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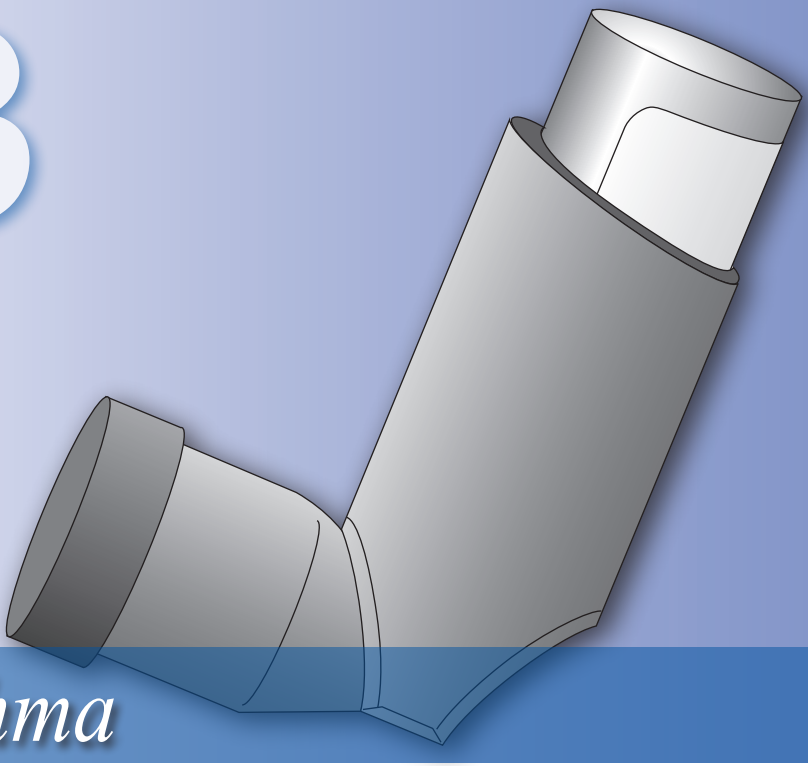


Asthma

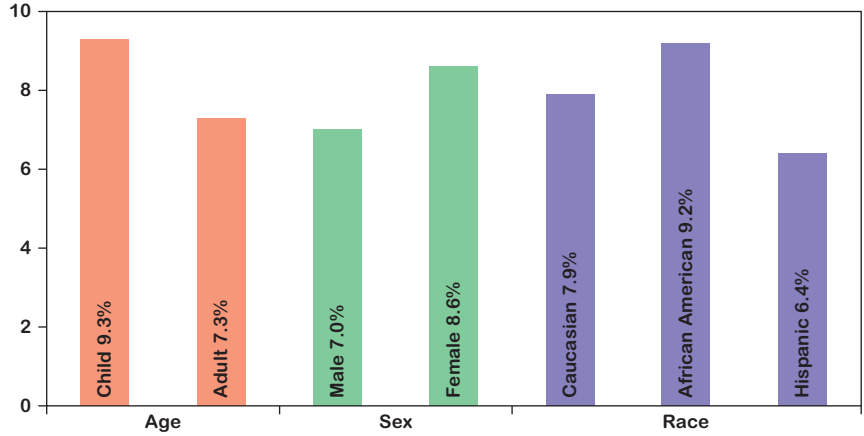
Asthma is a common but complex disease of the pulmonary airways (trachea, bronchi, and bronchioles) that is characterized by difficulties getting air in and out of the lungs (variable airflow obstruction), environmental triggers causing breathlessness (airway hyperresponsiveness), and cellular inflammation.

Whom does it affect?

Epidemiology, prevalence, economic burden, vulnerable populations

Epidemiological studies have established features of asthma and provided insight into many of its characteristics, including the age of onset, sex distribution, risk factors, and long-term consequences. The International Study of Asthma and Allergies in Childhood (ISAAC) surveyed nearly 200,000 children six to seven years old and over 300,000 children 13 to 14 years old in more than 50 countries (1). The results from this survey found the prevalence of asthma to be over 10 percent in some countries, including the United Kingdom, New Zealand, Australia, Costa Rica, the United States, and Brazil. In contrast, in other countries, like China, the prevalence of asthma is slightly over 5 percent. In recent years, some countries and locales have demonstrated a near doubling in the prevalence of asthma.

Asthma prevalence by age, gender, and race in the United States, 2006



Asthma poses a greater risk for children, women, and African Americans.
National Health Interview Survey, National Center for Health Statistics, Centers for Disease Control and Prevention.

From these and other surveys, it is apparent that asthma prevalence is influenced by a variety of factors (2,3). First, the presence of asthma is greatest in the more "westernized" areas of the world—the Americas, Europe, and Australia. Second, as more countries shift their lifestyle to a more western pattern of living (which includes fewer severe infections early in life, greater use of antibiotics, more processed foods, and a shift from rural to urban living) the prevalence of asthma increases. Finally, in countries with a less western lifestyle, the prevalence of asthma is low and remains at this level until such societal changes occur. These data suggest that factors associated with a western lifestyle are associated with a greater risk or frequency of asthma (2). These epidemiological changes led to the development of the "hygiene hypothesis," which proposes that a "cleaner" environment shifts the immune response toward the development of allergies and asthma (4).

In the United States, the prevalence of asthma has followed the increase seen worldwide over the past two decades (5). From 1980 to the late 1990s, the prevalence of asthma doubled, with rates of 6 percent in children and more than 4 percent in adults. Prevalence assessments are dependent on how the asthma is identified. For example, when asthma is characterized as an "attack," the

prevalence is less than 4 percent. If the question asked is, "Have you had asthma in your lifetime?" over 10 percent of respondents will answer yes, which more accurately reflects the at-risk population. By any measure, asthma is the most common pulmonary disease in children.

Individual risk factors for asthma include a family history of asthma or allergies, a mother who smokes, being raised in an urban environment, early development of eczema (atopic dermatitis), and the appearance of environmental allergies (6). For the at-risk child, certain environmental allergens—house dust mites, cockroaches, and molds such as *Alternaria*—are most likely to be important to the development of asthma. The contribution of animal dander from dogs and cats is undergoing re-evaluation, with some evidence saying that, depending on the age of exposure, the presence of dogs, more so than cats, protects against the development of asthma.

These epidemiological observations have also indicated that two components are necessary for asthma to develop: genetic and environmental factors. Both risks are needed: the right genes and the right environment. One without the other is not sufficient to lead to the expression of asthma.

In adolescence, a number of changes may occur in patients with asthma. First, some previously symptomatic patients will have a remission of their disease; whether it is "permanent" is not clear, nor is it known which patients are likely to experience this loss of symptoms. Second, some patients develop asthma at this time of their life; the factors associated with later onset are not clear. Third, there is a shift in the sex prevalence in the teen years, with adolescent girls or women more likely to have asthma than their male counterparts (7).

The burden of asthma is also significant and felt at many levels—personal, family, and societal. The costs of medications alone for this common and chronic disease can be $3,000 to $4,000 per patient annually. Asthma remains the number one cause of admission to the hospital for children, which has significant costs (8,9). Severe episodes of asthma that lead to hospitalization occur seasonally, with September and October the most common months, probably owing to cold viruses entering the community when children return to school. Asthma has other costs, including missed time from school of approximately 12.8 million days per year in the United States (10). Costs associated with asthma also arise in indirect ways, such as family members who need to miss work to obtain treatment for asthma, especially for children. In the United States, the annual cost of asthma exceeds $19 billion per year.

CASE STUDY

A 25-year-old woman had lifelong asthma. Coughing and wheezing began with a cold when she was two years old. She was initially diagnosed with bronchitis, but antibiotics were not effective. By age five, she had environmental allergies, including reactions to house dust mites and cats. She missed about two weeks of school per year, usually following a cold that led to an asthma episode. Systemic corticosteroids (prednisone) were required three or four times per year, along with the use of daily inhaled corticosteroids.

As a teenager, her symptoms remitted. Her need for medications lessened, prednisone bursts were less than one per year, and her ability to participate in physical activity was normal. However, at age 21, she developed a severe upper respiratory infection, which led to sinusitis and reoccurrence of her asthma. Her symptoms intensified; an emergency room visit was needed for an acute episode of breathlessness and wheezing. Eventually, a prolonged course of prednisone was required to achieve control of her asthma. She was able to stop prednisone and use only inhaled corticosteroids and a long-acting beta-agonist, but she continued to experience chest tightness, awoke at night about once per week, and had limitation to exercise. If she forgot to take her medications, asthma symptoms reappeared, which provided daily reminders of her disease.

Comment

The patient described in this case illustrates the natural history of asthma, which has provided essential clues to the mechanisms of the disease, enhanced diagnostic approaches, and led to improved and more specific treatments. For example, in most patients, asthma begins in the first six years of life. Early episodes of wheezing are frequently in association with viral respiratory infections, the most predominant of which are common cold viruses (rhinoviruses). For many children, these wheezing episodes become fewer and fewer as they grow older. However, many patients have progression of their symptoms, in terms of severity and persistence, with the development of respiratory allergies or infections.

What are we learning about asthma?

Pathophysiology, causes: genetic, environment, microbes

The past 15 to 20 years have seen progress in understanding the basic mechanisms of asthma, earlier recognition and treatment, and more effective and safe medications for asthma, with important new discoveries made on a yearly basis.

In addition to the appreciation of environmental and genetic factors involved in the expression of asthma, our understanding of the processes in the lung that lead to asthma and of the clinical manifestations has increased dramatically. Three decades

Among the best-know instigators and triggers of asthma are (starting at the bottom and going clockwise) pollens, cigarette smoke, respiratory viruses, pet dander, colds and allergies, house dust mites, cockroaches, and a genetic predisposition.

ago, asthma was considered a "bronchospastic" disease of airways. That is, it was thought that asthma consisted of the airway smooth muscles contracting too easily and too frequently. At that time, the primary treatment was bronchodilators, which were designed to relax the contracted airway muscle in order to reduce the bronchospasm and wheezing. Bronchodilators are still needed to treat asthma and are effective, but they address only one component of the disease.

Although asthma has been known to be a chronic disease, the driving elements of its persistence have been unclear. It is now well recognized that airway inflammation is an essential feature of asthma and is present on a chronic basis, but it will "wax and wane" to make asthma improve or worsen. Airway inflammation is also a key target to successful treatment of asthma.

It is also now appreciated that inflammation in asthma is complex and involves many different cells and mediators (11). For example, white blood cells, mast cells, airway lining cells (epithelium), smooth muscle, mucous glands, and nerves are involved. Each of these cells produces many chemical mediators that interact to promote and induce the inflammatory response. The overall consequence of inflammation is multi-factorial, with narrowing of the airways, increased likelihood of bronchospasm (hyperresponsiveness), and persistence of asthma.

Airway inflammation can be provoked by allergic reactions, viral respiratory infections, environmental material, and occupational exposures. The most effective remedy is avoidance, where and when possible. However, this approach is not always possible because of the ubiquitous nature of many environmental exposures.

How is it prevented, treated, and managed?

Prevention, treatment, staying healthy, prognosis

Asthma can begin at any age in life, but most commonly, onset occurs in children younger than six years of age. For these patients, asthma is often associated with hay fever (allergic rhinitis) and eczema (atopic dermatitis). For these patients, environment allergens play a large and significant role in the onset of disease and persistence of symptoms. Asthma can also begin in adulthood. In this setting, allergic diseases are usually not a major factor, but the disease is more severe, with co-existing sinusitis a frequent finding (7,11).

The diagnosis of asthma, particularly in children, is primarily based upon symptoms of cough, wheeze, and shortness of breath in the presence of other

allergic diseases and family history of these conditions. When possible, the demonstration of airflow obstruction on pulmonary function testing is of further assistance in establishing the diagnosis. Finally, improvement in control of asthma symptoms with appropriate medication helps substantiate the presence of asthma.

When asthma begins later in life, the diagnosis is often delayed. Commonly, these patients are misdiagnosed as having recurrent bronchitis and initially treated with antibiotics. In addition, when the onset of pulmonary symptoms begins later in life, a diagnosis of chronic obstructive pulmonary disease (COPD) is often made, even in the absence of smoking. Until asthma is recognized in these patients, symptom control is poor and morbidity is significant.

Medications used in asthma treatment are divided into two broad categories: relievers and controllers (12). “Relievers” are medications designed to give quick relief and are, generally, bronchodilators. Relievers can also be used to prevent symptoms associated with exercise or to give quick relief from acute airflow obstruction. All patients with asthma need relievers, which are most commonly inhaled beta-2 agonists, such as albuterol.

“Controllers” make up the other class of medications; they are used long term to maintain “control,” usually by reducing airway inflammation. The most commonly used controller is inhaled corticosteroids. Often, inhaled corticosteroids are used in combination with long-acting beta agonists. This combination provides enhanced control of asthma at a lower dose of inhaled corticosteroids and are used most commonly in patients with more severe disease.

The effectiveness of treatment can be judged on two major outcomes: current impairment and risk of future attacks. The medications required to control impairment and to manage risks are often different, but both outcomes need to be factored into judging the effectiveness of the treatment regimen. The medications available to treat asthma are generally safe and effective. The greatest shortcoming to asthma management occurs when patients fail to use them on a regular basis.

Are we making a difference?

Research past, present, and future

Advances in the study of asthma epidemiology, genetics, and mechanisms have been translated into improved diagnostic approaches and, most importantly, improved treatment.

A major step to more consistent and uniformly effective treatment has been the establishment of asthma guidelines. In 1991, the National Institutes of Health convened an expert panel of asthma investigators to develop guidelines for the diagnosis and management of the disease. The asthma guidelines have been periodically updated, most recently in 2007 (12). Asthma guidelines provide direction on diagnosis and treatment. Guidelines have classified asthma into levels of severity, which are, collectively, based upon symptoms, lung function, need for rescue treatment, and interference with activity (12). These classifications serve as a guide for clinicians to gauge the appropriate level of treatment.

Studies into the basic mechanisms of inflammation have identified a number of potential therapeutic targets. Some targets are based on a particular antibody, immunoglobulin E (IgE), which appears to be a key antibody in allergic asthma. Others target a cell, the eosinophil, which appears to participate in the inflammation of asthma. Other targets include the smooth muscle of the airway, which contracts to narrow the airway and cause the mechanical breathing problems. In addition, insights into factors regulating the inflammatory, injury, and repair processes have identified families of mediators (such as IL-4 and IL-13), which may also serve as targets for treatment.

A therapeutic agent, omalizumab, has been developed against IgE (13). Many patients with asthma have underlying allergic disease, which is regulated by IgE antibodies. Omalizumab reduces circulating and cell-bound IgE. The primary beneficial outcome of omalizumab in asthma is improved control, decreased dose of inhaled corticosteroids, and, most consistently, fewer asthma episodes.

Study of the eosinophil has also yielded important treatment leads. Eosinophils are regulated by the mediator (cytokine) IL-5 (14). Early results show that anti-IL-5 reduces circulating and airway eosinophils, but has had limited benefit on pulmonary functions and symptoms.

What we need to cure and eliminate asthma

Asthma results when a person with one of many genetic variations interacts with specific elements in the environment. There are more than a hundred components of both of these factors, and many of the host factors set off complicated sets of reactions involving hundreds of molecules. Understanding the timing, concentration, and interaction of these molecules with other molecules and the environmental stimuli makes curing asthma a difficult and probably distant goal.

Translating basic discoveries into therapeutic agents requires major additional effort. Discovery, however, has a cascading effect. Finding new treatments might not only improve asthma control but may provide insights into the disease process, which, in turn, could lead to further improved treatments. Currently, the goals for patients with asthma are to return to a normal lifestyle and obtain relief from the burdens of this disease. With an accelerated pathway to discovery, cure of this major respiratory disease is quite possible with treatment that is safe for long-term use for everyone.

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Web sites of interest

National Heart, Lung, and Blood Institute
Guidelines for the Diagnosis and Management of Asthma
www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

Medline Plus links to many resources
www.nlm.nih.gov/medlineplus/asthma.html

Asthma and Allergy Foundation of America
www.aafa.org/

The Environment Protection Agency's Asthma Program
www.epa.gov/asthma

Centers for Disease Control and Prevention Asthma Information
www.cdc.gov/ASTHMA