

Evaluation and Treatment of Asthma: An Overview

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Abstract

The delivery of optimal care to individuals with bronchial asthma remains a challenge to practicing physicians. Asthma is a chronic, inflammatory condition that requires diligent long-term follow-up. This article will address the diagnostic evaluation of patients with asthma and present an overview of drugs commonly used in treatment.

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Understanding the Basis of Asthma

Twenty years ago, asthma was largely viewed as a lung disease characterized by airway obstruction and caused primarily by bronchospasm. Although chronic cellular inflammation was noted as an associated finding, its central role in the pathogenesis of asthma was not widely recognized until the early 1990s. Since that time, numerous studies have demonstrated eosinophilic infiltration to be a key component of asthma and have shown the degree of tissue eosinophilia to be a determinant of airway hyperresponsiveness and symptom severity.^{1,2} Subsequent pathologic studies have highlighted the role of CD4 helper lymphocytes in directing eosinophils into the airway.³ With regard to the etiology of this inflammation, immunoglobulin E (IgE)-mediated hypersensitivity to airborne allergens, including mites, cockroaches, animal dander, molds, and pollens, has been shown to play an important role in up to 90% of children and 60% of adults with asthma.⁴ These new developments in our understanding of asthma have resulted in important changes in our therapeutic approach.

Clinical Evaluation

History. A number of studies have demonstrated that asthma may be both

underdiagnosed and overdiagnosed.⁵ Certainly, the first step in providing optimal care to patients with asthma is accurate diagnosis of their condition. Clinical evaluation should always begin with a precise description of symptoms, including wheezing, dyspnea, chest tightness, and cough. In many patients, particularly children, asthma may present as chronic cough with few, if any, other associated symptoms. Similarly, in the elderly, asthma may present as isolated dyspnea. Frequency of symptoms is another key feature of the evaluation, focusing on the number of times per week the patient experiences the above symptoms and whether they occur during the day or at night. When capturing information regarding symptom frequency, it is also important to determine the past number of severe attacks, and whether these exacerbations required emergency department visits or hospital care. Characterization of triggers should also be performed, including common influences, such as viral upper respiratory infections, cold air, exercise, airborne allergens (especially house dust mites, animal dander, and molds), airborne irritants, medications (including nonsteroidal anti-inflammatory agents and beta blockers), and foods (particularly sulfites used as preservatives). A patient's response to prior trials of therapy, particularly inhaled beta-adrenergic agonists, may be helpful in making a determination of asthma. Review of the patient's past medical history should include both upper airway symptoms and skin prob-

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lems dating back to the first few years of life. At least 50% of infants and children with atopic dermatitis will develop asthma, and teens with allergic rhinitis have at least a 3-fold greater risk of developing asthma.⁶ Finally, queries regarding a family history of atopic diseases should always be made. Individuals with 1 atopic parent have a 30% to 40% chance of developing allergic disease, whereas having 2 allergic parents confers a 50% to 60% risk of having these conditions.⁷

Physical Examination. The physical examination should focus on the skin, head, and chest. Evidence of nasal mucosal swelling and/or secretions and conjunctival injection are suggestive of chronic rhinitis and conjunctivitis, which are present in up to 90% of patients with asthma. A careful auscultatory examination of the chest should be conducted, listening for wheezing, a prolonged expiratory phase, and, in cases of acute deterioration, reduced breath sounds. Relatively asymptomatic patients may have evidence of mild wheezing during the examination. Conversely, patients with recent symptoms of asthma may have no evidence of wheezing. Because asthma is a disease that involves the airways diffusely, consistent findings of unilateral or localized wheezing should prompt a search for an alternative diagnosis (eg, mass lesion).

Objective Testing. In patients with chronic symptoms of asthma, it is always helpful to objectively define the degree of airway obstruction. This is best accomplished with a spirometer. A variety of models are available that automatically compute and display the most important measurements made during a forced expiratory blow, including the forced expiratory volume in 1 second (FEV₁), the forced expiratory vital capacity (FVC), the ratio of FEV₁ divided by FVC (FEV₁/FVC ratio), and the forced expiratory flow rate (FEF). The FEV₁ is the volume exhaled during the first second of a forced expiratory maneuver when the lungs are at full capacity. The FVC is the volume change of the lung between a full inspiration to total lung capacity and a maximal expiration to residual volume. The FEF_{25%-75%} is the average expiratory flow over the middle half of

the FVC, and may best reflect patency of the small airways. The most sensitive measures of obstruction are the FEV₁/FVC ratio, which is greater than 0.80 in people without asthma, and the FEF_{25%-75%}, which should be greater than 70% of the predicted value. In individuals with values lower than normal, 2 puffs of inhaled albuterol should be administered; a clinically significant bronchodilator response is defined as an improvement in FEV₁ of 12%.⁸ A hand-held peak flow meter can also be used in the clinic to assess airway obstruction; however, results of this test are both insensitive and nonspecific for the diagnosis of asthma. Nitric oxide analysis holds promise as an objective method for detecting asthma, but it is presently only available at specialized centers.⁹

In addition to measurement of lung function, all patients with persistent asthma should be assessed for the possibility of IgE-mediated hypersensitivities to airborne allergens. This is best accomplished by allergy skin prick testing, in which a drop of an allergenic extract is placed on the skin, the skin is then pricked by a standardized device, and results are interpreted 15 to 20 minutes later.⁸ Alternately, in vitro assays for specific IgE may also be used to demonstrate allergic reactivity. Allergens of greatest relevance to asthmatics with persistent disease include house dust mites, molds (particularly *Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus*), and animal dander. Confirmation of these sensitivities by objective testing will serve as the basis for allergen avoidance strategies directed at these specific allergens.

Classifying Asthma Severity. The National Heart, Lung, and Blood Institute has created a classification scheme categorizing asthma severity into 4 categories: mild intermittent, mild persistent, moderate persistent, and severe persistent asthma (Table 1).⁸ Daytime and nighttime frequency of symptoms and FEV₁ are the principal determinants of severity. This scheme has come to serve a critical purpose in asthma therapeutics, with recommendations for medication type and dose based on the patient's level of severity.

Two important caveats should be kept in mind when using this grading system. First,

Table 1. Classification of Asthma Severity

Step classification	Days with symptoms	Nights with symptoms	FEV ₁ or PEF (% pred)	PEF variability (%)
4 Severe persistent	Continual	Frequent	<60	>30
3 Moderate persistent	Daily	5/month	>60 - <80	>30
2 Mild persistent	>2/week but <once/day	>2/month	80	20-30
1 Mild intermittent	2/week	2/month	80	<20

Source: Adapted from reference 8.

FEV₁ indicates forced expiratory volume in 1 second; PEF, peak expiratory flow.

it is most relevant to patients who are not currently receiving asthma treatment. Although a patient might first present with moderate or severe persistent disease, appropriate therapy will usually alter the severity rating to a lesser level or even render the patient asymptomatic. A second and equally important issue is that even patients with mild, intermittent symptoms may develop severe, life-threatening exacerbations after certain triggers. Such attacks are most commonly caused by viral respiratory infections or acute exposure to airborne allergens.

Goals of Therapy

The goals of asthma therapy in individual patients are often widely divergent, ranging from the desire to take an after-dinner stroll without asthma symptoms to complete control of asthma, even during the most strenuous exercise. In general, the primary goal for most patients is the absence of asthma symptoms during the day and at night (Table 2). In addition, patients also value the ability to exercise without symptoms and a reduction in severe asthma attacks that result in a loss of work or school time.¹⁰

Prescribing physicians often have additional treatment goals that may not be specifically sought or understood by patients (Table 2), including reversal of chronic inflammatory changes in the lung and optimization of pulmonary function. In addition, it would be desirable to prevent long-term,

irreversible airway obstruction that is observed in select patients with asthma (“airway remodeling”). However, existing therapies have not been shown to significantly prevent this chronic loss of lung function. Increasingly, large organizations of specialty physicians (including the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the American Thoracic Society) have promoted these asthma care goals to prevent both acute and long-term sequelae of asthma.

First-line Treatment

For patients with persistent disease, the current guidelines stress the importance of daily use of a “controller” agent. Controller medications, which are taken daily on a long-term basis, include inhaled corticosteroids, long-acting beta2 adrenergic agonists, fixed-dose combination therapy, leukotriene modifiers, cromolyn, nedocromil, and theophylline.¹¹ The major categories of controller medications include inhaled corticosteroids, long-acting beta2 adrenergic agonists, fixed-dose combination therapy, and leukotriene modifiers.

Inhaled Corticosteroids. Inhaled corticosteroids are the most effective drug class for the treatment of persistent asthma and are considered the mainstay of treatment. Inhaled corticosteroids are the only class of drugs that consistently show a reduction in airway inflammation, as well as improvement in both pulmonary function and bronchial hyperresponsiveness.⁸ From a clinical perspective, regular use of these agents results in a significant reduction in daytime and nighttime symptoms, large improvement in quality of life, and reduction in acute exacerbations that lead to costly healthcare utilization. A recent meta-analysis by Sin et al evaluated the use of inhaled corticosteroids in clinical trials over the past decade. In this analysis of 11 placebo-controlled studies, 6 of the 11 studies showed a statistically significant impact on exacerbations of asthma, with a pooled relative risk of 0.46, meaning that there is a substantial reduction in the risk of exacerbations.¹² In addition to these randomized clinical trials, large, population-based

studies have demonstrated that regular use of inhaled corticosteroids significantly reduces rates of emergency department (ED) visits and hospitalization for asthma.¹³ Available inhaled corticosteroid formulations approved by the US Food and Drug Administration (FDA) for the treatment of asthma include beclomethasone dipropionate delivered in a hydrofluoroalkane (HFA) formulation; budesonide delivered by a dry powder inhaler (DPI) and by nebulized suspension; fluticasone propionate, recently formulated in an HFA vehicle; flunisolide delivered in a metered-dose aerosol system twice daily; triamcinolone acetonide delivered in a metered-dose aerosol unit with built-in spacer device; and mometasone furoate delivered in a DPI, which was recently approved by the FDA. As the newest of the available drugs, mometasone has been demonstrated to have in vitro potency similar to that of fluticasone, is approved for initial treatment with once-daily dosing, and appears to have negligible levels of active metabolites after administration, limiting its potential for systemic side effects.¹⁴

With regard to delivery systems, when formulated in the HFA vehicle, beclomethasone enters into a solution which is dispensed as an ultra-fine aerosol (average particle size 1-2 micron diameter) from a metered-dose actuator. These very small particles are able to penetrate into the region of the lung referred to as the "small" airways (diameter <2 mm). Drugs that do not dissolve in the HFA vehicle, such as triamcinolone acetonide and fluticasone propionate, form suspensions in HFA and are delivered as a larger-particle aerosol. The clinical importance of the ultra-fine aerosol has not yet been fully elucidated in clinical studies. Deciding on which inhaled corticosteroid and delivery system to use depends on a number of relevant considerations. Included among these are patient factors, such as inspiratory flow rates; in addition, the device itself may influence the amount of drug that is delivered to the lungs. Dosing recommendations for the available inhaled corticosteroids are shown in **Table 3**.

Two other inhaled corticosteroid drugs that are currently in development include ciclesonide, delivered as an HFA ultra-fine aerosol solution,¹⁵ and flunisolide, an older

Table 2. Goals of Asthma Management: Patient's Perspective

<p>Patient's goals:</p> <ol style="list-style-type: none"> 1. Control daily symptoms and eliminate nighttime awakening. 2. Minimize number and severity of attacks; no missed school or work due to attacks. 3. Minimize need to see doctor for treatment. 4. Increase ability to participate in desired physical activities. 5. No side effects of treatment. <p>Additional physician's goals:</p> <ol style="list-style-type: none"> 1. Eliminate exacerbations requiring emergency department care or hospitalization. 2. Reverse chronic inflammatory changes in the lung. 3. Optimize pulmonary function.

Source: Reference 10.

compound which has now also been reformulated as an HFA ultra-fine aerosol solution.¹⁶ Ciclesonide exists as a prodrug, which is metabolized by lung tissue into an active metabolite. It also appears to have a reduced capacity for causing systemic effects.

Despite the advantages of using inhaled corticosteroids and their superior efficacy, there are a number of pitfalls that must be recognized. Approximately 20% to 30% of patients manifest a less than satisfactory response, despite regular dosing, caused by a relative state of resistance. Inhaled corticosteroids have also been associated with negative effects on growth,¹⁷ although long-term studies of children demonstrate that these drugs do not have a significant effect on the attainment of final adult height.¹⁸ Although there have also been concerns regarding the effects of inhaled corticosteroids on bone mineral density, results from clinical studies have been mixed, with some studies demonstrating a significant effect whereas others have not.¹⁹ Although high doses of inhaled corticosteroids may also result in laboratory evidence of hypothalamic-pituitary-adrenal axis suppression, use of these drugs has not been associated with clinical signs of adrenal

Table 3. Currently Available Inhaled Corticosteroids

Compound	Delivery system	Potency (µg equivalence)*	Pulmonary deposition (%)	Recommended dosing (per day)
Beclomethasone dipropionate (QVAR®)	HFA	1	40	80-320 µg
Budesonide (Pulmicort Turbhaler®)	DPI Suspension (nebulization)	2	30	400-1600 µg 500-1000 µg
Fluticasone propionate (Flovent®)	HFA	1	18	88-880 µg
Mometasone furoate (Asmanex®)	DPI	1	Unknown	220-880 µg
Flunisolide (Aerobid®)	MDI	4	20	500-2000 µg
Triamcinolone acetonide (Azmacort®)	CFC	4	20	200-1600 µg

*Comparative number of micrograms required to exert same clinical effect.

HFA indicates hydrofluoroalkane; DPI, dry powder inhaler; MDI, metered-dose inhaler; CFC, chlorofluorocarbon.

Sources: All recommended dosing from current product prescribing information.

suppression except in the rarest of circumstances.¹⁷ Finally, patients may not feel an immediate improvement with these agents, thereby leading to reduced adherence to the therapeutic regimen.

Leukotriene Modifiers. Leukotriene D4 receptor antagonists, which include montelukast and zafirlukast, have also been employed as monotherapy for persistent asthma.²⁰ These compounds, which are oral formulations, have been approved for asthma in children and adults. They appear to act primarily as bronchodilators, although there is evidence for some anti-inflammatory effects. Another category of leukotriene modifiers, the 5-lipoxygenase inhibitors, block the synthesis of leukotriene B4, C4, D4, and E4.²⁰ Zileuton is the only 5-lipoxygenase inhibitor approved for the treatment of asthma and recently became commercially available in the United States.

Leukotriene modifiers, including both leukotriene receptor antagonists and 5-

lipoxygenase inhibitor, have demonstrated an approximate 40% reduction in exacerbations compared with placebo.¹² A pooled analysis of trials that compared leukotriene modifiers and inhaled corticosteroids as monotherapy showed that patients who were treated with inhaled corticosteroids had half the risk of an exacerbation compared with patients who received leukotriene modifiers.¹² Current asthma guidelines suggest leukotriene receptor antagonists as an alternative therapy to low-dose inhaled corticosteroids in patients with mild persistent asthma. Because montelukast has also been approved for use in allergic rhinitis, this agent offers another therapy option for patients with mild asthma and concomitant nasal allergy.²¹

Stepping Up Asthma Treatment

Repeated changes in clinical status can alert the physician that a patient's asthma has gradually worsened. Among these changes is an increase in daytime or night-

time asthma symptoms, an inability to participate in normal activities, an increase in use of inhaled, short-acting beta-agonists, or a reduction in pulmonary function or home peak flow. When these indicators of increased asthma severity arise, a number of issues must be addressed. Has there been a recent environmental change, such as the introduction of a new pet? Have there been changes in patient adherence with either medications or environmental control? Is the patient's inhaler technique satisfactory? Could the persistence of respiratory symptoms be a new medical problem, such as heart failure in an older patient or gastroesophageal reflux in a patient of any age who begins to have nocturnal asthma? Answering these questions is critical in determining the cause of the patient's deterioration, and in instituting the required changes in the patient's therapy and lifestyle.

In patients with mild-to-moderate persistent asthma whose symptoms are no longer controlled with an inhaled corticosteroid alone, the problem must be addressed by stepping up asthma controller therapy. Three options have been documented in the literature as viable choices in dealing with patients with chronically worsening asthma: (1) increasing the dose of inhaled steroid, (2) adding an inhaled long-acting beta₂ adrenergic agonist (LABA) to the prior dose of inhaled corticosteroid, or (3) adding a leukotriene modifier to the prior dose of inhaled corticosteroid.

A meta-analysis by Sin et al shows that increasing (usually doubling) the dose of inhaled corticosteroids does help to prevent exacerbations, with an overall reduction in relative risk of 23%.¹²

The effects of adding an inhaled LABA to a low to moderate dose of inhaled corticosteroid have been carefully studied for more than a decade. Clinical studies comparing low-dose inhaled corticosteroids plus a LABA have demonstrated significant improvement in both daytime and nighttime symptoms, pulmonary function, and quality of life. In addition, an analysis of pooled data showed that the above combination lessened exacerbations to a significantly greater degree when compared with a higher dose of inhaled corticosteroids alone.¹²

Currently, the combination of fluticasone propionate plus salmeterol is available in a single DPI with 3 different doses of fluticasone (100, 250, and 500 µg per puff).

The third option, adding a leukotriene modifier, has been shown to improve asthma symptoms and pulmonary function and reduce the daily requirement for inhaled corticosteroids.²² In a recent large meta-analysis, which compared leukotriene modifiers with a LABA as adjunctive therapy for poorly controlled asthma, all end points, including asthma symptom-free days, pulmonary function, and risk of exacerbations, significantly favored the addition of a LABA.²³

Beyond Dual Controller Treatment

In patients who continue to have asthma symptoms and/or frequent exacerbations despite use of a high-dose inhaled corticosteroid plus a LABA, adding either a leukotriene receptor antagonist or zileuton as a third-line therapy should be considered. Although there are currently no published data demonstrating additive efficacy with a leukotriene modifier, a short trial of 1 of these drugs may yield benefit in some patients.

In patients with severe perennial allergic asthma, typically due to dust mites, animal dander, and/or molds, omalizumab, an anti-IgE antibody treatment, may be beneficial. Omalizumab has been shown to reduce asthma exacerbations, including those requiring ED care or hospitalization, and improve quality of life when added to an inhaled corticosteroid aerosol plus a LABA treatment regimen. In a recent analysis of pooled data, there was a 50% reduction in ED visits and an approximate 97% reduction in hospitalizations in those patients randomized to the active treatment.²⁴ These results were found to be both clinically and statistically significant, forming a realistic rationale for the use of omalizumab in treating patients with poorly-controlled symptoms of allergic asthma. Use of omalizumab is predicated on demonstration, via skin or in vitro allergy testing, of an allergic hypersensitivity to 1 or more relevant perennial allergens. In addition, ultimate determination for the necessity of omalizumab should be made by

an asthma specialist, generally an allergist or pulmonologist, who is experienced in the treatment of severe asthma.

Long-term Monitoring

Asthma is a dynamic condition, and a patient's clinical status may change over a relatively short period of time. Several methods have been employed to monitor clinical status in asthmatics in the hope of preventing attacks which can lead to life disruption, hospitalization, or even death. Validated asthma questionnaires have been shown to accurately assess asthma control and are predictive of future exacerbations requiring hospital care.²⁵ Such surveys are administered to the patient at home or in the physician's office to determine recent changes in symptoms, rescue beta-agonist use, and ability to engage in normal activities. In addition, monitoring home peak expiratory flow may enable some patients to more accurately gauge their status, particularly if they have such atypical symptoms as an isolated cough.

Long-term monitoring of exhaled nitric oxide was recently demonstrated to improve the dosing of inhaled corticosteroid doses and subsequently reduce exacerbation rates.⁹ While not currently widely available, this new technology may find a wider audience in the future and help to control asthma attacks.

Referral to an Asthma Specialist

Patients who have poorly controlled asthma despite appropriate pharmacotherapy and avoidance of triggers should be evaluated by an asthma specialist. An allergist or pulmonary disease specialist will carefully consider the possibility of other comorbid conditions that might be contributing to asthma symptoms, such as sinus disease, gastroesophageal reflux, and vocal cord dysfunction. Careful assessment of the home and work environment may need to be considered, or even inspected, if unusual exposures are suspected. More detailed pulmonary function testing, such as body plethysmography (for measuring diffusion capacity and lung volumes), bronchial methacholine challenge testing, and/or exercise testing, may be required in some cases to distinguish asthma from other pulmonary

conditions. Finally, adjustment of existing therapies or initiation of a new treatment, as in the case of omalizumab, will also be carefully considered by an asthma specialist. Recent research has demonstrated that referral to allergists significantly improves asthma outcomes, including reductions in hospitalizations.²⁶ Although these effects were related, in part, to the increased use of inhaled corticosteroids, other factors also appear to have been operative.

Conclusion

To provide patients with the best asthma care possible, an in-depth patient evaluation must be conducted to accurately diagnose the condition, characterize its severity level, and identify important triggers. After this, a thoughtful, stepped-care approach should be employed. Most important, treatment of persistent asthma requires vigilance on the part of both patient and physician, with ready access to personalized medical advice when needed. A combination of evidence-based therapies and close follow-up will most certainly improve asthma outcomes in the future.

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REFERENCES

1. Bousquet J, Chanez P, Lacoste JY, et al. Eosinophilic inflammation in asthma. *N Engl J Med.* 1990;323:1033-1039.
2. Busse WW, Lemanske RF Jr. Asthma. *N Engl J Med.* 2001;344:350-362.
3. Robinson DS, Hamid Q, Ying S, et al. Prominent TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med.* 1992;326:298-304.
4. Platts-Mills TA. The role of immunoglobulin E in allergy and asthma. *Am J Respir Crit Care Med.* 2001;164:S1-S5.
5. van Weel C. Underdiagnosis of asthma and COPD: is the general practitioner to blame? *Monaldi Arch Chest Dis.* 2002;57:65-68.
6. Greisner WA 3rd, Settiple RJ, Settiple GA. Natural history of hay fever: a 23-year follow-up of college students. *Allergy Asthma Proc.* 1998;19:271-275.
7. Wright AL. The epidemiology of the atopic child: who is at risk for what? *J Allergy Clin Immunol.* 2004;113(suppl 1):S2-S7.
8. National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program (NAEPP) Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002. National Institutes of Health Publication 02-5074. Bethesda, Md: US Department of Health and Human Services; 2003.

- 9. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR.** Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med.* 2005; 352:2163-2173.
- 10. Global Strategy for Asthma Management and Prevention.** NIH Publication 02-3659. Issued January 1995 (updated 2002).
- 11. National Heart, Lung, and Blood Institute.** National Asthma Education and Prevention Program (NAEPP), Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma—Clinical Practice Guidelines. National Institutes of Health Publication 97-4051. Bethesda, Md: US Department of Health and Human Services; 1997.
- 12. Sin DD, Man J, Sharpe H, Gan WQ, Man SF.** Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis. *JAMA.* 2004;292:367-376.
- 13. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R.** Inhaled steroids and the risk of hospitalization for asthma. *JAMA.* 1997;277:887-891.
- 14. Chrousos GP, Ghaly L, Shedden A, Iezzoni DG, Harris AG.** Effects of mometasone furoate dry powder inhaler and beclomethasone dipropionate hydrofluoroalkane and chlorofluorocarbon on the hypothalamic-pituitary-adrenal axis in asthmatic subjects. *Chest.* 2005;128:70-77.
- 15. Reynolds NA, Scott LJ.** Ciclesonide. *Drugs.* 2004; 64:511-519.
- 16. Shafazand S, Colice G.** Flunisolide HFA for the treatment of asthma: an old friend reformulated. *Expert Opin Pharmacother.* 2004;5:1163-1173.
- 17. Allen DB.** Inhaled steroids for children: effects on growth, bone, and adrenal function. *Endocrinol Metab Clin North Am.* 2005;34:555-564.
- 18. Agertoft L, Pedersen S.** Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med.* 2000;343:1064-1069.
- 19. Lipworth BJ.** Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med.* 1999;159:941-955.
- 20. Kemp JP.** Recent advances in the management of asthma using leukotriene modifiers. *Am J Respir Med.* 2003;2:139-156.
- 21. Chervinsky P, Philip G, Malice MP, et al.** Montelukast for treating fall allergic rhinitis: effect of pollen exposure in 3 studies. *Ann Allergy Asthma Immunol.* 2004;92:367-373.
- 22. Phipatanakul W, Greene C, Downes SJ, et al.** Montelukast improves asthma control in asthmatic children maintained on inhaled corticosteroids. *Ann Allergy Asthma Immunol.* 2003;91:49-54.
- 23. Ram FS, Cates CJ, Ducharme FM.** Long-acting beta 2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev.* 2005;CD003137.
- 24. Corren J, Casale T, Deniz Y, et al.** Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. *J Allergy Clin Immunol.* 2003;111:87-90.
- 25. Vollmer WM, Markson LE, O'Connor E, et al.** Association of asthma control with health care utilization and quality of life. *Am J Respir Crit Care Med.* 1999;160:1647-1652.
- 26. Schatz M, Cook EF, Nakahiro R, Petitti D.** Inhaled corticosteroids and allergy specialty care reduce emergency hospital use for asthma. *J Allergy Clin Immunol.* 2003;111:503-508.