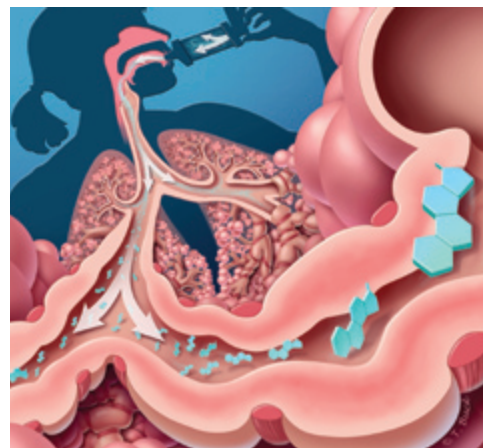


# Asthma Update: Part II. Medical Management

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The National Asthma Education and Prevention Program recently updated its guidelines for the management of asthma. An evidence-based approach was used to examine several key issues regarding appropriate medical therapy for patients with asthma. The updated guidelines have clarified these issues and should alter the way physicians prescribe asthma medications. Chronic inhaled corticosteroid use is safe in adults and children, and inhaled corticosteroids are recommended as first-line therapy in adults and children with persistent asthma, even if the disease is mild. Other medications, such as cromolyn, theophylline, and leukotriene modifiers, now are considered alternative treatments and should have a more limited role in the management of persistent asthma. The addition of a long-acting beta<sub>2</sub> agonist to an inhaled corticosteroid is superior to all other combinations as well as to higher dosages of inhaled corticosteroids alone. Combination therapy with an inhaled corticosteroid and a long-acting beta<sub>2</sub> agonist is the preferred treatment for adults and children with moderate to severe asthma. Antibiotic therapy offers no additional benefit in patients with asthma exacerbations. (*Am Fam Physicians* 2004;70:1061-6. Copyright© 2004 American Academy of Family Physicians.)



This is part II of a two-part article on asthma treatment recommendations. Part I, "Diagnosis, Monitoring, and Prevention of Disease Progression," appeared in the September 1, 2004, issue of *AFP*.

See page 1011 for definitions of strength-of-recommendation labels.

An article about how to design systems to improve asthma care in your practice will appear next month in the October 2004 issue of *AFP*'s sister publication, *Family Practice Management*.

The 1997 guidelines from the National Asthma Education and Prevention Program (NAEPP)<sup>1</sup> noted that inhaled corticosteroid therapy offered multiple benefits in patients with persistent asthma, but some uncertainty remained about its use in certain patients. The NAEPP's recent update<sup>2</sup> of the 1997 guidelines clarifies such treatment issues and should significantly change the way asthma is treated. Part I<sup>3</sup> of this two-part article reviewed diagnosis, monitoring, and prevention of disease progression in patients with asthma. Part II reviews updated recommendations for the treatment of asthma and discusses areas of controversy, including combination therapy and the use of antibiotics for asthma exacerbations.

## Inhaled Corticosteroids

The previous NAEPP guidelines<sup>1</sup> stated that inhaled corticosteroids were superior to other agents in the treatment of asthma. However, use of inhaled corticosteroids as initial therapy in patients with mild disease

and in children was controversial. In the recent guidelines update,<sup>2</sup> the NAEPP Expert Panel examined data comparing chronic use of inhaled corticosteroids and other agents in adults and children with mild or moderate persistent asthma. An overwhelming amount of the data showed that inhaled corticosteroids improve asthma control in children with mild or moderate persistent asthma, as measured by improvements in symptoms and forced expiratory volume in one second (FEV<sub>1</sub>) and reductions in airway hyperresponsiveness, emergency department visits, hospitalizations, and use of oral corticosteroids. No other medications (i.e., cromolyn [Intal], nedocromil [Tilade], theophylline, leukotriene modifiers) are as effective as inhaled corticosteroids in the long-term control of asthma.

## TREATMENT RECOMMENDATIONS

**Children.** The new asthma treatment recommendations<sup>2</sup> represent a major change from the previous guidelines, which had recommended cromolyn as initial maintenance

**Regular use of inhaled corticosteroids can reduce hospital admissions and dramatically decrease deaths from asthma.**

therapy in children.<sup>1</sup> Inhaled corticosteroids now are recommended in children older than five years with mild persistent asthma (Table 1).<sup>2</sup> According to data from Merck & Co., Inc., the use of leukotriene modifiers also is common, particularly in children (July 2003). However, the updated guidelines<sup>2</sup> state that leukotriene modifiers should not be used as first-line therapy; rather, they are considered second-line or alternative treatment, as are cromolyn, nedocromil, and theophylline. In children five years and younger, the guidelines also recommend inhaled corticosteroids (via dry powder inhaler, nebulizer, or metered-dose inhaler with a face mask) as first-line therapy, although cromolyn and leukotriene modifiers remain alternatives.<sup>2</sup>

Unfortunately, there have been few studies in children younger than five years, and the diagnosis of asthma in infants and children is complicated by the difficulty of obtaining objective measures of lung function.<sup>4</sup> Many children wheeze during the first years of life and do not progress to asthma,<sup>5</sup> and there are no reliable predictors for determining which children will develop asthma. However, physicians who are reluctant to diagnose infants or young children with asthma may be denying these patients life-saving and perhaps disease-modifying medications. To address this problem, the updated guidelines<sup>2</sup> recommend that physicians strongly consider starting long-term therapy for the control of asthma in infants and young children with four or more episodes of wheezing in the past year if the

**TABLE 1**  
**Preferred Medical Treatment Using a Stepwise Approach for Managing Asthma in Adults and Children**

*Clinical features before treatment or adequate control*

<i>Asthma classification</i>	<i>Symptom frequency</i>	<i>Lung function*</i>	<i>Medications required to maintain long-term control</i>
Mild intermittent	Daytime: 2 days per week or less Nighttime: 2 nights per month or less	PEF or FEV <sub>1</sub> : 80 percent or more of predicted function	No daily medication needed
Mild persistent	Daytime: more than 2 days per week, but less than one time per day Nighttime: more than 2 nights per month	PEF or FEV <sub>1</sub> : 80 percent or more of predicted function	Low-dose inhaled corticosteroid (delivered by nebulizer or metered-dose inhaler with holding chamber, with or without a face mask, or by dry powder inhaler in children 5 years and younger)
Moderate persistent	Daytime: daily Nighttime: more than 1 night per week	PEF or FEV <sub>1</sub> : 60 to 80 percent of predicted function	Children 5 years and younger: low-dosage inhaled corticosteroid and long-acting beta <sub>2</sub> agonist or medium-dosage inhaled corticosteroid Adults and children older than 5 years: low- to medium-dosage inhaled corticosteroid and long-acting inhaled beta <sub>2</sub> agonist
Severe persistent	Daytime: continual Nighttime: frequent	PEF or FEV <sub>1</sub> : 60 percent or less of predicted function	High-dosage inhaled corticosteroid and long-acting beta <sub>2</sub> agonist

PEF = peak expiratory flow; FEV<sub>1</sub> = forced expiratory volume in one second.

\*—Lung function measurements are used only in patients older than 5 years.

Adapted from National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma: update on selected topics—2002. Bethesda, Md.: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, 2003; NIH publication no. 02-5074:115.

**TABLE 2**  
**Goals of Asthma Therapy**

Maintain normal activity levels
Maintain normal pulmonary function
Prevent chronic symptoms
Prevent recurrent exacerbations
Provide optimal pharmacotherapy with minimal or no adverse events

*Information from reference 1.*

wheezing lasted more than one day and affected sleep and if the patient has risk factors for the development of asthma (i.e., parental history of asthma, atopic dermatitis, allergic rhinitis, or wheezing).<sup>2</sup> Table 2 lists the goals of asthma therapy.<sup>1</sup>

**Adults.** The treatment recommendations for adults also have changed. The previous guidelines<sup>1</sup> noted that the use of inhaled corticosteroids was preferred in patients with moderate or severe asthma but stopped short of recommending these agents as first-line therapy in patients with mild asthma. In addition to the previously known benefits of inhaled corticosteroid therapy in patients with asthma, recent data<sup>6,7</sup> show that regular use of inhaled corticosteroids can reduce hospital admissions and dramatically decrease deaths from asthma. One study<sup>8</sup> found that compliance with low-dosage inhaled corticosteroid therapy virtually eliminated the risk of death from asthma.

The NAEPP panel<sup>2</sup> reviewed 12 studies of the leukotriene modifiers montelukast and zafirlukast and found that outcome measures “clearly and significantly” favored therapy with inhaled corticosteroids.<sup>8</sup> A recent Cochrane review<sup>9</sup> concluded that leukotriene modifiers have only marginal benefit and should not be recommended as first-line therapy or add-on therapy. Thus, inhaled corticosteroids are recommended as first-line therapy in all patients with persistent asthma.<sup>2</sup>

#### **SAFETY**

Although the previous guidelines<sup>1</sup> noted that inhaled corticosteroids are the most effective

agents for treating asthma, concerns about adverse effects remained. Studies of older inhaled corticosteroids such as beclomethasone<sup>10</sup> showed a small reduction in children’s growth after 12 months of use, but other studies of newer, more potent agents showed no such risk.<sup>11,12</sup>

In the past, physicians may have erred on the side of caution by using the less potent agents in patients with mild disease. However, based on a review of clinical trials that followed children for up to six years, the NAEPP panel<sup>2</sup> found strong evidence that the use of inhaled corticosteroids in recommended dosages does not have long-term, clinically significant, or irreversible adverse effects.

The most significant evidence cited by the NAEPP panel came from the Childhood Asthma Management Program (CAMP) study,<sup>13</sup> which followed more than 1,000 children taking the inhaled corticosteroid budesonide, the mast-cell stabilizer nedocromil, or placebo for an average of six years. Although the CAMP study and other studies reviewed by the panel showed that low to medium dosages of inhaled corticosteroids decreased growth velocity in children (causing a small difference in the rate of growth [approximately 1 cm per year] in the first year of use), this effect was not sustained, and there was no difference in target adult height by the end of the study. A similar study,<sup>14</sup> which included fewer children but followed them for more than 10 years, found similar results. Not surprisingly, children with mild asthma who were taking inhaled corticosteroids had superior outcomes in both studies.<sup>13,14</sup> Thus, the negligible risk of growth reduction is far outweighed by the positive effects of inhaled corticosteroid use in children.

The NAEPP panel<sup>2</sup> also reviewed 16 studies that examined bone mineral density, subcapsular cataracts, glaucoma, and hypothalamic-pituitary-adrenal axis suppression in adults and children treated with corticosteroids; these studies also showed negligible adverse effects from corticosteroid use. A recent study<sup>15</sup> of women 18 to 45 years of age

**Inhaled corticosteroids are recommended as first-line therapy in all patients with persistent asthma.**

who were taking high dosages of triamcinolone found a potential statistically significant decrease in bone mineral density in the hip (but not the spine) in the older women. However, the decrease was not clinically significant because the rate of loss was very low, and this study has been criticized.<sup>16</sup> Thus, the NAEPP panel<sup>2</sup> concluded that inhaled corticosteroids are safe and recommends them as first-line therapy for children and adults with persistent asthma.

### Combination Therapy

The NAEPP panel<sup>2</sup> also considered whether the addition of another long-term asthma-control agent to inhaled corticosteroids

would improve outcomes in patients with moderate persistent asthma. The previous guidelines<sup>1</sup> offered several suggestions but did not recommend a specific agent. There is now strong evidence that the addition of a long-acting beta<sub>2</sub> agonist to a low or medium dosage of an inhaled corticosteroid improves lung function

and symptoms and reduces the need for use of a short-acting beta<sub>2</sub> agonist.<sup>2</sup> Doubling the dosage of the inhaled corticosteroid or adding a leukotriene modifier, theophylline, or cromolyn also improves outcomes, but not as substantially as the combination of an inhaled corticosteroid and a long-acting beta<sub>2</sub> agonist.

Individual studies<sup>17,18</sup> and a meta-analysis<sup>19</sup> comparing combined long-acting beta<sub>2</sub> agonists and inhaled corticosteroids with the doubling of the dosage of inhaled corticosteroids have shown that combination therapy reduces asthma exacerbations. The combination of a beta<sub>2</sub> agonist and an inhaled corticosteroid also has been proved superior to the addition of a leukotriene modifier.<sup>20-22</sup>

The benefits of combination therapy make sense pathophysiologically because of the dual components of asthma: airway inflammation and smooth muscle dysfunction. Inhaled corticosteroids are clearly the most potent anti-inflammatory agents,<sup>1</sup> and long-acting beta<sub>2</sub> agonists are the most potent

bronchodilators.<sup>23</sup> However, long-acting beta<sub>2</sub> agonists should not be used alone; studies have shown that asthma worsens when these agents are taken without an inhaled corticosteroid.<sup>24,25</sup>

One study<sup>26</sup> published since the updated guidelines were released found that the addition of a long-acting beta<sub>2</sub> agonist to an inhaled corticosteroid allows physicians to lower the corticosteroid dosage and still maintain asthma control. Thus, combination therapy can be steroid-sparing.

Although the safety of inhaled corticosteroid therapy has been established, physicians should prescribe the lowest dosage possible. In addition, there may be a need to increase the corticosteroid dosage and add a long-acting beta<sub>2</sub> agonist in patients at high risk for exacerbations, such as those with a history of hospitalizations or emergency department visits because of asthma.<sup>27,28</sup> Combination therapy with an inhaled corticosteroid and a long-acting beta<sub>2</sub> agonist is more cost effective than treatment with an inhaled corticosteroid plus a leukotriene modifier.<sup>29</sup>

The use of long-acting beta<sub>2</sub> agonists has been questioned recently because of results from the Salmeterol Multi-center Asthma Research Trial (SMART).<sup>30</sup> The SMART study was designed to assess the safety of the addition of salmeterol to current asthma therapy in patients who had never taken a long-acting beta<sub>2</sub> agonist. This study of 26,353 patients was stopped after 28 weeks because of concerns in a subset of patients. There were no significant differences between salmeterol and placebo in the primary end point of respiratory-related deaths and life-threatening events requiring interventions (e.g., intubation, ventilation). However, the number of asthma-related deaths was significantly higher in the patients who were taking salmeterol (13 patients) than in those who received placebo (four patients). There was no difference between salmeterol and placebo in the number of deaths among white patients, but eight black patients taking salmeterol died compared with one black patient who received placebo.

Although the findings of the SMART

**The addition of a long-acting beta<sub>2</sub> agonist to a low or medium dosage of an inhaled corticosteroid improves lung function and symptoms and reduces the need for use of a short-acting beta<sub>2</sub> agonist.**

study<sup>30</sup> are of potential concern, it should be noted that the number of asthma-related deaths was significantly lower in the patients taking inhaled corticosteroids (six of 12,254 compared with 11 of 14,099 nonusers), regardless of treatment with salmeterol. Asthma-related deaths also occurred more frequently in patients taking salmeterol who did not use an inhaled corticosteroid. Black patients, who have been shown to have more severe asthma and a higher risk for serious outcomes,<sup>31</sup> were less likely than white patients to use inhaled corticosteroids (38 percent compared with 49 percent). Thus, the SMART study<sup>30</sup> proved that long-acting beta<sub>2</sub> agonists should not be used without inhaled corticosteroids, that asthma is a serious and life-threatening disease, and that black patients seem to be at increased risk for serious outcomes.

The NAEPP recommendations for moderate persistent asthma have therefore been revised.<sup>2</sup> The preferred treatment for adults and children older than five years is a combination of a long-acting beta<sub>2</sub> agonist and a low to medium dosage of inhaled corticosteroids. The use of combination therapy in children five years of age and younger is under investigation. However, given the strong evidence from data in older children, the NAEPP guidelines<sup>2</sup> offer two options for treating moderate asthma in this group: the addition of a long-acting beta<sub>2</sub> agonist to a low dosage of an inhaled corticosteroid, or the use of a medium dosage of an inhaled corticosteroid alone.

### Antibiotic Therapy

The NAEPP panel<sup>2</sup> also examined whether patients with acute exacerbations of asthma benefited from antibiotic therapy. Two clinical trials<sup>32,33</sup> found that when antibiotics were prescribed routinely or when suspicion of bacterial infection (e.g., pneumonia, sinusitis) was low, no benefits were associated with antibiotic use. Although viral infections frequently are associated with asthma exacerbations,<sup>34,35</sup> the updated guidelines<sup>2</sup> note that chlamydial, mycoplasmal, and other bacterial infections do not contribute frequently to asthma exacerbations. In fact, data do

### Strength of Recommendation

Key clinical recommendations	Label	References
Inhaled corticosteroids are more effective than cromolyn (Intal), nedocromil (Tilade), theophylline, and leukotriene modifiers for the long-term control of asthma.	B	2
Inhaled corticosteroids are recommended as first-line treatment in children with acute asthma.	A	2, 8, 9
The combination of a beta <sub>2</sub> agonist and an inhaled corticosteroid is superior to the addition of a leukotriene modifier.	A	2, 20-22
Adding an antibiotic to usual care is not recommended in patients with asthma.	C	2

not support the use of antibiotics in patients with asthma, even when clinical suspicion of bacterial infection is high.

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