of pneumonia, which in large studies might negate a beneficial effect on mortality in patients who do not experience pneumonia. It is clear that future studies need to focus on the various "phenotypes" of COPD and consider the likelihood that patients with these phenotypes might benefit from specific therapies. In addition, studies are needed to define which statistically significant changes are clinically significant.

#### What do we know?

- Smoking cessation slows loss of lung function over time and reduces mortality.
- Most patients with COPD have a reversible component.
- Inhaled corticosteroids and tiotropium each reduce COPD exacerbations.
- Tiotropium improves lung function in patients with COPD, and this improvement is maintained over time.
- Salmeterol, fluticasone, and salmeterol plus fluticasone each slow the loss of lung function over time in patients with COPD.
- Inhaled corticosteroids are associated with increased risk of pneumonia in patients with COPD.

#### What is still unknown?

- Do subgroups of patients with COPD respond differently?
- Are different phenotypes of COPD defined by severity of lung function, symptoms, reversibility, frequency of exacerbations, genotype, or as-yet-undetermined characteristics?
- If decreased exacerbations do not correlate with decreased mortality, is this a valid end point?
- Are there systemic or lung biomarkers that can serve as surrogate markers for disease progression?

#### REFERENCES

1. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). *Lancet* 2004;364:613-20.
2. Willart MA, Lambrecht BN. The danger within: endogenous danger signals, atopy and asthma. *Clin Exp Allergy* 2009;39:12-9.

3. Eisner MD, Balmes J, Katz PP, Trupin L, Yelin EH, Blanc PD. Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. *Environ Health* 2005;4:7.
4. Liu S, Zhou Y, Wang X, Wang D, Lu J, Zheng J, et al. Biomass fuels are the probable risk factor for chronic obstructive pulmonary disease in rural South China. *Thorax* 2007;2007:889-97.
5. Adams NP, Bestall JB, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma. *Cochrane Database Syst Rev* 2000;(4):CD002738.
6. Willemsse BW, Postma DS, Timens W, ten Hacken NH. The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. *Eur Respir J* 2004;23:464-76.
7. Barnes PJ. The cytokine network in asthma and chronic obstructive pulmonary disease. *J Clin Invest* 2008;118:3546-56.
8. Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Comparison of a  $\beta_2$ -agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-92.
9. Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.
10. van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. *Am Rev Respir Dis* 1992;146:547-54.
11. Kerstjens HA, Brand PL, Hughes MD, Robinson NJ, Postma DS, Sluiter HJ, et al. A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. Dutch Chronic Non-Specific Lung Disease Study Group. *N Engl J Med* 1992;327:1413-9.
12. Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990;142:832-6.
13. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332-6.
14. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361:1071-6.
15. Hattotuwa KL, Gizycki MJ, Ansari TW, Jeffery PK, Barnes NC. The effects of inhaled fluticasone on airway inflammation in chronic obstructive pulmonary disease: a double-blind, placebo-controlled biopsy study. *Am J Respir Crit Care Med* 2002;165:1592-6.
16. Verhoeven GT, Hegmans JP, Mulder PG, Bogaard JM, Hoogsteden HC, Prins JB. Effects of fluticasone propionate in COPD patients with bronchial hyperresponsiveness. *Thorax* 2002;57:694-700.
17. Llewellyn-Jones CG, Harris TA, Stockley RA. Effect of fluticasone propionate on sputum of patients with chronic bronchitis and emphysema. *Am J Respir Crit Care Med* 1996;153:616-21.
18. Culpitt SV, Maziak W, Loukidis S, Nightingale JA, Matthews JL, Barnes PJ. Effect of high dose inhaled steroid on cells, cytokines, and proteases in induced sputum in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160:1635-9.
19. Brightling CE, McKenna S, Hargadon B, Birring S, Green R, Siva R, et al. Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease. *Thorax* 2005;60:193-8.
20. Thompson AB, Mueller MB, Heires AJ, Bohling TL, Daughton D, Yancey SW, et al. Aerosolized beclomethasone in chronic bronchitis. Improved pulmonary function and diminished airway inflammation. *Am Rev Respir Dis* 1992;146:389-95.
21. Ozol D, Aysan T, Solak ZA, Mogulkoc N, Veral A, Sebik F. The effect of inhaled corticosteroids on bronchoalveolar lavage cells and IL-8 levels in stable COPD patients. *Respir Med* 2005;99:1494-500.
22. Sin DD, Lacy P, York E, Man SF. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170:760-5.
23. John M, Bosse S, Oltmanns U, Schumacher A, Witt C. Effects of inhaled HFA beclomethasone on pulmonary function and symptoms in patients with chronic obstructive pulmonary disease. *Respir Med* 2005;99:1418-24.
24. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2008;300:2407-16.
25. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999;353:1819-23.
26. Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, et al. Long-term Treatment with Inhaled Budesonide in Persons with Mild Chronic Obstructive Pulmonary Disease Who Continue Smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *N Engl J Med* 1999;340:1948-53.
27. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;320:1297-303.
28. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;343:1902-9.
29. Yang IA, Fong KM, Sim EH, Black PN, Lasserson TJ. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007;(2):CD002991.
30. Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008;178:332-8.
31. Alsaedi A, Sin DD, McAlister FA. The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review of randomized placebo-controlled trials. *Am J Med* 2002;113:59-65.
32. Fabbri L, Pauwels RA, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary updated 2003. *COPD* 2004;1:105-41; discussion 103-4.
33. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932-46.
34. Decramer M, Stas KJ. Corticosteroid-induced myopathy involving respiratory muscles in patients with chronic obstructive pulmonary disease or asthma. *Am Rev Respir Dis* 1992;146:800-2.
35. Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med* 1994;150:11-6.
36. Rice KL, Rubins JB, Lebahn F, Parenti CM, Duane PG, Kuskowski M, et al. Withdrawal of chronic systemic corticosteroids in patients with COPD: a randomized trial. *Am J Respir Crit Care Med* 2000;162:174-8.
37. Renkema TE, Schouten JP, Koeter GH, Postma DS. Effects of long-term treatment with corticosteroids in COPD. *Chest* 1996;109:1156-62.
38. Walters JA, Walters EH, Wood-Baker R. Oral corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;(3):CD005374.
39. Brightling CE, Monteiro W, Ward R. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2000;356:1480-5.
40. Dorinsky PM, Reisner C, Ferguson GT, Menjoge SS, Serby CW, Witek TJ Jr. The combination of ipratropium and albuterol optimizes pulmonary function reversibility testing in patients with COPD. *Chest* 1999;115:966-71.
41. Westby M, Benson M, Gibson P. Anticholinergic agents for chronic asthma in adults. *Cochrane Database Syst Rev* 2004;(3):CD003269.
42. van Schayck CP, Folgering H, Harbers H, Maas KL, van Weel C. Effects of allergy and age on responses to salbutamol and ipratropium bromide in moderate asthma and chronic bronchitis. *Thorax* 1991;46:355-9.
43. Appleton S, Jones T, Poole P, Pilotto L, Adams R, Lasserson TJ, et al. Ipratropium bromide versus short acting beta-2 agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;(2):CD001387.
44. Disse B, Speck GA, Rominger KL, Witek TJ Jr, Hammer R. Tiotropium (Spiriva): mechanistical considerations and clinical profile in obstructive lung disease. *Life Sci* 1999;64:457-64.
45. Barnes PJ. The pharmacological properties of tiotropium. *Chest* 2000;117(suppl): 63S-66.
46. Vincken W, van Noord JA, Greefhorst AP, Bantje TA, Kesten S, Korducki L, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J* 2002;19:209-16.
47. Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;19:217-24.
48. O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;23:832-40.
49. Maltais F, Hamilton A, Marciniuk D, Hernandez P, Scierba FC, Richter K, et al. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. *Chest* 2005;128:1168-78.
50. Brusasco V, Hodder R, Miravittles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003;58:399-404.
51. Neweohner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005;143:317-26.
52. Barr RG, Bourbeau J, Camargo CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 2006;61:854-62.

53. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge SS, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543-54.
54. Sestini P, Renzoni E, Robinson S, Poole P, Ram FS. Short-acting beta 2 agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002;(4):CD001495.
55. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF, Sorkness CA, et al. Long-Acting  $\beta_2$ -agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma. A randomized controlled trial. *JAMA* 2001;285:2583-93.
56. National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma update on selected topics—2002. *J Allergy Clin Immunol* 2002;110(suppl):S141-219.
57. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, Group SS. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129:15-26.
58. National Asthma Education and Prevention Program. Expert panel report 3 (EPR3): guidelines for diagnosis and management of asthma—summary report. *J Allergy Clin Immunol* 2007;120(suppl):S94-138.
59. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.
60. Appleton S, Poole P, Smith B, Veale A, Lasserson TJ, Chan MM. Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;(3):CD001104.
61. Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler versus inhaled steroids for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007;(4):CD006826.
62. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins CR, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775-89.
63. Poole PJ, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;(3):CD001287.
64. Boogaard R, Smit F, Schornagel R, Vaessen-Verberne AA, Kouwenberg JM, Hekkelan M, et al. Recombinant human deoxyribonuclease for the treatment of acute asthma in children. *Thorax* 2008;63:141-6.
65. Grandjean EM, Berthet P, Ruffman R, Leuenberger P. Efficacy of oral long-term N-acetylcysteine in bronchopulmonary disease: a meta-analysis of published double-blind placebo-controlled clinical trials. *Clin Ther* 2000;22:209-21.
66. Stey C, Steurer J, Bachmann S, Medici TC, Tramer MR. The effect of oral N-acetylcysteine in chronic bronchitis: a quantitative systematic review. *Eur Respir J* 2000;16:253-62.
67. Poole PJ, Black PN. Oral mucolytic drugs for exacerbations of chronic obstructive pulmonary disease: systematic review. *BMJ* 2001;322:1271-4.
68. Decramer M, Rutten-van Molken M, Dekhuijzen PNR, Troosters T, van Herwaarden C, Pellegrino R, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo controlled trial. *Lancet* 2005;365:1552-60.
69. Smith VB, Spina D. Selective phosphodiesterase 4 inhibitors in the treatment of allergy and inflammation. *Curr Opin Invest Drugs* 2005;6:1136-41.
70. Grootendorst DC, Gauw SA, Verhoosel RM, Sterk PJ, Hoppers JJ, Bredenoord D, et al. Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD. *Thorax* 2007;62:1081-7.
71. Rabe KF, Bateman ED, O'Donnell D, Witte S, Bredenoord D, Bethke TD. Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2005;366:563-71.
72. Calverley PM, Sanchez-Toril F, McIvor A, Teichmann P, Bredenoord D, Fabbri LM. Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;176:154-61.
73. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. *Lancet* 2009;374:695-703.
74. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 2009;374:685-94.
75. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980;93:391-8.
76. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981;1:681-6.
77. Gorecka D, Gorzelak K, Sliwinski P, Tobiasz M, Zielinski J. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997;52:674-9.
78. Chaudhuri R, Livingston E, McMahon AD, Lafferty J, Fraser I, Spears M, et al. Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. *Am J Respir Crit Care Med* 2006;174:127-33.
79. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA* 1994;272:1497-505.
80. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005;142:233-9.
81. Postma DS, de Vries K, Koeter GH, Sluiter HJ. Independent influence of reversibility of air-flow obstruction and nonspecific hyperreactivity on the long-term course of lung function in chronic air-flow obstruction. *Am Rev Respir Dis* 1986;134:276-80.
82. Kanner RE, Renzetti AD Jr, Stanish WM, Barkman HW Jr, Klauber MR. Predictors of survival in subjects with chronic airflow limitation. *Am J Med* 1983;74:249-55.
83. Postma DS, Gimeno F, van der Weele LT, Sluiter HJ. Assessment of ventilatory variables in survival prediction of patients with chronic airflow obstruction: the importance of reversibility. *Eur J Respir Dis* 1985;67:360-8.
84. Siroux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. *Epidemiological study on the Genetics and Environment of Asthma. Eur Respir J* 2000;15:470-7.
85. Althuis MD, Sexton M, Prybylski D. Cigarette smoking and asthma symptom severity among adult asthmatics. *J Asthma* 1999;36:257-64.
86. Apostol GG, Jacobs DR Jr, Tsai AW, Crow RS, Williams OD, Townsend MC, et al. Early life factors contribute to the decrease in lung function between ages 18 and 40: the Coronary Artery Risk Development in Young Adults study. *Am J Respir Crit Care Med* 2002;166:166-72.
87. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194-200.
88. Marquette CH, Saulnier F, Leroy O, Wallaert B, Chopin C, Demarcq JM, et al. Long-term prognosis of near-fatal asthma. A 6-year follow-up study of 145 asthmatic patients who underwent mechanical ventilation for a near-fatal attack of asthma. *Am Rev Respir Dis* 1992;146:76-81.
89. Lazarus SC, Chinchilli VM, Rollings NJ, Boushey HA, Cherniack R, Craig TJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007;175:783-90.
90. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:47-55.
91. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:56-63.
92. Casaburi R, ZuWallack R. Pulmonary rehabilitation for management of chronic obstructive pulmonary disease. *N Engl J Med* 2009;360:1329-35.
93. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. *Chest* 2007;131(suppl):4S-42.
94. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;(4):CD003793.
95. Ram FS, Robinson SM, Black PN, Picot J. Physical training for asthma. *Cochrane Database Syst Rev* 2005;(4):CD001116.
96. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Engl J Med* 1994;331:778-84.
97. Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;(1):CD002733.
98. The ALA Asthma Clinical Research Centers. The safety of inactivated influenza vaccine in adults and children with asthma. *N Engl J Med* 2001;345:1529-36.
99. Cates CJ, Jefferson TO, Rowe BH. Vaccines for preventing influenza in people with asthma. *Cochrane Database Syst Rev* 2008;(2):CD000364.
100. Bueving HJ, Bernsen RM, de Jongste JC, van Suijlekom-Smit LW, Rimmelzwaan GF, Osterhaus AD, et al. Influenza vaccination in children with asthma: randomized double-blind placebo-controlled trial. *Am J Respir Crit Care Med* 2004;169:488-93.
101. Talbot TR, Harter TV, Mitchel E, Halasa NB, Arbogast PG, Poehling KA, et al. Asthma as a risk factor for invasive pneumococcal disease. *N Engl J Med* 2005;352:2082-90.
102. Juhn YJ, Kita H, Yawn BP, Boyle TG, Yoo KH, McGree ME, et al. Increased risk of severe pneumococcal disease in patients with asthma. *J Allergy Clin Immunol* 2008;122:719-23.
103. Centers for Disease Control and Prevention. Recommended adult immunization schedule—United States 2009. *MMWR* 2009;57(53).
104. Dransfield MT, Nahm MH, Han MK, Hamden S, Criner GJ, Martinez FJ, et al. Superior immune response to protein-conjugate versus free pneumococcal polysaccharide vaccine in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;180:499-505.