The Role of the Immune System in the Pathogenesis of Asthma and an Overview of the Diagnosis, Classification, and Current Approach to Treating the Disease

ELI O. MELTZER, MD

ABSTRACT

OBJECTIVE: To describe what is currently known about the role of allergy and immunologically active cells and mediators in the airway inflammation associated with asthma; to review the diagnosis, classification, and treatment of the disease in accordance with current National Asthma Education and Prevention Program guidelines published in 2002; and to discuss therapeutic issues related to asthma management.

DATA SOURCES: This article is based on a presentation given by the author at a symposium entitled "New Frontiers in Asthma Management: Biotechnology for Optimal Therapeutic and Economic Outcomes" at the Academy of Managed Care Pharmacy's 15th Annual Meeting and Showcase in Minneapolis, Minnesota, on April 10, 2003.

CONCLUSIONS: Type 2 helper T (Th2) cells, various other cell mediators and cytokines, and immunoglobulin E play important roles in the pathogenesis of asthma. Atopy is an inherited condition characterized by a predominance of Th2 cells and it predisposes to asthma. Objective measures of pulmonary function improve confidence in the diagnosis of asthma and should be used to monitor response to therapy. Asthma severity is often underestimated by patients and physicians, which can lead to inadequate treatment. Inhaled corticosteroids (ICSs) are the preferred maintenance treatment for patients with persistent asthma because these medications are the most potent and effective long-term controller pharmaceutical agents. Addition of a long-acting inhaled beta$_2$-agonist or a leukotriene modifier to ICS therapy provides added benefit to patients with moderate or severe persistent asthma inadequately controlled by corticosteroids. Choosing an appropriate delivery system for inhaled drug therapies can affect patient adherence and the effectiveness of therapy.

KEYWORDS: Asthma, Immune system, Inhaled corticosteriod therapy, Inhaled beta$_2$-agonist, Immunoglobulin E

Author Correspondence

ELI O. MELTZER, MD, codirector, Allergy & Asthma Medical Group and Research Center, 9610 Granite Ridge Dr., #B, San Diego, CA 92123. Tel: (858) 292-1144; Fax: (858) 268-5145

Asthma is a chronic inflammatory disorder of the airways.[1] Inflammation contributes to airway hyperresponsiveness (an exaggerated response to various exogenous and endogenous stimuli), airflow obstruction, and respiratory symptoms that include wheezing, coughing, chest tightness, and shortness of breath.[1,2] Inflammation may be present even in patients with minimal or no symptoms.[2]

Airflow obstruction usually is at least partially reversible, spontaneously or with treatment.[2] Obstruction may be the result of bronchoconstriction, bronchial edema, mucus plug formation, airway wall remodeling, or a combination of these factors.[2]

Role of the Immune System

Airway inflammation is an immune-mediated process involving inflammatory cells and mediators released by these cells. Airway inflammation is characterized by increased numbers of eosinophils, mast cells, macrophages, and T lymphocytes (T cells) in the mucosa and lumen.[2] The major trigger of airway inflammation is the allergic response. In persons with atopy (i.e., an inherited predisposition to produce immunoglobulin E [IgE] in response to exposure to common environmental allergens), inhaled allergens deposit on bronchial mucosal tissues where antigen-presenting cells (e.g., dendritic cells) process the allergen and present it to T cells (Figure 1).[3] Type 2 helper T (Th2) cells produce interleukin-4, interleukin-5, and other cytokines, resulting in a cascade of effects.[3] Interleukin-4 causes B cells to induce formation of IgE specific to the allergen. Some of the IgE binds to the membranes of mast cells and other cells that contain preformed inflammatory mediators (e.g., histamine, tryptase, and lipid mediators, including leukotrienes, prostaglandins, thromboxanes, and platelet-activating factor).[3] Subsequent exposure to the allergen causes cross linking of the membrane-bound IgE, degranulation of mast cells, and release of the inflammatory mediators. These mediators contribute to acute-phase symptoms (e.g., wheezing) by causing airway smooth-muscle contraction, vasodilation, and increased vascular permeability and mucus secretion.[3]

Most patients with asthma also experience a late-phase reaction characterized by airway obstruction and hyperresponsiveness.[2] These effects are mediated by interleukin-5 and other cytokines that cause inflammatory cells (e.g., eosinophils, basophils, and neutrophils) in the bloodstream to adhere to the vascular endothelium. Diapedesis and cellular infiltration into bronchial tissues follow. The cells contain substances (e.g., basic proteins) that cause epithelial cell damage and disrupt the mucosal lining and also affect blood vessels, resulting in increased vascular permeability

and leakage, edema, and swelling. Airway smooth-muscle hypertrophy and hyperplasia, increased angiogenesis, and collagen deposition (i.e., remodeling) may ensue in patients with chronic inflammation.[2]

Atopy

Genetics influence the likelihood of developing asthma.[2] Atopy runs in families and can be measured using allergen skin tests or in vitro assays of total or specific IgE. Atopy during childhood predisposes to asthma.[2] In a study of newborns followed past the age of 6 years, elevated IgE serum concentrations were a predictor of persistent wheezing at the age of 6 years.[4]

There is an imbalance between type 1 helper T (Th1) cells and Th2 cells in patients with asthma and other atopic diseases (e.g. allergic rhinitis), and Th2 cells predominate in these patients. Type 2 helper T cells predominate in all neonates. Persons without atopy develop a Th1-mediated immune response to allergens as a result of a process referred to as immune deviation.[3] By contrast, Th2 cells increase during infancy and childhood in atopic persons. Factors other than genetics that might contribute to atopy (e.g., exposure to allergens) are the subject of controversy.

Diagnosis

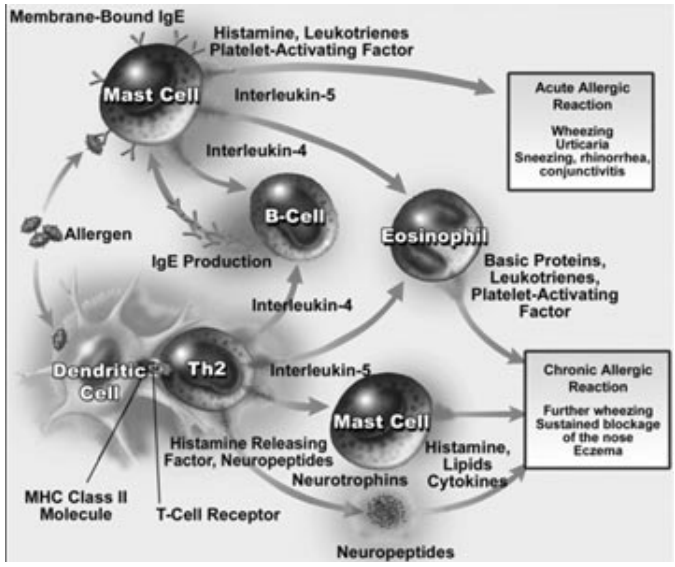
Asthma often is diagnosed on the basis of a patient's medical history (Table 1). Asthma should be suspected in patients with a recurrent history of bronchitis, croup, pneumonia, or bronchiolitis. Patients may have been told that they have reactive airway disease in the past to avoid labeling them with a chronic disease, but the term is synonymous with asthma.

Asthma symptoms follow a circadian rhythm (they tend to worsen at night), and they may be absent at the time of assessment despite abnormal pulmonary function. Objective measures of pulmonary function increase the confidence in the diagnosis of asthma.[2] They also provide a baseline for comparing the response to treatment. The forced expiratory volume in 1 second (FEV1) measured with spirometry provides one measure of pulmonary function. An improvement of at least 12% in FEV1 spontaneously, after inhalation of a bronchodilator or in response to corticosteroid therapy, supports the diagnosis of asthma.[2]

An improvement in the peak expiratory flow (PEF) rate of at least 15% after inhalation of a bronchodilator or in response to corticosteroid therapy also suggests the diagnosis of asthma.[2] The PEF rate is a less reliable measure of pulmonary function than FEV1. However, measuring PEF is a practical method for monitoring lung function in the home setting.

Airway hyperresponsiveness to stimuli (a methacholine challenge or an exercise challenge) is another measure of pulmonary function that may help in the diagnosis of asthma in patients with symptoms despite normal FEV1 and PEF values.[2] These tests sometimes have false positive results, but negative responses often are useful for ruling out asthma. Airway hyperresponsiveness is associated with chronic obstructive pulmonary disease and other

FIGURE 1 Pathways Leading to Acute and Chronic Allergic Reactions



Mackay IR, Rosen FS. NEJM. 2001;344(1):30-37

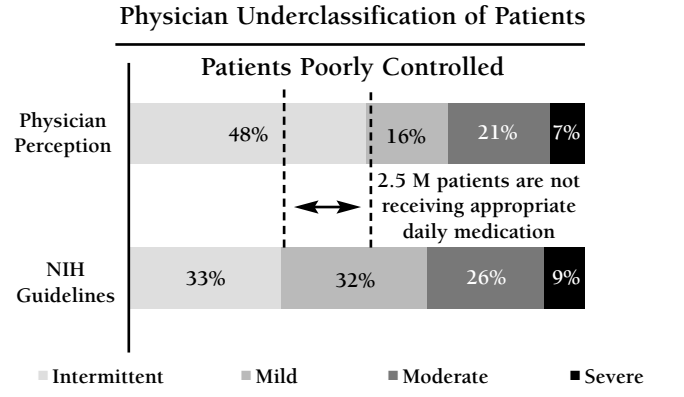
TABLE 1 Components of the Patient Medical History Used to Diagnose Asthma[1,5]

- Type of symptoms (wheezing, coughing, shortness of breath, and chest tightness)
- Frequency and severity of symptoms
- Factors that provoke or exacerbate symptoms (i.e., triggers, such as upper-respiratory-tract infections, pet dander, and exercise)
- Impact of symptoms on quality of life
- A personal history of allergies or other atopic diseases (e.g., atopic dermatitis)
- A family history of asthma or other atopic diseases
- Response of symptoms to asthma medications
- Required frequency of asthma medication use

TABLE 2 National Asthma Education and Prevention Program Classification of Asthma Severity[5]

Step	Daytime Symptoms	Exacerbations	Nighttime Symptoms	PEF or FEV1 (PEF variability)
4: Severe Persistent	Continual	Frequent; limits activity	Frequent	≤60% (>30%)
3: Moderate Persistent	Daily	≥2 times/week affects activity	>1 night/week	>60% to <80% (>30%)
2: Mild Persistent	>2 times/week but <1 time/day	May affect activity	>2 nights/month	≥80% (20%-30%)
1: Mild Intermittent	≤2 days/week	Brief, with normal lung function and no symptoms between episodes	≤2 nights/month	≥80% (<20%)

FIGURE 2 *Asthma Severity Using National Asthma Education Prevention Program Criteria Compared With Physician Perception of Asthma Severity*



**Physician perception based on calculation from M/A/R/C, 1995 and MMI's Therapeutic Class Study—Asthma, 1996; NHLBI guidelines based on calculation from Migliara/Kaplan Outcomes study, 1996 and MMI's Therapeutic Class Study—Asthma, 1996.*

conditions as well as asthma.[2]

The diagnosis of asthma is not based on a physical examination of the respiratory system (i.e., auscultation) because wheezing may be absent despite substantial airflow limitation.[2]

Classification

Asthma severity is classified in one of 4 steps on the basis of daytime and nighttime symptom frequency, duration, and severity: impact on activity levels; exacerbations (clinically important decreases in PEF rate; increases in short-acting inhaled beta$_2$-agonist use; and pulmonary function (PEF or FEV1 and PEF variability) before treatment (Table 2). Asthma is classified as persistent if symptoms occur more than twice a week and/or nocturnal symptoms occur more than twice a month.[5]

Asthma severity is a continuum, and it may change over time in a particular patient. Moreover, patients may experience exacerbations that vary in severity regardless of how their asthma severity is classified. For example, a patient with mild persistent asthma may experience a severe exacerbation.

Patients tend to underestimate the severity of their asthma. In the Asthma in America Survey of roughly 2,500 patients with asthma, patient self-ratings of asthma severity were compared with the severity classification determined using the National Asthma Education and Prevention Program (NAEPP) criteria (Table 2). A total of 28% of patients with mild persistent, moderate persistent, or severe persistent asthma using the NAEPP criteria reported no symptoms (i.e., they underestimated the severity of their asthma). Seventy-nine percent of patients with asthma that was moderate persistent or severe persistent reported only mild symptoms, and 41% of patients with severe persistent asthma reported only moderate symptoms. This tendency for patients to underestimate the severity of their asthma has serious implications if perceived severity affects the likelihood that patients will seek and use asthma medication (i.e., asthma may be inadequately treated, leading to exacerbations).

Physicians also may underestimate asthma severity. Asthma is estimated to be mild intermittent, mild persistent, moderate persistent, or severe persistent in 33%, 32%, 26%, and 9%, respectively, of the population with asthma (Figure 2), using the NAEPP criteria for classifying severity. However, the results of a study of physician perception of asthma severity revealed that severity was classified by the physicians as mild intermittent in 48% of patients, mild persistent in 16% of patients, moderate persistent in 21% of patients, and severe persistent in 7% of patients (i.e., the percentage of patients with mild intermittent asthma was overestimated and the percentage of patients with mild persistent asthma was underestimated). Extrapolation of these findings suggests that asthma severity is underestimated and inadequately treated in 2.5 million patients with mild persistent asthma.

Treatment

The components of asthma management used to meet the therapeutic goals are patient education and formation of a partnership between the patient and clinician, environmental control measures to reduce allergen exposure, pharmacotherapy, and immunotherapy. Asthma management is almost certain to fail without appropriate patient education. Objective assessment of pulmonary function using spirometry or PEF measurements also is vital to asthma management.[2]

Proper use of the PEF meter is essential to obtain a meaningful value, and patients should be taught and asked to demonstrate proper use of the device.[2] Patient counseling should address the importance of knowing one's personal best PEF value as a benchmark for comparison and using the PEF meter periodically to monitor pulmonary function. This counseling should be repeated at regular intervals to reinforce the concepts.

Environmental control measures may prevent or minimize asthma symptoms. Advantages of using environmental control measures include the lack of adverse effects and drug interactions and the safety of the approach for all age groups.

Asthma medications fall into one of 2 groups: quick relievers and long-term controllers. Quick relievers include short-acting inhaled or oral beta$_2$-agonists, inhaled ipratropium bromide (an anticholinergic agent), and short courses of oral corticosteroids (slow onset of action >4 hours). These agents are used as rescue agents to treat acute symptoms. Short-acting inhaled beta$_2$-agonists are the drugs of choice for this purpose. The short-acting inhaled beta$_2$-agonists are also prescribed to prevent exercise-induced bronchospasm. Increasingly frequent use of a short-acting inhaled beta$_2$-agonist may indicate the need to initiate or increase long-term controller therapy.[5]

Long-term controllers include inhaled and systemic corticosteroids, long-acting inhaled and oral beta$_2$-agonists, inhaled cromones (cromolyn sodium and nedocromil sodium), oral leukotriene modifiers, and oral sustained-release theophylline. These agents are used daily on a long-term basis to maintain control of persistent asthma and prevent exacerbations.

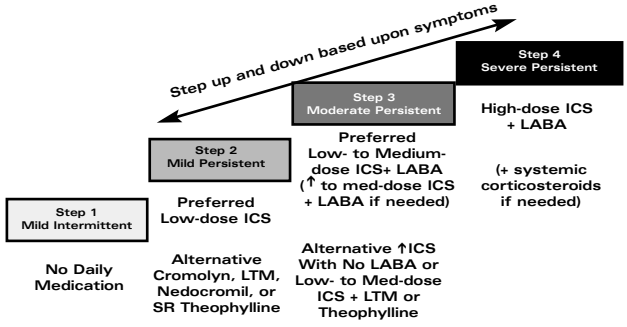
The current NAEPP asthma treatment guidelines (published in 2002) reflect what has been learned in recent years about the pathogenesis of asthma and the comparative efficacy of various drug therapies.[5] As in the past, the current guidelines recommend a stepwise approach for managing asthma (Figure 3). However, because inhaled corticosteroids (ICSs) are the most potent and effective long-term preventive medications, they are now considered the preferred treatment for patients with persistent asthma (low-, low-to-medium-, and high-dose therapy is recommended for asthma that is mild persistent, moderate persistent, and severe persistent, respectively).[5] ICSs improve asthma symptoms, pulmonary function, and quality of life and reduce airway hyperresponsiveness, the frequency and severity of exacerbations,[2] and the need for hospitalization,[6] short-acting inhaled beta$_2$-agonists, and oral corticosteroids.[7] Systemic corticosteroids may be required to control severe persistent asthma.[2,5]

Current (2002) NAEPP guidelines recommend the use of long-acting inhaled beta$_2$-agonists in combination with ICSs for patients with asthma that is moderate persistent or severe persistent.[5] In previous (1997) NAEPP guidelines, increased doses of ICSs were an alternative to adding long-acting inhaled beta$_2$-agonists for moderate persistent asthma. However, the combination is now recommended because adding the long-acting inhaled beta$_2$-agonist improves lung function and symptoms and reduces the need for short-acting inhaled beta$_2$-agonists for quick relief.[1,5]

Patients should be advised that long-acting inhaled beta$_2$-agonists are not substitutes for ICSs and should not be used alone or to treat acute symptoms or exacerbations. A large safety study of the long-acting inhaled beta$_2$-agonist salmeterol xinafoate was terminated early because an interim analysis revealed an increased risk of life-threatening asthma episodes or asthma-related deaths, although these serious adverse events were rare.[8] The risk appeared to be increased in African-American patients and in patients not receiving ICSs. Nevertheless, the benefits of the long-acting inhaled beta$_2$-agonists for the asthma population continue to outweigh their risks, according to the U.S. Food and Drug Administration.[8]

Leukotriene modifiers include 2 leukotriene receptor antagonists (montelukast and zafirlukast) and, until recently, zileuton, a leukotriene synthesis inhibitor that acts by interrupting the 5-lipoxygenase pathway.[9] Zileuton was not widely used because of hepatic toxicity and the need for frequent administration (4 times daily) of large tablets (i.e., patient nonadherence can be a problem).[9] Current NAEPP guidelines reflect the position of leukotriene modifiers in asthma drug therapy for the first time. Leukotriene modifiers were not among the therapeutic options in previous NAEPP guidelines because the agents were new and clinical experience with the drugs was insufficient at the time.[1]

FIGURE 3 Stepwise Approach to Managing Asthma in Adults and Children Older Than 5 Years



ICS = inhaled corticosteriod LABA = long-acting β2-agonist;
LTM = leukotriene modifier SR = sustained release.

NIH/NHLBI Guideline Update, June 2002. NIH Publication No. 02-5075

In the current NAEPP guidelines, leukotriene modifiers are an alternative to ICSs for patients with mild persistent asthma,[5] although ICSs are preferred because they are more effective for improving FEV1 and reducing the need for hospitalization than leukotriene modifiers.[10,11] Adding a leukotriene modifier to an ICS is an alternative to an ICS plus a long-acting inhaled beta$_2$-agonist (the preferred therapy) for patients with moderate persistent asthma[5] because the combination of the leukotriene modifier and ICS is more effective for improving FEV1 and reducing nocturnal awakenings and asthma exacerbations than the ICS alone.[10]

In previous (1997) NAEPP guidelines, cromones and corticosteroids were alternatives for treating mild persistent asthma, and neither of the 2 therapies was preferred.[1] The position of cromones in current NAEPP guidelines represents a change from previous guidelines because ICSs are now the preferred therapy for mild persistent asthma, and cromones are an alternative.[5] When an ICS was compared with nedocromil sodium in children aged 5 to 12 years with mild to moderate asthma, the corticosteroid was significantly more effective than nedocromil sodium in improving airway responsiveness and controlling asthma.[12] Cromones also may be used prophylactically before exposure to asthma triggers (e.g., exercise).[2]

Oral sustained-release theophylline may be used as an alternative to ICSs for mild persistent asthma.[5] Theophylline also may be used in combination with an ICS for patients with moderate persistent asthma,[5] although these combinations are less effective than an ICS plus a long-acting inhaled beta$_2$-agonist, which is the preferred therapy.[2] The use of theophylline is limited by its adverse effect profile (e.g., nausea, vomiting, tachycardia, nervousness, and insomnia[13]) and the need to monitor serum drug concentrations.

Two approaches may be used for initial drug therapy to gain control of asthma: (1) starting therapy at the step corresponding to

TABLE 3 Key Clinical Activities for Providing Quality Asthma Care[15]

1. Establish asthma diagnosis
2. Classify severity of asthma
3. Schedule routine follow-up care
4. Assess for referral to specialty care
5. Recommend measures to control asthma triggers
6. Treat or prevent comorbid conditions (e.g., rhinitis, sinusitis, gastroesophageal reflux disease, chronic obstructive pulmonary disease, influenza)
7. Prescribe medications according to severity
8. Monitor use of beta$_2$-agonists
9. Develop a written asthma management plan
10. Provide routine education on patient self-management

the severity of disease and gradually stepping up if control is not achieved, and (2) starting therapy at a step higher than the severity and stepping down once control is achieved. The latter step-down approach is preferred because it provides rapid control.[1]

Indications of the need to step up or increase long-term controller therapy in a patient with good previous asthma control include an increase in symptoms, nocturnal awakening because of symptoms, diminished ability to participate in exercise or customary daily activities, daily or increased use of short-acting inhaled beta$_2$-agonists, reduction in PEF rate by roughly 20% or more, or failure to achieve therapeutic goals.[2]

Therapeutic Issues

In its 2002 update report, the NAEPP expert panel addressed several therapeutic issues in asthma management, including the question of whether the use of antibiotics in addition to standard treatment improves the outcomes of treatment for acute asthma exacerbations.[5] Most asthma exacerbations are associated with infection by a respiratory virus.[14] Infections caused by bacteria are infrequent causes of asthma exacerbations.[14] The presence of phlegm in the lungs may reflect mucus associated with asthma or viral infection. Viral infections often resemble bacterial infections. The expert panel determined that the results of clinical trials do not support the use of antibiotics routinely or when suspicion of bacterial infection is low.[5]

The 2002 NAEPP expert panel report also addressed the question of whether the use of a written asthma action plan improves outcomes compared with medical management alone and whether use of an action plan based on PEF rate monitoring improves outcomes compared with a plan based on symptoms.[5] Insufficient data were available to draw conclusions about the benefits of written action plans or whether plans should be based on PEF monitoring. Nevertheless, written actions plans were recommended by NAEPP as part of an overall effort to educate patients in self-management, especially patients with moderate persistent or severe persistent asthma or a history of severe exacerbations.[5] Developing a written asthma management plan was one of 10 key clinical activities that are essential for quality asthma care recommended by NAEPP in 2003 (Table 3).[15] In 2002, NAEPP also recommended that PEF monitoring be considered because it may enhance communication between the clinician and patient and increase patient awareness of his or her disease status and control.[5]

In the Asthma in America Survey, there were large discrepancies between patients and physicians in perceptions about whether actions plans had been developed, PEF meter use had been recommended, lung function testing had been performed, follow-up visits had been scheduled, and inhaler use had been demonstrated.[16] Although nearly all physicians thought that a follow-up visit had been scheduled, only 55% of patients were under that impression, a situation that has serious implications because of the need for ongoing monitoring of asthma.

Patient Adherence

A study of adherence to asthma pharmacologic therapy over a 13-week period in 24 patients aged 8 to 12 years who received ICSs and short-acting beta$_2$-agonists by pressured metered-dose inhaler (pMDI) found that the rate of compliance with the corticosteroids was 13.7% for patients who experienced asthma exacerbations and 68.2% % for patients without exacerbations, a difference that is significant.[17] Compliance was measured both electronically, using a device attached to the pMDI, and with diary cards filled out by the child or a parent, although neither the subjects nor their parents were aware of the electronic monitoring. The electronic device revealed that 58% of prescribed corticosteroid doses were taken, with only 31% of prescribed doses taken on time. By contrast, the diary cards suggested that 95% of prescribed doses were taken as directed. Thus, poor asthma control may reflect patient nonadherence, even in patients who report taking their medications as prescribed because some patients exaggerate the extent to which they are compliant.

Effectiveness

The effectiveness of long-term controller therapy in patients with asthma may differ from the efficacy demonstrated in clinical trials because of patient nonadherence, which usually comes less into play in clinical trials. Factors that can affect adherence to the therapeutic regimen include route of administration, type of delivery system for inhaled drug therapies, administration frequency, adverse effects, cost, and patient education (e.g., understanding of proper inhalation technique, the medication regimen, and the importance of adherence).

Immunotherapy

Allergen immunotherapy is effective for reducing symptoms of allergic asthma and should be considered for patients with demonstrable evidence of specific IgE to clinically relevant allergens. The decision to initiate allergen immunotherapy depends on the extent to

which symptoms can be reduced by allergen avoidance and medications and the amount, type, and adverse effects from pharmacotherapy.[18]

In a meta-analysis of 20 randomized, placebo-controlled, double-blind trials of allergen immunotherapy for asthma, the combined odds of symptomatic improvement from immunotherapy for any allergen was 3.2.[19] The odds of reduction in bronchial hyperreactivity were 6.8. In studies of immunotherapy for mites, the odds of reduction in medication requirements were 4.2. The mean predicted improvement in FEV1 from any immunotherapy was 7.1%.[19]

Conclusions

Asthma is often the result of an allergic cascade involving antigen presentation by dendritic cells to Th2 cells, which predominate in atopic individuals. Mast cells, eosinophils, and various other inflammatory cells; interleukins and other cytokines; and IgE appear to play key roles in this cascade. Asthma should be diagnosed on the basis of a patient medical history, but objective measures of pulmonary function can confirm the diagnosis and monitor response to therapy.

Although asthma severity is classified in one of 4 categories, severity is a continuum and it changes over time in an individual. Patients and physicians tend to underestimate asthma severity, which can lead to inadequate treatment and exacerbations. Current NAEPP guidelines reflect what has been learned recently about the greater efficacy of ICSs compared with leukotriene modifiers and cromones and the benefits of using corticosteroids in combination with long-acting inhaled beta$_2$-agonists for moderate persistent and severe persistent asthma. The route of administration, type of delivery system for inhaled drug therapies, administration frequency, adverse effects, cost, and patient education can affect patient adherence to and the effectiveness of pharmacotherapy. Immunotherapy is a valuable option in patients with a significant allergic component to their asthma.

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