

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by an obstruction of airflow, which may be completely or partially reversed with or without specific therapy. Airway inflammation is the result of interactions between various cells, cellular elements, and cytokines. In susceptible individuals, airway inflammation may cause recurrent or persistent bronchospasm, which causes symptoms that include wheezing, breathlessness, chest tightness, and cough, particularly at night (early morning hours) or after exercise. Airway inflammation is associated with airway hyperreactivity or bronchial hyperresponsiveness (BHR), which is defined as the inherent tendency of the airways to narrow in response to various stimuli (eg, environmental allergens and irritants) (*Busse et al., 1993*).

The 2007 Expert Panel Report 3 (EPR-3) of the National Asthma Education and Prevention Program (NAEPP) noted several key changes in the understanding of the pathophysiology of asthma (*NAEPP, 2007*).

- The critical role of inflammation has been further substantiated, but evidence is emerging for considerable variability in the pattern of inflammation, thus indicating phenotypic differences that may influence treatment responses
- Of the environmental factors, allergic reactions remain important. Evidence also suggests a key and expanding role for viral respiratory infections in these processes.

- The onset of asthma for most patients begins early in life, with the pattern of disease persistence determined by early, recognizable risk factors including atopic disease, recurrent wheezing, and a parental history of asthma.

- Current asthma treatment with anti-inflammatory therapy does not appear to prevent progression of the underlying disease severity

The pathophysiology of asthma is complex and involves the following components:

Airway inflammation, Intermittent airflow obstruction ,
Bronchial hyperresponsiveness

Asthma affects an estimated 300 million individuals and 250,000 asthma deaths are reported worldwide (**Bateman et al., 2008**).

Global Initiative for Asthma (GINA) researchers noted that, with regard to asthma in general, there have been increases in prevalence, morbidity, mortality, and economic burden over the past 40 years, especially in children. Asthma affects more than 300 million people worldwide, and some reports suggest that asthma prevalence is increasing by 50% every decade (**Braman, 2006**).

AIM OF THE WORK

The aim of this essay is to: Focus on the pathogenesis of pediatric bronchial asthma and recent modalities for its diagnosis, follow up and management.

BACKGROUND, DEFINITION AND EPIDEMIOLOGY

Background

Asthma is a chronic inflammatory condition of the lung airways resulting in episodic air flow obstruction (*Liu et al., 2012*).

The pathophysiology of asthma is complex and involves airway inflammation, intermittent airflow obstruction, and bronchial hyperresponsiveness. The mechanism of inflammation in asthma may be acute, subacute, or chronic, and the presence of airway edema and mucus secretion also contributes to airflow obstruction and bronchial reactivity. Varying degrees of mononuclear cell and eosinophil infiltration, mucus hypersecretion, desquamation of the epithelium, smooth muscle hyperplasia, and airway remodeling are present (*Horwitz and Busse, 1995*). It is thought to be caused by a combination of genetic and environmental factors (*Martinez, 2007*).

Common symptoms of asthma include wheezing, shortness of breath, chest tightness and coughing, and use of accessory muscle. Symptoms are often worse at night or in the early morning, or in response to exercise or cold air (*British Guideline, 2009*). Some people with asthma only rarely experience symptoms, usually in response to triggers, whereas others may have marked persistent airflow obstruction (*GINA, 2009*).

Its diagnosis is usually made based on the pattern of symptoms and/or response to therapy over time (**Lemanske and Busse1, 2010**). The prevalence of asthma has increased significantly since the 1970s. As of 2010, 300 million people were affected worldwide (**GINA, 2010**). In 2009 asthma caused 250,000 deaths globally (**GINA, 2009**). Asthma management is aimed at reducing airways inflammation by minimizing proinflammatory environmental exposures, using daily controller anti-inflammatory medications, and controlling comorbid conditions that can worsen asthma (**Liu et al, 2012**).

Pharmacologic management includes the use of relief and control agents. Control agents include inhaled corticosteroids, inhaled cromolyn or nedocromil, long-acting bronchodilators, theophylline, leukotriene modifiers, and anti-IgE antibodies. Relief medications include short-acting bronchodilators, systemic corticosteroids, and ipratropium. With severe exacerbations, indications for hospitalization are based on findings after the patient receives 3 doses of an inhaled bronchodilator. In general, patients should be assessed every 1-6 months for asthma control (**Morris and Mosenifar, 2012**).

Definition of asthma

Asthma is defined by the Global Initiative for Asthma (GINA) as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread, but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment (*GINA, 2010*).

Asthma is clinically classified according to the frequency of symptoms, forced expiratory volume in 1 second (FEV₁), and peak expiratory flow rate (*Yawan, 2008*). There is now good evidence that the clinical manifestations of asthma-symptoms, sleep disturbance, limitations of daily activity, impairment of lung function, and use of rescue medications-can be controlled with appropriate treatment. When asthma is controlled there should be no more than occasional recurrence of symptoms and severe exacerbation should be rare (*Reddel et al., 1999*).

Epidemiology

Asthma affects an estimated 300 million individuals worldwide. Annually, the World Health Organization (WHO) has estimated that 15 million disability-adjusted life-years are lost and 250,000 asthma deaths are reported worldwide (*Bateman et al., 2008*).

Asthma is a common chronic disease, causing considerable morbidity. In 2007, 9.6 million children (13.1%) had been diagnosed with asthma in their lifetimes. Of this group, 70% had asthma currently, and 3.8 million children (5.2%), nearly 60% of those with current asthma, had experienced at least one asthma attack in the prior year. Boys (14% vs. 10% girls) and children in poor families (16% vs. 10% not poor) are more likely to have asthma.

Worldwide, childhood asthma appears to be increasing in prevalence, despite considerable improvements in our management and pharmacopeia to treat asthma. Numerous studies conducted in different countries have reported an increased in asthma prevalence of about 50% per decade (*Liu et al., 2012*).

An estimated 300 million people in the world currently have asthma and there may be an additional 100 million persons with asthma by 2025 (*Masoli et al., 2004*).

Childhood asthma seems more prevalent in modern metropolitan locales and more affluent nations, and it is strongly linked with other allergic conditions.

In contrast, children living in rural areas of developing countries and farming communities are less likely to experience asthma and allergy.

Approximately 80% of all asthmatic patients report disease onset prior to 6 yr of age (*Liu et al., 2012*).

It is estimated that asthma has a 7-10% prevalence worldwide (*Lazarus, 2010*). The prevalence of asthma among Egyptian children aged 3 - 15 years was estimated to be 8.2%. Of major concern is the annual increase in mortality (*Hossny et al., 2009*). Asthma is a common cause of emergency room visits and hospital admissions. The burden of asthma is higher than generally recognized, particularly in children. For example, in Egypt up to one in four children with asthma is unable to attend school regularly because of poor asthma control (*Bassili et al., 2000*).

As of 1998, there was a great disparity in the prevalence of asthma across the world, with a trend toward more developed and westernized countries having higher rates of asthma (*ISAAC, 1998*) with as high as a 20 to 60-fold difference. Westernization however does not explain the entire difference in asthma prevalence between countries, and the disparities may

also be affected by differences in genetic, social and environmental risk factors (*Gold and Wright, 2005*).

Prognosis

Recurrent coughing and wheezing occurs in 35% of preschool aged children. Of these, approximately one third continue to have persistent asthma into later childhood, and approximately two thirds improve on their own through their teen years. Asthma severity by the ages of 7-10yr of age is predictive of asthma persistence in adulthood. Children with moderate to severe asthma and with lower lung function measures are likely to have persistent asthma as adults. Children with milder asthma and normal lung function are likely to improve over time, with some becoming periodically asthmatic (disease-free for months to years); however, complete remission for 5 yr in childhood is uncommon (*Liu et al., 2012*).

Asthma also is one of the most frequent causes of school absence among children; accounting for more than 10 million lost school days annually (*American lung association., 2001*).

Approximately 500,000 annual hospitalizations (40.6% in individuals aged 18 y or younger) are due to asthma. Each year, an estimated 1, 81 million people (47.8% of them aged 18 y or younger) require treatment in an emergency department (*Moorman et al., 2007*).

ASTHMA RISK FACTORS

Asthma is a complex multifactorial disease influenced by a strong genetic-environmental interaction (*Martinez et al., 2007*).

Allergens play a major role in the persistence of asthma symptoms (*Illi et al., 2006*). Climate change, immigration, diet changes and allergen concentrations, both indoor and outdoor, could play a major role. Air pollution, particularly tobacco smoking and second hand smoking (SHS) have a deleterious effect on asthma and rhinitis outcomes (*Baena-Cagnani et al., 2009*).

Tobacco smoking, SHS and exposure during pregnancy facilitate allergic sensitization and the appearance of asthma symptoms (*Keil et al., 2009*).

Certified allergists are very well trained and experienced in managing asthma in children, including the allergic/immunological aspects of the disease, environmental control, tobacco cessation programs and the management of immunotherapy (*Penagos et al., 2008*). Factors that influence the risk of asthma can be divided into those that cause the development of asthma and those that trigger asthma symptoms; some do both. The former include host factors (which are primarily genetic) and the latter are usually environmental factors (*Busse and Lemanske, 2001*).

Table (1): Factors Influencing the Development and Expression of Asthma.

HOST FACTORS

- Genetic, e.g.,
 - Genes pre-disposing to atopy
 - Genes pre-disposing to airway hyperresponsiveness
- Obesity
- Sex

ENVIRONMENTAL FACTORS

- Allergens
 - Indoor: Domestic mites, furred animals(dogs ,cats, mice),cockroach allergen, fungi, molds ,yeasts
 - Outdoor: pollens , fungi, molds, yeasts
- Infections (predominantly viral)
- Occupational sensitizers
- Tobacco smoke
 - Passive smoking
 - Active smoking
- Outdoor/Indoor pollution
- Diet

(Busse and Lemanske, 2001).

Table (2): Asthma Triggers.

Asthma triggers
Common viral infections of the respiratory tract Aeroallergens in sensitized asthmatic patients: Animal dander Indoor allergens Dust mites Cockroaches Molds Seasonal aeroallergens: Pollens(trees ,grasses ,weeds) Seasonal molds Environmental tobacco smoke Air pollutants: Ozone Sulfur dioxide Particulate matter Wood- or coal-burning smoke Endotoxin , mycotoxins Dust Strong or noxious odours or fumes: Perfumes, hairsprays Cleaning agents Occupational exposures: Farm and barn exposures Formaldehydes, cedar, paint fumes Cold air, dry air Exercise: Crying, laughter, hyperventilation Co-morbid conditions: Rhinitis Sinusitis Gastroesophageal reflux

(Liu et al., 2012).

- **Host factors**

- **1. Genetics:**

Family and twin studies have indicated that genetics plays an important role in the development of asthma and allergy (*Willemsen et al., 2008*) likely through several genes of moderate effect (i.e., genes associated with relative risks in the range of 1.2–2) (*Holberg et al., 1996*).

Genome-wide linkage studies and case–control studies have identified 18 genomic regions and more than 100 genes associated with allergy and asthma in 11 different populations. In particular, there are consistently replicated regions on the long arms of chromosomes 2, 5, 6, 12 and 13. Association studies of unrelated individuals have also identified more than 100 genes associated with allergy and asthma, 79 of which have been replicated in at least one further study (*Ober and Hffjan, 2006*)

Current data show that multiple genes may be involved in the pathogenesis of asthma (*Hollowyet et al., 1999*). The search for genes linked to the development of asthma has focused on four major areas:

- Production of allergen-specific IgE antibodies (atopy);
- expression of airway hyperresponsiveness;
- generation of inflammatory mediators, such as cytokines, chemokines, and growth factors
- Determination of the ratio between Th1 and Th2 immune response.

(Strachan, 1989).

In addition to genes that predispose to asthma there are genes that are associated with the response to asthma treatment. For example, variations in the gene encoding the beta-adrenoreceptor have been linked to differences in subjects responses to B2-agonists (*Israel et al., 2004*).

Other genes of interest modify the responsiveness to glucocorticosteroides (*Ito et al., 2006*) and leukotriene modifiers (*In et al., 1997*). These genetic markers will likely become important not only as risk factors in the pathogenesis of asthma but also as determinants of responsiveness to treatment (*Tattersfield and Hall, 2004*).

Research on genetic mutations casts further light on the synergistic nature of multiple mutations in the pathophysiology of asthma. Polymorphisms in the gene that encodes platelet-activating factor hydrolase, an intrinsic neutralizing agent of platelet-activating factor in most humans, may play a role in susceptibility to asthma and asthma severity-(*Ito et al., 2002*). In addition, some studies highlight the importance of genotypes in children's susceptibility to asthma and response to specific antiasthma medications (*Thompson et al., 2007*).

2. Obesity

A study by (*Cottrell et al., 2011*) explored the relationship between asthma, obesity, and abnormal lipid and glucose metabolism . The study found that community-based data linked

asthma, body mass, and metabolic variables in children. Specifically, these findings described a statistically significant association between asthma and abnormal lipid and glucose metabolism beyond body mass association. Accelerated weight gain in early infancy is associated with increased risks of asthma symptoms according to one study of preschool children (*Sonnenschein-van der et al., 2012*). Obese people with asthma have lower lung function and more co-morbidities compared with normal weight people with asthma (*Shore, 2008*).

It has been proposed that obesity could influence airway function due to its effect on lung mechanics, development of a pro-inflammatory state, in addition to genetic, developmental, hormonal or neurogenic influences (*O'Byrne et al., 2009*). in this regard, obese patients have a reduced expiratory reserve volume, a pattern of breathing which may possibly alter airway smooth muscle plasticity and airway function (*Shore and Fredberg, 2005*). Furthermore, the release by adipocytes of various pro-inflammatory cytokines and mediators such as interleukin-6, tumor necrosis factor (TNF α), eotaxin, and leptin, combined with a lower level of anti-inflammatory adipokines in obese subjects can favour a systemic inflammatory state although it is unknown how this could influence airway function (*Cohen et al., 2010*).