INTRODUCTION

Asthma is 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. As noted in the definition of asthma, airway inflammation involves an interaction of many cell types as mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells and multiple mediators as (chemokines, cytokines, cysteinyl-leukotrienes, histamine, prostaglandin D2 and nitric oxide) and the airways that eventually results in the characteristic pathophysiological features of the disease: bronchial inflammation and airflow limitation that result in recurrent episodes of cough, wheeze, and shortness of breath. [(1)]

Asthma prevalence has increased very considerably in recent decades such that it is now one of the commonest chronic disorders in the world. [(2)] Asthma is estimated to affect 300 million people worldwide, with an expected increase to 400 million worldwide by 2025.[(3)] In a population of children and adolescents, bronchial asthma occurs with frequency of 5-10 %. [(4)]

In Egypt, the prevalence of asthma among school children aged 5-15 years was found to be increased up to 8.2%. [(5)] Prevalence of asthma among children aged 6-14 years in Alexandria in scholastic year 2001-2002 was 18%. [(6)] Asthma was found to affect the social life of the patients,[(7)] and to be a leading cause of school and work absenteeism. [(8)]

Approximately 80% of all asthmatics report disease onset prior to 6 years of age. Of all young children who experience recurrent wheezing, however, only a minority will go on to have persistent asthma in later childhood. Early childhood risk factors for persistent asthma have been identified as parental asthma, allergic rhinitis, atopic dermatitis, food allergy, inhalant allergen sensitization, food allergen sensitization, wheezing apart from colds, male gender and low birth weight, environmental tobacco smoke exposure, reduced lung function at birth. [(9,10,11)]

Factors influencing the development and expression of asthma

Factors that influence the risk of asthma can be divided into those that cause the development of asthma and those that trigger asthma symptoms. The former include host factors (which are primarily genetic) and the latter are usually environmental factors.[(12)]

Host factors include genetic, e.g. genes pre-disposing to atopy, genes pre-disposing to airway hyper responsiveness, [(13)] obesity and sex. Environmental factors include indoor allergens; domestic mites, furred animals (dogs, cats, mice), cockroach allergen, fungi, molds, yeasts and tobacco smoke and outdoor allergens; pollens, fungi, molds, yeasts, infections (predominantly viral), occupational sensitizers, outdoor/indoor air pollution and diet.

Host factors

Genetic: asthma has a heritable component, but it is not simple. Current data show that multiple genes may be involved in the pathogenesis of asthma and different genes may be involved in different ethnic groups. 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 hyper responsiveness, generation of inflammatory mediators, such as cytokines, chemokines, and growth factors; and determination of the ratio between Th1 and Th2 immune responses. (14)

In addition to genes that predispose to asthma there are genes that are associated with the response to asthma treatments. For example, variations in the gene encoding the beta-adrenoreceptor have been linked to differences in subjects' responses to β2-agonists. (15) Other genes of interest modify the responsiveness to glucocorticosteroids (16) and leukotriene modifiers. 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. (15, 17, 18)

Obesity: asthma is more frequently observed in obese subjects (Body Mass Index >30kg/m^2) and is more difficult to control.(19-23) Obese people with asthma have lower lung function and more co-morbidities compared with normal weight people with asthma. (24)

Sex: male sex is a risk factor for asthma in children. Prior to the age of 14, the prevalence of asthma is nearly twice as great in boys as in girls. As children get older the difference between the sexes narrows and by adulthood the prevalence of asthma is greater in women than in men. The reasons for this sex-related difference are not clear. However; lung size is smaller in males than in females at birth but larger in adulthood. (14)

Environmental factors

Allergens: indoor and outdoor allergens are well known to cause asthma exacerbations. Exposure to indoor air pollutants may have a more important effect on childhood asthma than may exposure to outdoor air pollutants. The primary indoor air pollutants associated with asthma exacerbation include biologic allergens (dust mites, cockroaches, animal dander, mold, etc.), environmental tobacco smoke (ETS), irritant chemicals and fumes, and products from combustion devices. (25)

Biologic allergens can be found throughout the home, school, and work environments. Although concentrations of dust mites, cockroaches, and animal dander allergens (pets, mice and rats) vary with geographic location, however, dust mite allergen, mold, and cat and dog allergens can be found in most homes, including homes where there are no pets at present. (25)

Sensitization to house dust mites is an important risk factor for asthma exacerbations and the development of asthma. The dust mite grows optimally at warm temperatures and with humidity greater than 50% in cloth-covered objects such as soft toys, upholstered furniture, bedding, mattresses and carpets. (11)

Exposure to environmental tobacco smoke is a risk factor for asthma attacks in children. Children with asthma and whose parents smoke have more frequent asthma

attacks and more severe symptoms.[26] Tobacco smoking is associated with accelerated decline of lung function in people with asthma, [27] increases asthma severity, may render patients less responsive to treatment with inhaled [28,29] and systemic [28] glucocorticosteroids, and reduces the likelihood of asthma being controlled. [31]

Exposure to tobacco smoke both prenatally and after birth is associated with measurable harmful effects including a greater risk of developing asthma like symptoms in early childhood. [30,31] Infants of smoking mothers are 4 times more likely to develop wheezing illnesses in the first year of life. [32]

Infections: During infancy, a number of viruses have been associated with the inception of the asthmatic phenotype. Respiratory syncytial virus (RSV) and parainfluenza virus produce a pattern of symptoms including bronchiolitis that parallel many features of childhood asthma.[33] A number of long-term prospective studies of children admitted to the hospital with documented RSV have shown that approximately 40% will continue to wheeze or have asthma into later childhood.[33]

The "hygiene hypothesis" of asthma suggests that exposure to infections early in life influences the development of a child's immune system along a "no allergic" pathway, leading to a reduced risk of asthma and other allergic diseases. Although the hygiene hypothesis continues to be investigated, this mechanism may explain observed associations between family size, birth order, day-care attendance, and the risk of asthma. For example, young children with older siblings and those who attend day care are at increased risk of infections, but enjoy protection against the development of allergic diseases, including asthma later in life.[34]

Diet: infants fed formulas of intact cow's milk or soy protein have a higher incidence of wheezing illnesses in early childhood compared with those fed breast milk. [35]

Certain characteristics of Western diets such as increased use of processed foods and decreased antioxidant (in the form of fruits and vegetables), increased n-6 polyunsaturated fatty acid (found in margarine and vegetable oil) and decreased n-3 polyunsaturated fatty acid (found in oily fish) intakes have contributed to the recent increases in asthma and atopic disease. [36]

Diagnosis of asthma

A correct diagnosis of asthma is essential if appropriate drug therapy is to be given. Asthma symptoms may be intermittent and their significance may be overlooked by patients and physicians or because they are non-specific, they may result in misdiagnosis.

Clinical diagnosis

Medical history:

Symptoms: A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough, and chest tightness. [37] Episodic symptoms after an incidental allergen exposure, seasonal variability of symptoms and a positive family history of asthma and atopic disease are also helpful diagnostic guides. Asthma associated with rhinitis may occur intermittently, with the patient being entirely asymptomatic between seasons or it may involve seasonal worsening of asthma symptoms or a background of persistent asthma. The patterns of these symptoms that strongly suggest an asthma diagnosis are variability, precipitation by non-specific irritants, such as smoke, fumes, strong smells, or exercise, worsening at night and responding to appropriate asthma therapy. In some sensitized individuals, asthma may be exacerbated by seasonal increases in specific aeroallergens as grass, and ragweed pollens. [14]

Cough-variant asthma: Patients with cough-variant asthma have chronic cough as their principal, if not only, symptom. It is particularly common in children, and is often more problematic at night; so evaluations during the day can be normal. For these patients, documentation of variability in lung function or of airway hyperresponsiveness, and possibly a search for sputum eosinophils, is particularly important. [14]

Exercise-induced bronchoconstriction: Physical activity is an important cause of asthma symptoms for most asthma patients and for some it is the only cause. Exercise-induced bronchoconstriction typically develops within 5-10 minutes after starting exercise. Patients experience typical asthma symptoms, or sometimes a troublesome cough, which resolve spontaneously within 30-45 minutes. Some forms of exercises, such as running, are more potent triggers. [38]

Exercise-induced bronchoconstriction may occur in any climatic condition, but it is more common when the patient is breathing dry, cold air and less common in hot, humid climates. Rapid improvement of post-exertion symptoms after inhaled β2 -agonist use, or their prevention by pretreatment with an inhaled β2-agonist before exercise, supports the diagnosis of exercise-induced asthma. Some children with asthma present only with exercise-induced symptoms. In this group, or when there is doubt about the diagnosis, exercise testing is helpful. An 8-minute running protocol is easily performed in clinical practice and can establish a firm diagnosis of asthma. [38]

Physical examination:

Because asthma symptoms are variable, the physical examination of the respiratory system may be normal. The most usual abnormal physical finding is wheezing on auscultation, a finding that confirms the presence of airflow limitation. However, in some people with asthma, wheezing may be absent or only detected when the person exhales

forcibly, even in the presence of significant airflow limitation. Occasionally, in severe asthma exacerbations, wheezing may be absent owing to severely reduced airflow and ventilation. However, patients in this state usually have other physical signs reflecting the exacerbation and its severity, such as cyanosis, drowsiness, difficulty speaking, tachycardia, hyperinflated chest, use of accessory muscles, and intercostal recession. [14]

Other clinical signs are only likely to be present if patients are examined during symptomatic periods. Features of hyperinflation result from patients breathing at a higher lung volume in order to increase outward retraction of the airways and maintain the patency of smaller airways (which are narrowed by a combination of airway smooth muscle contraction, edema, and mucus hyper secretion). [14]

Tests for diagnosis and monitoring

Measurements of lung function

The diagnosis of asthma is usually based on the presence of characteristic symptoms. However, measurements of lung function, and particularly the demonstration of reversibility of lung function abnormalities, greatly enhance diagnostic confidence. This is because patients with asthma frequently have poor recognition of their symptoms and poor perception of symptom severity, especially if their asthma is long-standing. [39] Measurement of lung function provides an assessment of the severity of airflow limitation, its reversibility and its variability, and provides confirmation of the diagnosis of asthma.

Various methods are available to assess airflow limitation, but two methods have gained widespread acceptance for use in patients over 5 years of age. These are spirometry, particularly the measurement of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), and peak expiratory flow (PEF) measurement. [14]

Spirometry; is the recommended method of measuring airflow limitation and reversibility to establish a diagnosis of asthma. Measurements of FEV1 and FVC are undertaken during a forced expiratory maneuver using a spirometer.

The degree of reversibility in FEV1 which indicates a diagnosis of asthma is generally accepted as 12% and 200 ml from the pre-bronchodilator value. [40] However most asthma patients will not exhibit reversibility at each assessment, particularly those on treatment, and the test therefore lacks sensitivity.

The peak flow meter; is an inexpensive, portable, handheld device that provides a mean to obtain simple and quantitative assessments of the existence and severity of airflow obstruction. Measuring the peak flow using this meter is an important part of managing asthma symptoms and preventing an asthma attack.[41] It must be stressed that peak flow meters function best as tools for ongoing monitoring, not diagnosis. Because the measurement of peak expiratory flow (PEF) is dependent on effort and technique, patients need instructions, demonstrations, and frequent reviews of technique. Diurnal variation in PEF of more than 20% suggests a diagnosis of asthma but spirometry is generally recommended over measurements by a peak flow meter.

Measurement of airway responsiveness is done for patients with symptoms consistent with asthma, but normal lung function, measurements of airway responsiveness to direct airway challenges such as inhaled methacholine and histamine or indirect airway

challenges such as inhaled mannitol [42] or exercise challenge may help establish a diagnosis of asthma. [43] The test results are usually expressed as the provocative concentration of the agonist causing a given fall (often 20%) in FEV1.

Measurements of allergic status: Because of the strong association between asthma and allergic rhinitis, the presence of allergic diseases and allergic rhinitis in particular, increases the probability of a diagnosis of asthma in patients with respiratory symptoms. [14]

Skin tests with allergens represent the primary diagnostic tool in determining allergic status. They are simple and rapid to perform, and have a low cost and high sensitivity. Measurement of specific IgE in serum does not surpass the reliability of results from skin tests and is more expensive. The main limitation of methods to assess allergic status is that a positive test does not necessarily mean that the disease is allergic in nature or that it is causing asthma, as some individuals have specific IgE antibodies without any symptoms and it may not be causally involved.[14]

Diagnostic challenges and differential diagnosis

The diagnosis of asthma in early childhood is challenging and has to be based largely on clinical judgment and an assessment of symptoms and physical findings. Since the use of the label "asthma" for wheezing in children has important clinical consequences, it must be distinguished from other causes of persistent and recurrent wheeze. Episodic wheezing and cough are very common even in children who do not have asthma and particularly in those under age 3. [11]

Three categories of wheezing have been described in children 5 years and younger:

- Transient early wheezing, this is often outgrown in the first 3 years. This is often associated with prematurity and parental smoking.
- Persistent early-onset wheezing (before age 3). These children typically have recurrent episodes of wheezing associated with acute viral respiratory infections, have no evidence of atopy [44] and, have no family history of atopy. The symptoms normally persist through school age and are still present at age 12 in a large proportion of children. The cause of the episode is usually the respiratory syncytial virus in children younger than age 2, while other viruses predominate in older preschool children.
- Late-onset wheezing/asthma. These children have asthma which often persists throughout childhood and into adult life. [45] They typically have an atopic background, often with eczema, and airway pathology is characteristic of asthma.

Alternative causes of recurrent wheezing must be considered and excluded. These include:

- Chronic rhino-sinusitis.
- Gastroesophageal reflux.
- Recurrent viral lower respiratory tract infections.
- Cystic fibrosis.
- Bronchopulmonary dysplasia.

• Tuberculosis.

• Congenital malformation causing narrowing of the intrathoracic airways.

• Foreign body aspiration.

• Primary ciliary dyskinesia syndrome.

• Immune deficiency.

• Congenital heart disease.

• Upper airway obstruction.

• Vocal cord dysfunction. [46]

Classification of asthma

Asthma severity is the intrinsic intensity of disease. Initial assessment of patients who have confirmed asthma begins with a severity classification because the selection of type, amount, and scheduling of therapy should then correspond to the level of asthma severity. This initial assessment of asthma severity is made immediately after diagnosis, or when the patient is first encountered, generally before the patient is taking some form of long-term control medication. Assessment is made on the basis of current spirometry or peak flow meter measures and the patient's recall of symptoms over the previous 2–4 weeks, because detailed recall of symptoms decreases over time.

The asthma is classified into intermittent, mild persistent, moderate persistent and severe persistent as defined by the National Heart Lung and Blood Institute (NHLBI) Guidelines (Table1). [47]

Table (1): Classification of asthma severity

Classification	**Step**	**Days with symptoms**	**Nights with symptoms**	**For adults and children age > 5 years who can use a spirometer or peak flow meter**	
				FEV_1 or PEF% Predicted Normal	**PEF Variability (%)**
Severe persistent	4	Continual	Frequent	≤60	>30
Moderate persistent	3	Daily	>1/wk	>60–<80	>30
Mild persistent	2	>2/wk, but not daily	>2/mo	≥80	20–30
Mild intermittent	1	≤2/wk	≤2/mo	≥80	<20

Asthma control may be defined in a variety of ways. In lay terms, control may indicate disease prevention, or even cure. However, in asthma, where neither of these are realistic options at present, it refers to control of the manifestations of disease. The aim of treatment should be to achieve and maintain control for prolonged periods [48] with due regard to the safety of treatment, potential for adverse effects, and the cost of treatment required to achieve this goal.

Therefore, the assessment of asthma control should include not only control of the clinical manifestations (symptoms, night waking, reliever use, activity limitation, lung function), but also control of the expected future risk to the patient such as exacerbations, accelerated decline in lung function, and side-effects of treatment. In general, the achievement of good clinical control of asthma leads to reduced risk of exacerbations. [49]

Table (2): Levels of Asthma Control according to the GINA guidelines

Characteristic	Controlled (All of the following)	Partially controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/ week	Three or more features of partially controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV1) if feasible	Normal	<80% predicted or personal best (if known)	
Exacerbations	None	One or more/year	One in any week

Asthma Management

Optimal asthma management includes patient education, regular assessment and monitoring, elimination or reduction of problematic environmental exposures as smoking, dust mite and pets, treatment of co-morbid conditions: rhinitis, sinusitis, and gastro esophageal reflux, and asthma pharmacotherapy: long-term-control and quick-relief medications. (11)

Optimal goals of asthma management are to; obtain normal activity (regular school or daycare attendance, full participation in physical exercise, athletics and other recreational activities), prevent sleep disturbance, prevent chronic asthma symptoms, keep asthma exacerbation from becoming severe, maintain normal lung function and experience little to no adverse effects of treatment. (11)

Patient education

Specific educational elements in the clinical care of children with asthma are believed to make an important difference in the home management and adherence of families to an optimal plan of care. With education, the child and family become essential partners in the asthma management process, as the key optimal management depends on their daily assessments and implementation of any management plan.

In initial patient visits, a basic understanding of the pathogenesis of asthma (chronic inflammation and airway hyperresponsiveness (AHR) underlying a clinically intermittent presentation) can help children with asthma and their parents to understand the importance of recommendations aimed at reducing airways inflammation.

The expectations of good asthma control resulting from optimal asthma management should be specified. Explaining and readdressing the importance of steps to reduce airways inflammation in achieving good asthma control and addressing concerns about potential adverse effects of asthma pharmacotherapy, and especially their risks relative to their benefits, are essential in achieving long-term adherence with asthma pharmacotherapy and environmental control measures.(11)

Children with asthma and their families benefit from a written asthma management plan with 2 main components: (1) a daily "routine" management plan describing regular asthma medication use and other measures to keep asthma under good control; and (2) an action plan for asthma exacerbations, describing actions to take when asthma worsens, including what medications to take and when to contact the regular physician and/or obtain urgent/emergent medical care. Regular follow-up visits can help to maintain optimal asthma control. In addition to assessing disease severity and revising daily and exacerbation management plans accordingly, follow-up visits should be used to encourage open communication of concerns with asthma management recommendations (daily administration of controller medications).(11,50)

Reassessing the role of different medications in asthma management and the technique used with inhaled medications can be insightful and help to guide teaching to improve adherence to a management plan that might not have been adequately or properly implemented.

Regular assessment and monitoring

During a patient's initial presentation, if the patient is not currently taking long-term control medication, asthma severity is assessed to guide clinical decisions on the appropriate medication and other therapeutic interventions. Once therapy is initiated, the emphasis there after for clinical management is changed to the assessment of asthma control. The level of asthma control will guide decisions either to maintain or adjust therapy.

Asthma management can be optimized through regular clinic visits every 2–4 wk until good asthma control is achieved. Two to 4 asthma checkups per year are recommended for maintaining good asthma control.

During these visits, the optimal goals of asthma control can be assessed by determining the: (1) Frequency of asthma symptoms during the day, at night, and with physical exercise; (2) Frequency of "rescue" short acting β2- agonist (SABA) medication use and refills; (3) Number and severity of asthma exacerbations since the last visit; and (4) Participation in school, sports, and other preferred activities. Lung function testing (spirometry) is recommended at least annually and more often if asthma is inadequately controlled or lung function is abnormally low. [11]

Control of factors contributing to asthma severity

Eliminating and reducing problematic environmental exposures:

The majority of children with asthma have an allergic component to their disease; steps should be taken to investigate and minimize allergen exposures in sensitized asthmatics. [51] For sensitized asthmatics, reduced exposure to perennial allergens in the home decreases asthma symptoms, medication requirements, AHR, and asthma exacerbations. The important home allergens that are linked to asthma worsening differ between locales and even between homes. Common perennial allergen exposures include furred or feathered animals as (cats, dogs, ferrets, birds) or as pests (mice, rats) and occult indoor allergens such as dust mites, cockroaches, and molds. Domestic mite allergy is a universal health problem so there are recommended actions to control mites include : encase the mattress in an allergen-impermeable cover, encase the pillow in an allergen-impermeable cover or wash it weekly, wash the sheets and blankets on the patient's bed weekly in hot water, minimize the number of stuffed toys, and wash them weekly.[52] Complete avoidance of pet allergens is impossible, as the allergens are ubiquitous and can be found in many environments outside the home, including schools, public transportation, and cat-free buildings .

Although some sensitized children may report an increase in asthma symptoms on exposure to the allergen source, improvement from allergen avoidance may not become apparent without a sustained period of days to weeks away from the offending exposure. Tobacco, wood and coal smoke, dusts, strong odors, and noxious fumes can all aggravate asthma. These airways irritants should be eliminated or reduced from the homes and automobiles used by asthmatic children. School classrooms and daycare settings can also be sites of asthma-worsening environmental exposures. [11]

Eliminating or minimizing these exposures (furred pets in classrooms with sensitized asthmatic children) can reduce asthma symptoms, disease severity, and the amount of medication needed to achieve good asthma control. Annual influenza vaccination continues to be recommended for all asthmatic children (except for those with egg allergy). [11]

Treatment of co-morbid conditions:

Rhinitis, sinusitis, and gastro esophageal reflux often accompany asthma and can mimic asthma symptoms and worsen disease severity. Indeed, these conditions with asthma are the 3 most common causes of chronic coughing. Effective management of these co-morbid conditions can often improve asthma symptoms and disease severity, such that less asthma medication is needed to achieve good asthma control.

Gastroesophageal reflux disease (GERD) is common in asthmatics, with a reported incidence of up to 64% with GERD-related asthma symptoms. [11] GERD may worsen asthma through 2 postulated mechanisms: (1) aspiration of refluxed gastric contents (micro- or macro-aspiration); and (2) vagally-mediated reflex bronchospasm. Occult GERD should be suspected in individuals with difficult-to-control asthma [53], especially patients with prominent asthma symptoms while eating or sleeping (in a horizontal position), or who prop themselves up in bed to reduce nocturnal symptoms.

GERD can be demonstrated by reflux of barium into the esophagus during a barium swallow procedure or by esophageal pH monitoring. Because radiographic studies lack sufficient sensitivity and specificity, extended esophageal pH monitoring is the method of choice for diagnosing GERD. If significant GERD is noted, reflux precautions should be instituted (no food 2 hr before bedtime, head of the bed elevated , avoid caffeinated foods and beverages) and medications such as proton pump inhibitors (omeprazole, lansoprazole) or H_2-receptor antagonists (cimetidine, ranitidine) administered for 8 to 12 wk.[54]

Rhinitis: The majority of patients with asthma have a history or evidence of rhinitis and up to 30% of patients with persistent rhinitis have or develop asthma. Rhinitis frequently precedes asthma, and is both a risk factor for the development of asthma [55] and is associated with increased severity and health resource use in asthma. Rhinitis and asthma share several risk factors: common indoor and outdoor allergens such as house dust mites, animal dander, and, less commonly, pollen affecting both the nose and bronchi. For these reasons, the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative recommends that the presence of asthma must be considered in all patients with rhinitis, and that in planning treatment, both should be considered together [56] Treatment of rhinitis may improve asthma symptoms.[57]

Anti-inflammatory agents including glucocorticosteroids and cromones as well as leukotriene modifiers and anticholinergics can be effective in both conditions. Use of intra-nasal glucocorticosteroids for concurrent rhinitis has been found to have a limited benefit in improving asthma and reducing asthma morbidity in some but not all studies.[58-60] Leukotriene modifiers [61], allergen specific immunotherapy [62], and anti-IgE therapy [63]are effective in both conditions.

Sinusitis: Sinusitis is a complication of upper respiratory infections, allergic rhinitis, nasal polyps, and other forms of nasal obstruction. Both acute and chronic sinusitis can worsen asthma. Clinical features of sinusitis lack diagnostic precision, and CT scan

confirmation is recommended when available. In children with suspected rhinosinusitis, antibiotic therapy for 10 days is recommended. Treatment should also include medications to reduce nasal congestion, such as topical nasal decongestants or topical nasal or even systemic glucocorticosteroids. These agents remain secondary to primary asthma therapies.[11]

Respiratory infections:

Respiratory infections have an important relationship to asthma as they provoke wheezing and increased symptoms in many patients [64] and are commonly found in children with asthma exacerbation.[65] Epidemiological studies have found that infectious microorganisms associated with increased asthma symptoms are often respiratory viruses, but seldom bacteria.[66]

Respiratory syncytial virus is the most common cause of wheezing in infancy, while rhinoviruses (which cause the common cold), are the principal triggers of wheezing and worsening of asthma in older children and adults. Other respiratory viruses, such as parainfluenza, influenza, adenovirus, and coronavirus, are also associated with increased wheezing and asthma symptoms.

Several organizations (such as the Canadian National Advisory Committee on Immunization) advocate annual influenza vaccination for children with asthma. Despite these recommendations, many children with asthma do not receive influenza vaccines. One of the barriers to compliance is the uncertainty of parents and physicians about the benefits of influenza vaccination in this population and the role of immunization in preventing asthma exacerbations. [11]

Asthma pharmacotherapy

The National Asthma Education and Prevention Program (NAEPP) guidelines offer a stepwise approach to management based on asthma severity (table 3). [47] A major objective of this approach is to identify and treat all "persistent" asthma with anti-inflammatory controller medication. The "three strikes" rule is a handy memory aid for determining if an asthmatic child should receive controller therapy. Simply put, if an asthmatic child has asthma symptoms or uses quick-relief medication at least 3 times per week, awakens at night due to asthma at least 3 times per month, requires a refill for a quick-relief inhaler prescription at least 3 times per year, experiences asthma exacerbations at least 3 times per yr, or requires short courses of systemic corticosteroids at least 3 times a yr, then that patient should receive daily controller therapy. In addition, according to the NAEPP guidelines, controller therapy can be considered for children who present with frequent exacerbations (at least 2 exacerbations occurring <6 wk apart).

Table (3): Stepwise Approach for Long Term Management of Asthma

TABLE 3 2007 NHLBI STEPWISE TREATMENT RECOMMENDATIONS BY AGE

		STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
		INTERMITTENT	PERSISTENT: DAILY MEDICATIONS				
0–4 YEARS OF AGE	Preferred	SABA as needed	Low-dose ICS	Medium-dose ICS	Medium-dose ICS + LABA OR montelukast	High-dose ICS + LABA OR montelukast	High-dose ICS + LABA OR montelukast + oral steroids
	Alternative		Cromolyn OR montelukast				
5–11 YEARS OF AGE	Preferred	SABA as needed	Low-dose ICS	Low-dose ICS + LABA, LTRA, theophylline OR medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA	High-dose ICS + LABA + oral steroids
	Alternative		Cromolyn, LTRA, nedocromil, OR theophylline		Medium-dose ICS + LTRA OR theophylline	High-dose ICS + LTRA OR theophylline	High-dose ICS + LTRA OR theophylline + oral steroids
≥12 YEARS OF AGE – ADULTS	Preferred	SABA as needed	Low-dose ICS	Low-dose ICS + LABA OR medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA AND consider omalizumab	High-dose ICS + LABA + oral steroids AND consider omalizumab
	Alternative		Cromolyn, LTRA, nedocromil, OR theophylline	Low-dose ICS + LABA, LTRA, zileuton, OR theophylline	Medium-dose ICS + LTRA, zileuton OR theophylline		
		For all ages at each step: patient education, environmental control, management of comorbidities					
		For 5-11 years of age and ≥12 years of age-adults groups: Consider subcutaneous immunotherapy for patients with persistent allergic asthma					

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting beta agonist; NHLBI, National Heart, Lung, and Blood Institute.
From Reddy AP, et al.[4]

Controller medications

Inhaled glucocorticosteroids:

Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. Studies have demonstrated their efficacy in reducing asthma symptoms, improving quality of life, improving lung function, decreasing airway hyperresponsiveness, [67] controlling airway inflammation, reducing frequency and severity of exacerbations, and reducing asthma mortality.[68] However, they do not cure asthma, and when they are discontinued deterioration of clinical control follows within weeks to months in a proportion of patients.[69] Dose-response studies and dose titration studies in children demonstrate marked and rapid clinical improvements in symptoms and lung function at low doses of inhaled glucocorticosteroids (e.g., 100-200 μg budesonide daily) [70-72], and mild disease is well controlled by such doses in the majority of patients.[70]

Different age groups require different inhalers for effective therapy, so the choice of inhaler must be individualized (table 4). The choice of inhaler device should include consideration of the efficacy of drug delivery, cost, safety, ease of use, convenience, and documentation of its use in the patient's age group.[73] In general, a metered-dose inhaler (MDI) with spacer is preferable to nebulized therapy due to its greater convenience, more effective lung deposition, lower risk of side effects and lower cost.

Table (4): Choosing an Inhaler Device for Children with Asthma [73]

Age Group	Preferred Device	Alternate Device
Younger than 4 years	Pressurized metered dose inhaler plus dedicated spacer with face mask	Nebulizer with face Mask
4 – 6 years	Pressurized metered dose inhaler plus dedicated spacer with mouthpiece	Nebulizer with Mouthpiece
Older than 6 years	Dry powder inhaler, or breath-actuated pressurized metered dose inhaler, or pressurized metered dose inhaler with spacer and mouthpiece	Nebulizer with Mouthpiece

High doses (≥1,000 µg/day in children) and frequent administration (4 times/day) are more likely to cause local and systemic adverse effects. Children who are maintained on higher inhaled corticosteroid (ICS) doses are also likely to require systemic corticosteroid courses for asthma exacerbations, further increasing the risk of corticosteroid adverse effects.

The most commonly encountered **adverse effects** from ICSs are local: oral candidiasis (thrush) and dysphonia (hoarse voice). Thrush results from propellant-induced mucosal irritation and local immunosuppression. Dysphonia occurs from vocal cord myopathy. These effects are dose-dependent and are most common in individuals on high-dose ICS and/or oral corticosteroid therapy. The incidence of these local effects can be greatly minimized by using a spacer with MDI ICS because spacers reduce oropharyngeal deposition of the drug and propellant. Mouth rinsing using a "swish and spit" technique after ICS use is also recommended. [74]

Growth retardation may be seen with all inhaled glucocorticosteroids when a high dose is administered. Glucocorticosteroid-induced changes in growth rate during the first year of treatment appear to be temporary. Children with asthma treated with inhaled glucocorticosteroids attain normal adult height (predicted from family members) but at a later age. [75]

No studies have reported any statistically significant decreased bone density or increased risk of fractures in children taking inhaled glucocorticosteroids. [14]

Through differences exist between the various inhaled glucocorticosteroids and inhaler devices, treatment with inhaled glucocorticosteroid doses of less than 200 µg budesonide or equivalent daily is normally not associated with any significant suppression of the HPA axis in children. At higher doses, small changes in HPA axis function can be detected with sensitive methods. [76]

ICS therapy has allowed the large majority of children with asthma to maintain good disease control without maintenance oral corticosteroids. Oral corticosteroid therapy is used primarily to treat asthma exacerbations and in rare patients with severe disease who remain symptomatic despite optimal use of other asthma medications. [14]

Leukotriene modifiers:

Leukotriene modifiers provide clinical benefit in children older than 5 years at all levels of severity [77-80], but generally less than that of low-dose inhaled glucocorticosteroids. [81] Leukotriene modifiers provide partial protection against exercise-induced bronchoconstriction within hours after administration. [82] As add-on treatment in children whose asthma is insufficiently controlled by low doses of inhaled glucocorticosteroids, leukotriene modifiers provide moderate clinical improvements, including a significant reduction in exacerbations. Combination therapy is less effective in controlling asthma in children with moderate persistent asthma than increasing to moderate doses of inhaled glucocorticosteroids. [83]

Montelukast has not been demonstrated to be an effective inhaled glucocorticosteroid sparing alternative in children with moderate-to-severe persistent asthma. [84] In addition to

the efficacy as described above [85,86], leukotriene modifiers reduce viral induced asthma exacerbations in children ages 2-5 with a history of intermittent asthma.[86]

Long-acting inhaled β2-agonists:

Long-acting inhaled β2- agonists have mainly been studied as add-on therapy for patients whose asthma is not controlled on low to high doses of inhaled glucocorticosteroids. Significant improvements in peak flow and other lung function measurements have been found in most studies. [87-90] Inhalation of a single dose of long-acting inhaled β2-agonists effectively blocks exercise-induced bronchoconstriction for several hours. Combination products containing an inhaled glucocorticosteroid and long-acting inhaled β2-agonists are preferred to long-acting inhaled β2-agonists and inhaled glucocorticosteroids administered by separate inhalers.

Theophylline:

Theophylline has been shown to be effective as monotherapy and as add-on treatment to inhaled or oral glucocorticosteroids in children older than 5 years. Maintenance treatment offers a marginal protective effect against exercise-induced bronchoconstriction. Add-on treatment with theophylline has been found to improve asthma control and reduce the maintenance glucocorticosteroid dose necessary in children with severe asthma treated with inhaled or oral glucocorticosteroids. Theophylline has a narrow therapeutic window; therefore, when used, serum theophylline levels need to be routinely monitored. The most common side effects of theophylline are anorexia, nausea, vomiting, and headache. [14]

Anti-IgE:

Anti-IgE (omalizumab) has proven efficacy in children age 6 to 12 years with moderate-to-severe and severe persistent allergic (IgE-mediated) asthma. Anti-IgE treatment was associated with a significantly lower exacerbation rate and the overall incidence of serious adverse events was significantly lower in the children receiving anti-IgE than placebo. Anti-IgE therapy is expensive and requires regular injections and observation after each injection. A cost benefit analysis suggested that there would be a financial saving if this treatment is given to children with five or more hospital admissions and cumulatively twenty days or more in hospital. [91] Drug-related adverse events in anti-IgE treated patients are mild to moderate in severity and include urticarial rash, flushing, and pruritus. [92]

Cromones: Sodium cromoglycate and nedocromil sodium:

Cromolyn and nedocromil are non-corticosteroid anti-inflammatory agents that can inhibit allergen-induced asthmatic responses and reduce exercise-induced bronchospasm. According to the NAEPP guidelines, both drugs are considered alternative anti-inflammatory drugs for children with mild persistent asthma. [93]

Quick-reliever medications

Rapid-acting inhaled ß2-agonists and short-acting oral ß2-agonists:

Rapid-acting inhaled ß2-agonists are the most effective bronchodilators available and therefore the preferred treatment for acute asthma in children of all ages. The inhaled route results in more rapid bronchodilation at a lower dose and with fewer side effects than oral or intravenous administration. Furthermore, inhaled therapy offers significant protection against exercise-induced bronchoconstriction and other challenges for 0.5 to 2 hours (long-acting ß2-agonists offer longer protection). This is not seen after systemic administration. Oral therapy is rarely needed and reserved mainly for young children who cannot use inhaled therapy. [14]

Anticholinergic agents:

As bronchodilators, the anticholinergic agents (ipratropium bromide) are much less potent than the β-agonists. Inhaled ipratropium is primarily used in the treatment of acute severe asthma. When used in combination with albuterol, ipratropium can improve lung function and reduce the rate of hospitalization in children who present to the emergency department with acute asthma. Ipratropium is the anticholinergic formulation of choice for children because it has few central nervous system adverse effects and it is available in both MDI and nebulizer formulations. [11] Inhaled anticholinergics are not recommended for long-term management of asthma in children. [94]

Reasons for poor asthma control

The presence of asthma is associated with a significant socioeconomic burden [14] due to both direct (such as hospital care, visits, and medications) and indirect costs (such as time lost from work and premature death). Moreover, asthma exerts a considerable social impact not only because it is highly prevalent in many parts of world but also because its presence interferes significantly with many aspects of daily life. [95] Patients with asthma are bothered by the symptoms (in particular cough, shortness of breath, chest tightness, and wheezing) and report considerable impairment in physical activities (such as sports, going up stairs, and shopping). They may have difficulty getting a goodnight's sleep and may be limited in their work and social life. In addition, the burden of illness has emotional aspects that is, increased levels of anxiety and depression, fear and so on. [96]

Asthmatic patients should reach an optimal level of disease control, which implies minimal or absent disease impact on patient life. Though research has shown that good control can be achieved in most patients and valid tools are available to reach this aim, the reality in clinical practice is that asthma remains poorly controlled. That can be considered the result of the complex interaction among different variables (table 5).

- **Role of guidelines diffusion and implementation**

Available guidelines for asthma management represent an important and suitable tool aimed at making the entire medical process more effective and efficient: their purpose is to help doctors and patients to make the best decisions about treatment for asthma, by choosing the most appropriate strategies in each specific clinical situation. Despite the effort made to develop and divulge evidence-based guidelines, failure in guidelines implementation remains a sticky issue: about 30–40% of patients do not benefit from a cure program based on scientific evidence, whereas 20–25% of therapeutic choices may be unnecessary and sometimes even harmful. [97] This failure in guidelines implementation has a strong influence on appropriateness of care, clinical efficiency, healthcare costs, and patients' quality of life.

- **Disease-related factors that influence asthma control**

The presence of common comorbidities in asthma such as gastroesophageal reflux disease (GERD), rhinitis, sinusitis and recurrent upper respiratory tract infections affect the airways and can complicate the disease management and the achievement of asthma control.

- **Non adherence**

The active involvement of patients in their disease and their therapy and management is essential in reaching and maintaining asthma control. In this perspective the adherence to the treatment plan has become one of the major issues to be faced by medical practice. Adherence to a medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers. [98]

Adherence is enhanced by regular visits to health care providers, along with monitoring of symptoms and reemphasis of the avoidance of aggravating factors, changes in lifestyle, and correct management of the therapeutic regimen. The problem of non-

adherence to the therapeutic plan is a serious problem to be addressed in the management of chronic disease, such as asthma. Non adherence is reported to range between 20%and 40% in acute illness, 30–60% in chronic diseases, and reaches 50–80% for preventive treatments. [99]

It is a common misconception to think that patients with severe disease are more conscientious and follow a treatment plan to avoid symptoms. [100] Patients with severe asthma may be at greater risk for non-adherence than those with less severe asthma for 4 reasons.

First, they require more asthma medication to control severe symptoms. [101,102] Second, coexisting conditions that may aggravate asthma (such as gastro esophageal reflux and rhino sinusitis) require additional medical treatments to reduce oral corticosteroid use. [103] Third, patients with severe asthma have higher rates of depression and anxiety, which may contribute to poor adherence.[104,105] Fourth, persons with severe asthma must cope with the immediate and long-term impact of the illness, which affects their daily functioning, employability, and ability to pay for health care and medication.[106]

Patients may fail to comply with prescribed medication regimens for a variety of reasons. They may intend to comply but may misunderstand or forget complicated drug regimens. They may be physically unable to cope with inhaler devices. Patients may also have fears about their medication; a fear of becoming dependent on medication is common. Many patients express concerns about possible side effects of inhaled corticosteroids used for the treatment of asthma. In addition, asthma patients may think that treatment is unnecessary during symptom-free periods. Alternatively, patients may consider the medicine to be ineffective or unnatural, or wish to balance its risks and benefits according to internal, cultural and social criteria. Socioeconomic factors also play an important role. [107]

Table (5): Causes of non-adherence [107]

Factors linked to the Patient	(i) Presence of physical disorders (ii) Psychiatric comorbidities (iii) Age (children, adolescents, and elderly present high risk of non-adherence) (iv) Knowledge (v) Social and family support
Variables linked to the disease	(i) Chronicity (ii) Symptom stability (iii) Absence of symptoms
Variables linked to the treatment	(i) High number of daily doses (ii) Presence of side effects (iii) Complexity of the therapeutic regimes (iv) Ease of use (v) Costs
Variables related to the doctor-patient relationship	(i) Bad relationship (ii) Inappropriate doctor or patient Behavior

- **Doctor-patient relationship:**

A major contributor to non-compliance is poor communication between the doctor and patient. This partnership depends on education of both healthcare providers' and patients, and on doctor-patient communication. This is to ensure that the best available information is supplied to patients and that they are willing and able to follow the treatment regimen at home. The partnership is hindered if patients feel that they are wasting the doctor's time or that they have not been listened to, and by an inability to understand the information given. In turn, patients may omit details that they deem unimportant or embarrassing but may be important in deciding the optimal treatment. [108]

Improved listening and communication skills can assist in identifying patients' problems and concerns and in delivering education, reassurance, advice and encouragement in the most accessible and acceptable way for each individual patient. The way in which information is presented is also important. Non-verbal behavior, such as sitting next to the patient or leaning forward, reduces any perceived social distance and indicates attention. Verbal praise and encouragement are extremely important to patients and reward positive disease management. Participating in interactive conversation, using open-ended questions and providing reassuring messages helps patients feel part of a partnership that is working to control their condition. Tailoring messages specifically to patients is also very important. [108]

- **Ongoing allergen exposure:**

Among the wide variety of allergen sources in human dwellings are domestic mites, furred animals, cockroaches and fungi. However, there is conflicting evidence about whether measures to create a low-allergen environment in patients' homes and reduce exposure to indoor allergens are effective at reducing asthma symptoms. [109] The majority of single interventions have failed to achieve a sufficient reduction in allergen load to lead to clinical improvement. [109-111] It is likely that no single intervention will achieve sufficient benefits to be cost effective. However, among inner-city children with atopic asthma; an individualized, home-based, comprehensive environmental intervention decreased exposure to indoor allergens and resulted in reduced asthma-associated morbidity.[112] More properly powered and well-designed studies of combined allergen-reduction strategies in large groups of patients are needed.

The aforementioned factors affecting asthma control have motivated us to carry out this work to study causes behind failure of optimal asthma control in asthmatic patients attending the outpatients' asthma clinic in Alexandria University Children's Hospital.