Asthma Update: Epidemiology and Pathophysiology

Margaret F. Guill, MD*

Objectives  
After completing this article, readers should be able to:

1. Characterize asthma, including its prevalence in the United States.
2. Describe the interaction of immunologic mechanisms producing airway inflammation and hyperreactivity in asthma.
3. Discuss the major risk factor for persistent asthma in young children.

This is the first of a two-part article on asthma. Readers should consider both parts for a complete review.

Introduction
Asthma continues to be the leading serious chronic illness among children, responsible for 10 million lost school days each year and costing more than $12 billion per year. Asthma is not a series of episodic events over time, but a state of airway inflammation and hyperresponsiveness that has variable manifestations within a given patient and between individuals. In this first of two articles, we review the epidemiology and pathophysiology of asthma. The second part reviews diagnosis, classification of severity, and management of asthma.

Definition
The Expert Panel of the National Asthma Education and Prevention Program defined asthma in its 1997 report as a “chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.” Although convoluted and a bit difficult to follow, this definition captures the chronic and inflammatory nature of asthma, its pathophysiology involving multiple cell types, and the variable nature of its manifestations.

Epidemiology
According to the National Center for Health Statistics, the prevalence of asthma in children younger than 18 years of age increased from 36 per 1,000 children to 62 per 1,000 between 1980 and 1996. Since 1997, when the survey tool was redesigned to measure attack prevalence (one or more episodes in the last 12 mo) rather than the diagnosis prevalence, the rate has remained at about 54 per 1,000 (Fig. 1). At all time points, African-American children have been affected more frequently than Caucasian children such that in 2000, the ratio was almost 2:1. Hospitalization rates also were markedly higher for African-American children, by a margin of 3 to 4:1. The overall death rate due to asthma rose annually from 1980 to 1998 to 3.3 deaths per 1 million children in 1998 (Fig. 2). African-American children continued to have the highest death rates, which are four to five times higher than those for Caucasians. One explanation for the progressive rise in incidence from 1980 to 1995 may be better recognition of asthma, with improved diagnosis as physicians changed their understanding of “recurrent” or “chronic bronchitis” and “recurrent bronchiolitis” to asthma. However, there is not a satisfactory

*Professor of Pediatrics; Chief, Pediatric Pulmonology, Medical College of Georgia, Augusta, Ga.
explanation for the increased prevalence of asthma in African-Americans. Increased morbidity may be explained by lack of access to health care or by use of episodic care rather than appropriate, consistent preventive management. Other potential contributing factors may include early and high exposure to allergens, particularly house dust mites and cockroaches often found in urban settings that have poor hygiene, and high prevalence of tobacco smoke exposure in urban and crowded environments. Lack of educational opportunities for parents and other caregivers to understand the pathophysiology and appropriate management of asthma and lack of the personal educational background to apply the asthma education that is offered also may play a role.

Multiple factors contribute to the incidence and persistence of asthma in children. In a landmark study of the epidemiology of respiratory symptoms in children, Martinez et al enrolled more than 1,200 newborns from the Tucson area in a longitudinal evaluation of respiratory symptoms. They followed more than 800 of these newborns to 6 years of age with interval assessments at 1 and 3 years. By 6 years of age, 50% never had had a wheezing illness, 20% had had early wheezing that resolved by 3 years of age, 15% had had the onset of wheezing after 3 years of age, and 14% had developed wheezing that persisted from infancy to age 6 years. The primary risk factor for transient early wheezing was maternal smoking. These children also had reduced pulmonary function in the first postnatal year that normalized by 6 years, suggesting an effect of prenatal tobacco smoke exposure on lung development. Late-onset wheezing was associated with maternal asthma and male gender. Persistent wheezing was associated with maternal asthma, Hispanic ethnicity, eczema, maternal smoking, rhinitis apart from colds, and male gender (decreasing order of importance). Despite normal lung function in the first year after birth, the reduced function at 6 years suggests the early onset of potentially irreversible anatomic changes. Late-onset and persistent wheezing also were associated with elevated serum immunoglobulin (Ig) E and positive allergy skin tests at 6 years of age. As these children were followed into the second decade of life, those who wheezed in the first 3 years were found to be at greatest risk of having active asthma at 6 to 13 years of age if they...
had either a personal history of eczema or parental history of asthma or two of the following—physician-diagnosed allergic rhinitis, greater than 4% peripheral eosinophils, or wheezing apart from upper respiratory tract infections.

It has been suggested that early intervention with anti-inflammatory treatment in this population of wheezing, at-risk infants and children could result in prevention of persistent asthma at school age, although hard data to support this hypothesis do not yet exist.

Allergy plays a major role in childhood asthma. The predominant risk factor for persistent asthma in childhood is a personal or family history of allergy. In large population studies, 40% to 80% of children who have asthma have at least one positive allergen skin test. In the past, major educational efforts have focused on limiting allergen exposure in the home by controlling the presence of house dust mites, cockroaches, mold, and indoor pets. Ironically, several recent studies suggest that exposure to indoor pets or living in a farming environment in the first year after birth may decrease allergen sensitization and asthma manifestations in later life. This apparent paradox is explained by the role of T-helper (Th) lymphocytes and their cytokines in the development of asthma.

Th-1 and Th-2 lymphocytes represent opposing populations that are important in defending against infection (Th-1) and production of allergic inflammation (Th-2). The “hygiene hypothesis” of asthma suggests that in Western society, where environments are sanitized and antibiotic treatment is abundant, the normal switch from Th-2 predominance at birth (inflammatory cytokines associated with allergy) to a balance of Th-1/Th-2 relationships is inhibited by lack of exposure to environmental endotoxins and infections. The increase in allergy and asthma in society as a whole may be promoted by lack of exposure to infection and endotoxin. The proposed protective effect of indoor pets and farming environments lies in endotoxin exposure, which promotes Th-1 predominance. Increased levels of endotoxin have been found in dust samples from mattresses of children who had indoor pets (United States) and who lived in environments with farm animals (Europe). There is an inverse relationship between endotoxin level at 1 year of age and allergen sensitization at 6 to 7 years.

Although this is an oversimplification of complex immunologic interactions, it provides a context in which to place the role of early infection and later asthma as well as the role of allergens in asthma. The Tucson study, among others, also has demonstrated that early child care...
exposure with frequent viral infections affords relative protection from allergies and asthma at 6 to 7 years of age. The same is said for second and subsequent siblings in a household having a lower incidence of asthma and allergy. However, those children in child care and those who had older siblings did have a higher incidence of wheezing before 2 years of age. Therefore, 60% of children who experience wheezing in the first 3 years of life have resolution of the wheezing by school age, and allergy is the major predictor of persistence. Also, 60% of all children who have asthma have resolution of the condition by adulthood. Adolescence often is a time when children who have asthma symptoms seem to improve, although those who have severe asthma and significant atopy are less likely to “outgrow” their asthma.

Despite our better understanding of the pathophysiology and management of asthma, mortality has not improved significantly in the last 20 years. The most significant risk factors for fatal asthma include having one or more life-threatening episodes, the need for chronic systemic steroids, and poor perception of severity of obstruction. Additional factors are listed in the Table. Atopy is a poor discriminator of risk because most children who have asthma also have atopy.

### Pathophysiology

The recognition over the past 10 to 15 years that asthma is an inflammatory process that involves multiple cell types and mediators has revolutionized the approach to prevention and management. For years, asthma was perceived only as episodic bronchospasm and approached from the standpoint of smooth muscle physiology. Subsequently, the understanding of airway inflammation, with infiltration of eosinophils chronically and neutrophils during acute episodes, led to treatment with anti-inflammatory agents as well as to the concept of underlying bronchial hyperreactivity as a baseline state. More recently, the demonstration of basement membrane thickening and understanding of airway remodeling in association with nonreversible airflow obstruction has led to concerns that early and aggressive intervention may be needed to affect the natural history of disease. There is no evidence yet that early intervention with anti-inflammatory agents in young children who have asthma can change the long-term outcome. It is too early to tell from current studies what the change in natural history will be.

Inflammation is the underlying abnormality present in patients who have even mild asthma. The spectrum of inflammatory changes may include submucosal infiltration with activated lymphocytes and eosinophils, activation of mast cells, epithelial changes, and basement membrane thickening. These changes occur along a continuum from mild to severe asthma. In fatal asthma, additional findings of mucus plugging in airways, goblet cell hyperplasia, and smooth muscle hypertrophy/hyperplasia also usually are present and represent extension of the inflammatory continuum.

Laboratory and clinical studies performed in the late 1980s and 1990s demonstrated the inflammatory nature of allergic asthma, the role of multiple cell types and cytokines, and the biphasic response to allergen provocation. These concepts have provided the foundation for current understanding of the pathophysiology and for therapeutic approaches. The seminal role of allergy and atopic sensitization is related to specific IgE fixed to airway mast cells and basophils and their activation causing release of multiple mediators of inflammation and bronchospasm (Fig. 3). Mast cell activation releases histamine and leukotrienes, which are responsible for the immediate bronchospastic response to allergen exposure. Proinflammatory cytokines and chemokines released at the same time stimulate chemotaxis of eosinophils, neutrophils, and activated lymphocytes, which provide ongoing inflammation and whose mediators trigger a delayed bronchospastic response 4 to 12 hours after the

### Table. Risk Factors for Asthma Deaths

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<tr>
<td>Past history of sudden severe exacerbations</td>
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<td>Prior intubation and mechanical ventilation for asthma</td>
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<td>Prior asthma admission to the intensive care unit</td>
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<td>Two or more asthma hospitalizations in the last year</td>
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<td>Three or more emergency department visits for asthma in the last year</td>
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<td>Hospitalization or emergency department visit in the last month</td>
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<td>Use of &gt;2 canisters per month of short-acting bronchodilators</td>
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<td>Current use of systemic steroids or recent withdrawal from steroids</td>
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<td>Difficulty perceiving airflow obstruction and its severity</td>
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<td>Comorbidity that may affect cardiopulmonary status (eg, heart disease)</td>
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<td>Serious psychiatric disease or psychosocial problems</td>
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<td>Low socioeconomic status and urban residence</td>
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<td>Illicit drug use</td>
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<td>Sensitivity to Alternaria</td>
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initial antigen exposure (Fig. 4). The early bronchospasm may be severe, but usually responds promptly to short-acting bronchodilators, indicating primarily smooth muscle involvement. The delayed bronchospasm is poorly responsive to bronchodilators and may last hours to days unless treated with systemic steroids, indicative of the more inflammatory nature of this response. These studies also demonstrated an overall increase in nonspecific airway hyperresponsiveness that lasted up to 2 weeks after a single allergen exposure, linking the delayed bronchospasm, airway inflammation, state of hyperreactive airways, and clinical manifestation of chronic asthma.

Our understanding of asthma pharmacology also is linked to these very important studies of 10 to 15 years ago. Inhaled cromolyn was found to prevent both the early and late airway responses to allergen challenge, confirming its role as a mast cell stabilizer and the importance of mast cells in allergic asthma. Inhaled steroids were found to inhibit the late, but not the early bronchospastic response, helping us to understand their role in preventing inflammation but not bronchospasm. Inhaled steroids given prior to an antigen challenge also prevent the increased airway responsiveness associated with the late-phase response and airway inflammation, again helping to demonstrate the relationship between pathophysiology and pharmacotherapy.

The second major pathophysiologic mechanism in asthma is related to the interaction of Th-1 and Th-2 lymphocytes and their respective cytokines. Th-1 cells generate interleukin (IL)-2 and interferon-gamma, important mediators in defense against infection. Th-2 cells produce multiple mediators of allergic inflammation, including IL-4, -5, -6, -7, and -13. Early and persistent Th-2 predominance may be important in promoting ongoing airway inflammation and asthma symptoms. Early life events that promote Th-1 ascendency (exposure to endotoxins, child care, older siblings, viral infections, and minimal antibiotics) may inhibit progression of airway inflammation and atopic sensitization.

Humanized monoclonal IgG anti-IgE antibodies have been developed and marketed recently for children and adults who have atopic asthma. The antibodies are administered subcutaneously at 2- to 4-week intervals for an extended period of time. There is no modulation of IgE production, but rather binding of serum IgE, making less antibody available for mast cell sensitization, which has led to decreased asthma symptoms and decreased steroid need in premarketing studies.

Antibodies against IL-5 also have been administered systemically and found to decrease circulating eosinophils, but there has been no effect on late-phase responses to antigen challenge and no change in airway hyperreactivity. An inhaled soluble IL-4 receptor also has been developed that binds and antagonizes free IL-4, an inflammatory mediator that stimulates B-cell activation and, potentially, specific IgE production (Fig. 3). Trials have shown variable benefits in promoting asthma control. Therapeutic measures directed toward specific immune mechanisms have demonstrated good effects in vitro and in animal models but less-than-desired outcomes in human trials. Much of this may represent individual idiosyncrasies of human phenotypes in asthma and inflammation. The impetus for the development of specific immune modulators has been a desire to avoid some of the global effects of steroids, which control multiple immune functions simultaneously. However, long-term use of inhaled steroids has been demonstrated to decrease bronchial hyperreactivity and airway inflammation, whereas none of the specific modulator therapies has had such an effect. Current studies reiterating the safety of long-term use of inhaled steroids in children, in the context of their global anti-inflammatory action,
have helped to secure the primary role of inhaled steroids in chronic asthma management.

Much remains to be learned about the natural history of asthma in light of new treatments and about the pharmacophysiology of immunologically directed treatments. The advances in knowledge of the epidemiology and pathophysiology of asthma in the last 15 years have been astounding when viewed retrospectively. There is every expectation that the next 15 years will bring equally dramatic changes in the knowledge base and therapeutic expectations.

**Suggested Reading**


Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA*. 2002;288:963–972


PIR Quiz
Quiz also available online at www.pedsinreview.org.

1. Which of the following statements regarding the epidemiology of asthma in children is true?
   A. African-American children are hospitalized more frequently than Caucasian children.
   B. Caucasian children die from asthma more frequently than African-American children.
   C. The incidence of asthma has increased steadily over the last 20 years.
   D. The incidence of asthma is higher in Caucasian children than in African-American children.
   E. The presence of allergic rhinitis increases the risk of death from asthma.

2. A young mother who has asthma asks you about her son’s risk for developing asthma. The child is now 8 months old and has had one prior episode of wheezing. Of the following, you are most likely to tell her that:
   A. He has a higher risk of developing asthma if he also has eczema.
   B. If his mother does not smoke cigarettes, he has a low risk for developing asthma.
   C. If pulmonary function test results are normal now, he has a low risk for developing asthma.
   D. Keeping him out of child care will reduce the risk of asthma.
   E. Treating him with anti-inflammatory medication will prevent him from developing asthma.

3. Which of the following increases the risk of dying from asthma?
   A. Chronic concurrent use of inhaled steroids and leukotriene inhibitors.
   B. Exposure to indoor pets in the first year after birth.
   C. Having the first episode of wheezing in the first postnatal month.
   D. History of one prior admission to the inpatient ward for asthma.
   E. Monthly emergency department visits for asthma in the last year.

4. Which of the following best describes the mechanism of the early bronchospastic response to allergen exposure in an asthma exacerbation?
   A. Cytokine-stimulated chemotaxis of eosinophils.
   B. Generation of interleukin-2 and interferon-gamma by Th-1 lymphocytes.
   C. Infiltration of the submucosa by activated lymphocytes.
   D. Leukotriene and histamine release from activated mast cells.
   E. Mucus plugging and goblet cell hyperplasia.

5. Which of the following medications has been shown to prevent both the early and late phases of bronchospasm in asthma exacerbations?
   A. Inhaled corticosteroids.
   B. Inhaled cromolyn sodium.
   C. Inhaled long-acting bronchodilators.
   D. Inhaled short-acting bronchodilators.
   E. Interleukin-5 antibody.