Asthma Epidemiology, Pathophysiology, and Initial Evaluation

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Asthma Epidemiology, Pathophysiology, and Initial Evaluation

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Objectives

After completing this article, readers should be able to:

1. Describe the underlying pathophysiology of asthma.
2. Discuss the role of atopy in the development of asthma.
3. Identify risk factors for death from asthma.
4. List conditions to be considered in the differential diagnosis of wheezing in children.

Introduction

Asthma is a disease of airway inflammation characterized by hyperresponsiveness and airflow obstruction that lead to symptoms such as cough and wheezing (Fig. 1). Childhood asthma continues to cause significant morbidity and burden in the United States. This article reviews the pathophysiology, epidemiology, and recommendations for initial evaluation of asthma. Recommendations are based on the *2007 Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* ("2007 Guidelines"). (1)

Epidemiology

Prevalence and Burden of Disease

The prevalence of asthma rose steadily from 1980 until the late 1990s, when it reached a plateau. In 2007, 9% of children 0 to 17 years of age (6.7 million children) had asthma, according to data from the National Health Interview Survey. The lifetime prevalence of asthma in children is 13%. (2)

The burden of disease in the United States from pediatric asthma is alarming, according to a recent report based on national surveys. In 2003, 12.8 million days of missed school were attributed to asthma. In 2004, hospitalizations for asthma totaled 198,000 or 3% of all pediatric admissions. Asthma resulted in 750,000 emergency department (ED) visits in that same year (2.8% of all pediatric ED visits). Although children ages 0 to 4 years of age represent only a small proportion of the total asthma population, they account for a sizeable proportion of the hospitalizations and ED visits. (3)

Natural History

The natural history of asthma is variable. Most individuals who develop chronic asthma, measured by a decrease in lung function and persistence of symptoms, have a genetic predisposition. In addition, exposure of the airway epithelium to environmental insults in such susceptible individuals contributes to the development, severity, and persistence of asthma.

The Tucson Children's Respiratory Study, a longitudinal community-based study of 1,246 children who were followed from birth until early adulthood, provides data on the natural history of respiratory disease in children. (4) Data from this study show that wheezing in the first 3 years after birth often is associated with a lower respiratory tract infection, most commonly respiratory syncytial virus (RSV). Thirty-two percent of all children have wheezing with acute lower respiratory tract infections in the first year after birth, 17% in the second year, and 12% in the third year. More than 80% of infants who have a history of wheezing in the first postnatal year do not wheeze after age 3 years.

Abbreviations

ED: emergency department
FEV_1: forced expiratory volume in 1 second
Ig: immunoglobulin
IL: interleukin
RSV: respiratory syncytial virus
Th: T-helper
VCD: vocal cord dysfunction

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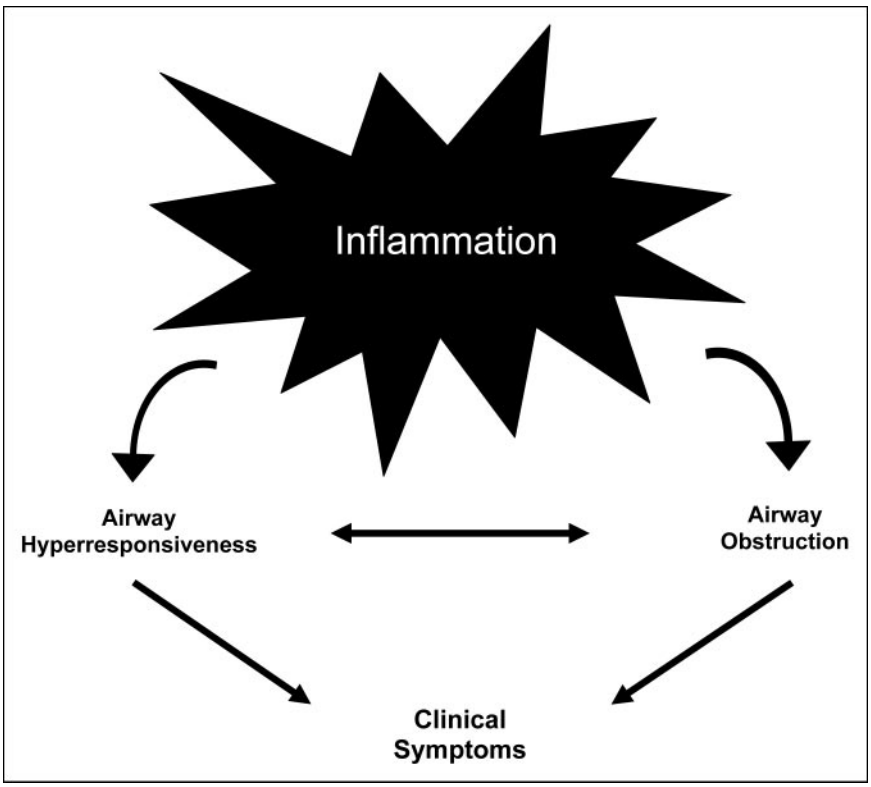

Figure 1. Mechanisms underlying the clinical symptoms of asthma. Adapted from the National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma.* 2007.

The investigators also identified three distinct wheezing phenotypes that occur during childhood. "Transient wheezers" are those infants whose wheezing is associated with one or more lower respiratory tract infections and who cease to wheeze after 3 years of age. "Nonatopic wheezers" are children who have relatively more reactive airways, a higher incidence of previous RSV infection, and persistent wheezing after age 3 years, which may resolve over time. "Atopic wheezers" are the group of children who are most likely to develop persistent asthma. They have higher immunoglobulin E (IgE) concentrations, are prone to allergen-mediated airway hyperresponsiveness, and have more profound lung function deficits at an early age compared with "nonatopic wheezers." In general, 60% of children who have asthma are symptom-free by adulthood. However, only 5% to 30% of children who have severe asthma or asthma associated with atopy outgrow their asthma by adulthood. (5)

Mortality and Health Disparities

Although mortality rates have fallen since 1999, asthma remains a preventable cause of death in children. In 2004, the mortality rate from asthma was 2.5 per 1 million children for a total of 186 deaths per year. Therefore, it is crucial to identify children at risk of death from asthma. In general, the rate of death from asthma is higher in severe, uncontrolled disease. Specific risk factors include: one or more life-threatening exacerbations of asthma, severe asthma requiring chronic oral corticosteroids, poor control of daily asthma symptoms requiring frequent short-acting $beta_2$ agonist medication, abnormal forced expiratory volume in 1 second (FEV_1), frequent ED visits, low socioeconomic status, family dysfunction, and patient psychological problems. (6)

Racial disparities are significant in asthma. Prevalence rates for asthma are highest among Puerto Rican and African American children. Compared with white children, African American children have higher rates of ED visits but lower outpatient and ambulatory visits. African American children continue to have higher rates of mortality than other children, despite a downward trend in overall asthma mortality rates. (3) Such disparity reflects limited access to outpatient health services compared with other children. (7)

Pathophysiology

Inherent to asthma is airway inflammation that is mediated by a variety of cell subtypes, resulting in hyperresponsive airways, ultimately limiting airflow and causing variable symptoms. Initial airway bronchoconstriction is followed by airway edema and exaggerated mucus production, accompanied by airway hyperresponsiveness, and followed by chronic changes in the airway epithelium (airway remodeling). Current medical management targets various points along this continuum. However, no clear evidence suggests that early or aggressive treatment with anti-inflammatory medications, such as inhaled corticosteroids, can prevent airway remodeling.

Airway inflammation is mediated by a variety of cytokines and chemokines (cytokines that are specific for chemotaxis and activation of leukocytes). Cytokines are

produced by a number of cell types, including lymphocytes, eosinophils, and mast cells. Proinflammatory cytokines (interleukin-4 [IL-4], IL-5, and IL-13), produced primarily by the T-helper (Th)2 lymphocytes, are believed to trigger the intense inflammation of allergic asthma. An imbalance between Th1 and Th2 lymphocytes (specifically, decreased Th1 activity with increased Th2 activity) contributes to chronic inflammatory asthma. Chemokines play a key role in inflammation. These proteins recruit proinflammatory cells, including Th2 lymphocytes, mast cells, neutrophils, and eosinophils. Eosinophils and mast cells have a distinct role in asthma pathogenesis. These cell types produce proinflammatory cytokines as well as leukotrienes, which cause bronchoconstriction.

The airway epithelium is a target for infectious, noxious, and environmental insults that cause injury via influx of proinflammatory cells and cytokines (Fig. 2). Both viral infections and airborne allergens can precipitate a biphasic response that ultimately leads to asthma symptoms. IgE plays a pivotal role in this process, as shown by evidence that administration of anti-IgE monoclonal antibodies reduces asthma symptoms and improves lung function. (8) The IgE-mediated "early-phase" or "immediate" response to an allergen challenge causes mast cells and basophils to degranulate, precipitating bronchospasm as well as the release of proinflammatory cytokines and chemokines. This cascade of inflammatory responses results in the subsequent "late-phase" obstruction of air flow, which occurs 4 to 12 hours following exposure to the environmental insult. Bronchodilators can relax airway smooth muscle, if administered during the initial period of bronchospasm. However, due to the increased airway hyperresponsiveness and inflammation that occur with the late-phase response, bronchodilator therapy is not as effective, and anti-inflammatory medication is required.

Asthma also is characterized on a cellular level by structural alterations in the airway epithelium. Airway remodeling can occur and is associated with the following changes in the underlying structural components of the epithelium: mucous gland hyperplasia, thickening of the epithelial basement membrane, fibrotic changes in the sub-basement membrane, bronchial smooth muscle hypertrophy, and eventually angiogenesis.

Clinical Aspects

Asthma is characterized by intermittent, recurrent symptoms of airway obstruction that is at least partially reversible. Common symptoms include cough (which may be the only symptom), wheezing, difficulty breathing, and "chest tightness." Nighttime symptoms are common. In addition, symptoms often occur or worsen in the presence of common asthma "triggers," such as exercise, changes in the weather, viral respiratory infections, and exposure to allergens or airway irritants (eg, environmental tobacco smoke). To diagnose asthma, the physician must exclude other conditions. The diagnosis may be particularly difficult in very young children because wheezing is common in early childhood and many diseases can cause symptoms similar to those seen in asthma.

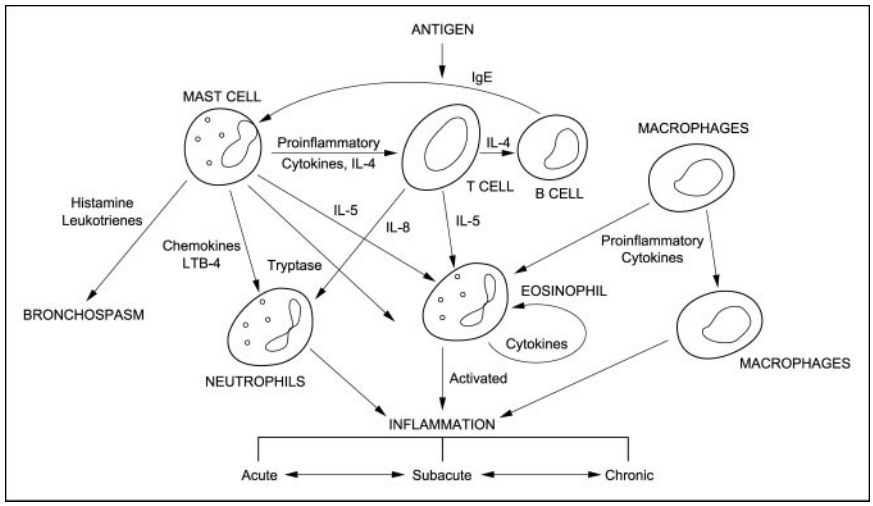

Figure 2. Cellular mechanisms involved in airway inflammation. IL=interleukin, IgE=immunoglobulin E, LTB4=leukotriene B4. From the National Asthma Education and Prevention Program. *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.* 1997.

Evaluation

Initial evaluation should begin with a detailed medical history, including the pattern of symptoms and observed precipitating factors (asthma triggers). Past medical history should include information about risk factors for asthma (particularly atopy), prior exacerbations, treatments used, and their effects. A positive family history of parental asthma substantially increases the risk of asthma in a child. Evaluation also should include an assessment of the impact of asthma on the child and family. The physical examination of a child who has asthma often yields normal find-

ings, although there may be signs of atopy, such as eczema or allergic rhinitis, which are strongly associated with asthma.

The 2007 Guidelines recommend objective measurement of pulmonary function (spirometry) as part of the initial evaluation. Most children older than age 6 or 7 years are capable of performing a forced expiratory maneuver, if coached by an experienced technician. Some centers can test children as young as 5 years of age. Spirometry should be performed before and after administration of a short-acting bronchodilator. FEV_1 that increases by 12% or more following the administration of bronchodilators indicates reversible airway obstruction, even if baseline FEV_1 is normal. Spirometry results may be normal, particularly in children who have mild asthma. Baseline chest radiography may be useful to rule out other conditions, particularly in very young children or in patients manifesting atypical signs and symptoms.

Differential Diagnosis

The differential diagnosis of asthma is broad and includes upper airway disease as well as obstruction of large airways and other causes of small airway obstruction. Upper airway disease, such as allergic rhinitis or sinusitis, can cause recurrent coughing, particularly at night, but often has other signs or symptoms that help distinguish it from asthma. Extrinsic or intrinsic obstruction of the large airways (eg, tracheomalacia, vascular ring, mass, or foreign body) may present with signs and symptoms similar to those of asthma. Specific findings, such as a change in airway symptoms with position or failure of symptoms to respond to usual asthma treatment, may be helpful in the diagnosis. Individuals who have ingested a foreign body often have a history of acute onset of symptoms following a choking episode, but this history is more difficult to elicit in very young children. Recurrent aspiration or gastroesophageal reflux also can result in recurrent bouts of coughing or other respiratory symptoms that might be confused with asthma. A careful history that examines the pattern of symptoms and looks for evidence of risk factors for reflux or aspiration, such as prematurity, feeding difficulties, or neurologic impairment, may be helpful.

Vocal cord dysfunction (VCD) presents with wheezing or breathlessness associated with paradoxic vocal cord adduction during inspiration and may be difficult to distinguish clinically from asthma. Although VCD is a distinct diagnosis, it also may coexist with asthma and complicate its management. VCD, which is more common in adolescents and young adults, does not respond to asthma medications and, therefore, should be included in the differential diagnosis of atypical or difficult-to-control asthma. The diagnosis may be suspected based on clinical history and spirometry that shows a flattened inspiratory loop. Definitive diagnosis usually is made by a specialist and based on viewing of the vocal cords during an episode.

A number of conditions that cause obstruction of the small airways may result in wheezing or other symptoms similar to those found in asthma. These include bronchiolitis, cystic fibrosis, congestive heart failure, and chronic lung disease of prematurity. Recurrent episodes of bronchiolitis may occur in young children and sometimes are difficult to distinguish from asthma. A detailed past medical history and careful physical examination often help to distinguish the latter three conditions from asthma.

Asthma is particularly difficult to diagnose in infants and toddlers. Recurrent wheezing episodes are common in young children. Data from the Tucson Children's Respiratory Study showed that almost 50% of children have at least one wheezing episode prior to age 6 years; in most of these children, the wheezing is transient and resolves prior to age 6 years. (4) These data were used to build a "risk index" for asthma in young children. Specifically, children experiencing four or more episodes of wheezing per year that last more than 1 day and affect sleep are likely to develop asthma if they also have one of the following major risk factors: 1) parental history of asthma, 2) atopic dermatitis, and 3) sensitization to aeroallergens or two of the following minor risk factors: 1) sensitization to foods, 2) more than 4% eosinophilia, or 3) wheezing apart from colds. According to the 2007 Guidelines, the young child who has a positive risk index is at a high risk of developing asthma and should be started on anti-inflammatory therapy.

In summary, asthma cannot be diagnosed based on a single episode of wheezing, but rather requires observation of the pattern of symptoms over time. Individuals manifesting atypical signs and symptoms or clinical asthma that does not respond to asthma medications may

Summary

- The prevalence of asthma and the burden of disease remain high, despite efforts to improve public awareness about and medical management of asthma.
- Asthma is a disease of airway inflammation that has a variable natural history.
- Atopy is the most important risk factor for the development of asthma.

require additional diagnostic studies (eg, specialized imaging of the chest or bronchoscopy) and referral to a pulmonary specialist for additional evaluation.

NOTE. An article on the management of asthma will be published in next month's issue of *Pediatrics in Review*.

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PIR Quiz

Quiz also available online at pedsinreview.aappublications.org.

1. An 11-month-old boy presents with fever, runny nose, and difficulty breathing for 1 day. Physical examination shows an axillary temperature of 37.8°C, respiratory rate of 32 breaths/min, and heart rate of 110 beats/min. Diffuse expiratory wheezes are audible bilaterally. He had similar illness 2 months ago. The mother is concerned about her son developing asthma during his childhood. Which of the following is the *most* appropriate response to her concerns about her son?

   A. If he has two more episodes of wheezing during the next year, his chances of having asthma during childhood are greater than 80%.
   B. If he responds to bronchodilators such as albuterol, there is a greater than 80% risk that he will have asthma during childhood.
   C. If the respiratory infection is due to RSV, he should have less than a 20% risk of developing asthma during childhood.
   D. More than 80% of infants who have a history of wheezing after respiratory infection in the first postnatal year do not wheeze after age 3 years.
   E. More than 80% of infants younger than 1 year of age who have respiratory tract infections wheeze during their illness.

2. A 3-year-old boy who has a previous history of allergic rhinitis and eczema presents to your office with cough and wheezing for 2 days. The symptoms started after he visited his uncle's house and played with a cat. Which of the following statements about his current state is true?

   A. Airway inflammation has occurred due to action of cytokines and chemokines.
   B. Airway remodeling has occurred, characterized by mucous gland hyperplasia and bronchial smooth muscle hypertrophy.
   C. Current illness represents the early phase of mast cell activation, causing bronchospasm.
   D. Eosinophils have been activated by IgE, causing IL-4 release.
   E. Th1 lymphocyte activation by IgA has caused airway hyperreactivity.

3. A 6-year-old girl is brought in for evaluation of nighttime cough and wheezing after being exposed to secondhand smoke. A pulmonary function test (PFT) using a forced expiratory maneuver to display a flow-volume curve is ordered. Which of the following statements is *most* accurate regarding PFT in this situation?

   A. Flattening of the inspiratory portion of the flow volume loop and decreased forced vital capacity suggest the presence of asthma.
   B. Increase in FEV_1 by at least 12% after administration of a bronchodilator is indicative of asthma.
   C. Normal PFT indicates that the patient does not have airway hyperresponsiveness and, therefore, retesting with a bronchodilator is unnecessary.
   D. PFT assessment in those younger than age 8 years is unreliable due to lack of patient cooperation.
   E. PFT should be performed after challenging the patient with secondhand smoke and retesting after administration of a bronchodilator.

4. A 15-year-old girl who has a known history of asthma is hospitalized for exacerbations of cough, wheezing, and shortness of breath. Her asthma has become increasingly unresponsive to bronchodilators and corticosteroids in the past 5 years. Flow-volume loop using a forced expiratory maneuver shows flattening of the inspiratory loop. Flexible fiberoptic laryngoscopy shows adduction of vocal cords and narrowing of the subglottic area during inspiration. Which of the following is the *most* likely diagnosis?

   A. Laryngomalacia.
   B. Subglottic hemangioma.
   C. Subglottic stenosis.
   D. Tethered vocal cord.
   E. Vocal cord dysfunction.

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