acta medica

REVIEW ARTICLE

# Asthma

Alpaslan KILICARSLAN[1*], [MD]
Seha AKDUMAN[2], [MD]
Emir Charles ROACH[3], [MD]

1 Hacettepe University Faculty of Medicine Department of Internal Medicine, Section of General Internal Medicine
2 Hacettepe University Faculty of Medicine Department of Chest Diseases
3 Cleveland Clinic Department of Chest Diseases
* *Corresponding Author: Alpaslan Kilicarslan Hacettepe University Faculty of Medicine, Department of Internal Medicine*
*Sihhiye, 06100 Ankara, Turkey*
*e-mail* kalpaslan2003@yahoo.com

*Received 31 October 2013; accepted 06 December 2013; published online 20 January 2014*

ABSTRACT

Asthma is an airway obstruction characterized by restriction in airflow accompanied by wheezing and coughing and attacks of difficulty in breathing. The most significant pathological finding is chronic inflammation, and many inflammatory cells and mediators play a role in this process. Although it is known that there are genetic and environmental factors that play role in asthma, the exact etiopathogenesis has not been established. It is known that asthma effects 300 million people world wide, and is the cause of 250.000 deaths annually. This entity is an important school and work force loss. The main purpose of asthma treatment is to clinically control disease and its progression.

**Key words:** Asthma, risk factors, pathogenesis, treatment

## DESCRIPTION AND EPIDEMIOLOGY

### DESCRIPTION

The primary physiological characteristic of asthma is the obstruction of airway with decreased airflow. The accompanying clinical characteristics include shortness of breath, wheezing and cough, which occur in attacks. The most significant pathological finding, on the other hand, is chronic airway inflammation accompanied by permament structural changes. Although it is known that genetic and environmental factors play role in the development of asthma, the etiopathogenesis has not been elucidated. Because of this, the description is based on the diseases properties. Asthma is a chronic inflammatory disease of the airway.

### EPIDEMIYOLOGY

It is estimated that approximately 300 million people worldwide suffer from asthma. Research studies conducted in around the world, have shown large differences in the prevalence numbers. Research studies that were conducted with standardized and comparable techniques, in children and adults, have shown that the rate is between 1–18% in different countries. In some countries, there is an increasing trend of asthma cases. It is estimated that annually, 250.000 die due to asthma, worldwide [1–5].

In our country, there are big differences in the prevalence of asthma, between different cities and regions. It usually seen more in shore owns, big metropolitan cities and in families of low socioeconomic status. Asthma is more common in males, during childhood, and females, in adulthood. In control studies that were conducted using similr techniques, in our metropolitan cities, an increasing trend of prevalence has been shown in some regions [1–5]. The regional prevalence studies conducted with children, adults and risk factors in Turkey, has been summarized in table - 1.

### Social and Economic Burden

Asthma does effect the population only economically but also socially. Around the world, this disease is an important cause of school performance, and work performance loss. There is a significant lack of data regarding this issue in our country. In a prospective study conducted among adult asthma patients, in Ankara, Turkey, the annual cost of the diseases has been shown to be 1467 ±111,8 USD per person (6). This cost increases as the disease progresses.

**Table 1.** Regional Prevalence Studies Conducted in Turkey and Risk Factors

| City | Child/Adult | Prevalence | Year | Technique | Risk Factors |
|---|---|---|---|---|---|
| Ankara (1) | Child | 6.4% | 2002 | Aberg | Milk and meat consumption |
| Adana (11) | Child | 12.6% | 1997 | ISAAC | Animal, dust, atopia in family history, frequent sinusitis |
| Afyon (22) | Child | Cumulative 7.5% | 2000-1 | ECRHS | Smoking |
| Antalya (23) | Adult | 9.4% | 2006 | ECRHS | Male gender, low socioeconomic status |
| Bursa (24) | Child | Wheezing at anytime 27.5%, wheezing at instance 14.8% | 2006 | ISAAC | Starting supplementary food before 2 months of age, prematurity, maternal smoking, mold in house, presence of allergic eczema, history of atopia in mother or siblings, croup |
| Diyarbakir (15) | Child | Cumulative 14.1% | 2001 | ISAAC | History of atopia in the family |
| Edirne (16) | Child | Cumulative 16.4%<br>5.6% at instance | 1997 | Aberg | Multiple risk factors |
| Elazig (25) | Adult | 5.5% in city, 3.1% in rural areas | 2002 | ECHRS | |
| Eskisehir (26) | University students | Asthma like symptoms 17% | 1997-8 | ECHRS | |
| Istanbul (20) | Child | Cumulative 17% | 1996-7 | ISAAC | |
| Izmir (27) | Child | 4.8% diagnosis by physician, 13.7% cumulative, 7.2% at instance | 2006 | ISAAC | Living in the city, shore towns |
| Manisa (28) | Adult | 1.2% at instance, 1% cumulative | 2006 | ECRHS | Age, gender, smoking, socioeconomic status |
| Samsun (29) | Child | Diagnosis by physician 2.3% | 2006 | ISAAC | Living in the city, shore towns |
| Sivas (30) | Adult | 4.5% within the last year | 2006 | ECRHS | Family history |
| Urfa (31) | Child | Diagnosis by physician 1.9% | 2006 | ISAAC | Living in the city, family history of atopia, socioeconomic status |
| Zonguldak (32) | Child | Diagnosis by physician 4.9% | 2006 | ISAAC | Family history, gender, allergic rhinits |
| Ankara (33) | Adult | 3% within the last year | 1999 | ECRHS | Atopia |

Adapted from Turkish Throacic Society Diagnosis and Treatment Guideline (2009)

## RISK FACTORS

Risk factors can be summarized in two groups, as personal factors, which make an individual susceptible to asthma, and environmental factors, which lead to asthma in genetically susceptible individuals. In addition to factors, which lead to the development of asthma, there are also factors, which trigger the asthma symptoms. The most significant risk factors that cause asthma are the genetic risk factor. On the other hand, environmental factors are mostly the cause for exacerbation of asthma symptoms. It is theorized that, interplay, both among genes, and between genes and the environment, lead to a propensity to develope asthma [6–8].

## PERSONAL FACTORS

### Genetics

There is sufficient data to show that asthma is a genetic disease. When either a mother or father is asthmatic, the probability of their child to be an asthmatic increases to up to 20–30%, whereas if both parents are asthmatics, this probability increases up to 60–70%. There are many genes that play a role in the pathogenesis of asthma. [9,10]. The genetic changes that lead to athma usually take place in four regions:

a) Allergen specific antibody production (IgE structure),
b) Genes that act in airway hyperreactivity;

c) Genes affecting the synthesis of inflammatory mediators (cytokines, chemokines and growth factors)
d) The balance between Th1 and Th2 immune response (related to the hygiene hypothesis)

**Obesity:** Obesity has been shown to be a risk factor for asthma. It might be due to the effects of certan mediators such as Leptin on the airway, which in turn, increases the risk for asthma [6,7].

**Gender:** Being a male is an important risk factor during childhood. The prevalence of asthma among boys, before the age fourteen, has been shown to be twice of that of girls. This gap narrows as the age increases, and during adulthood, asthma is more frequently seen among women. Gender also affects the persistence of the disease and clinical remission [6–8].

## ENVIRONMENTAL FACTORS

**Allergens:** Although it is known that both indoor and outdoor allergens may lead to asthma exacerbations, their role in the development of asthma has not been completely elucidated. It has been shown that cockroaches may cause allergic sensitization. The prevalence of asthma has been shown to be relatively low among people who have been raised in rural areas. This can be explained with the hygiene hypothesis. [6, 8–11].

**Infections:** The effect of childhood infections on asthma is not exactly known. The "hygiene hypothesis" put forth for asthma, puts forth the argument that if a child is subject to infections during early childhood, the child's immune system is channelized into a "non-allergic" pathway, and the risk of asthma is decreased (9). Research is still being conducted to validate this hypothesis.

**Cigarettes:** Both prenatal and postnatal exposure to tobacco smoke, leads to asthma like symptoms, in addition to having many detrimental effects. It is known that smoking of a mother impairs lung development, and increases the risk of wheezing 4 times within the first year of life (6).

**Indoor and Outdoor Pollution:**

The relationship between outdoor contaminants and asthma has not been clearly established. Some studies have shown that, there is a relationship between increases in air pollution, and the number of patients applying to health institutions due to asthma exacerbations and attacks. Similar relationships have been established for indoor contaminants also (gas and fumes from "biomass", cockroaches and mold).

**Diet:** Diets based on ready-made food, low levels of antioxidant intake, increased n–6 polyunsaturated fatty acid consumption, insufficient n–3 polyunsaturated fatty acid consumption has been theorized to contribute to the increase in asthma and atopic diseases [12].

### Factors causing occupational asthma:

More than three hundred materials have been shown to be related to occupational asthma [6]. Amonh these are highly reactive small molecules called isocyanates, irritants like platinum salt which are known to be immunogenic and effect airway response, and complex animal and plant based molecules which stimulae IgE production (Table 2). Asthma is the most common occupational respiratory system disease in developed industrialized countries and [13,14], it is estimated that occupational sensitizers are responsible for every one in 10 asthma cases in adults [15].

## PATHOGENESIS

Asthma is an inflammatory disease of the airways and is characterised by the presence inflammatory cells and mediators in addition to pathophysiological changes. The inflammation pattern that is present in the airways, is similar in all forms asthma; namely allergic, non allergic and aspirin induced asthma. Also, the findings are similar in all age groups. Mast cells, eosinophils, T lymphocytes, dendritic cells, macrophages and neutrophils are among the cells that play a role in the inflammation. Also, epithelial cells, smooth muscle cells, endothelial cells, fibroblasts, myofibroblasts and airway nerves are the structural cells, which take place in the inflammation process.

The chemokines and cysteinyl leukotrienes which play a role in asthma pathogenesis include; IL1α, TNF-α, GM-CSF, $IL_4$, $IL_5$ ve $IL_{13}$; histamine, nitric oxide and prostaglandin D2 [16–18].

### Physiopathology

The main event in asthma is the narrowing of the airway and other physiological changes. The smooth musle contraction, edema, thickening of the airway wall, increase in mucous seretion and concurrent plug formation are the causes for the narrowing of the airway. Airway hyper-reactivity that is one of the characteristic features of asthma is the response that the airway gives to a normally harmless agent. Although there are many hypothesis which have

**Table 2.** Agents Causing Occupational Asthma

| Field of Work/Job | Agent |
|---|---|
| | Animal and Plant Based Proteins |
| Bakers | Flour, amylase |
| Dairyman | Storage mites |
| Detergent Production | Bacillus subtilis enzymes |
| Soldering | Pine resin |
| Farmers | Soy powder |
| Fishing goods | Parasites |
| Food processing | Coffee powder, meat processing, preservatives, tea, amylase, egg proteins, pancreatic enzymes, papain |
| Grain workers | Grain dust |
| Health workers | Psyllium, latex |
| Poultry workers | Mites, feces, feathers |
| Researchers/ Veterinarians | Bugs, feathers, urine proteins |
| Carpenters | Wood dusts, trees |
| Ship Loaders | Grain dusts (containing fungi, insects) |
| Silk workers | Silkworm larvae |
| | Inorganic Chemicals |
| Beauty Shop workers | Persulfate |
| Laminators | Nickel salts |
| Refinery workers | Platinum salts, vanadium |
| | Organic chemicals |
| Car painters | Ethanolamine, diisocyanates |
| Hospital workers | Disinfectants (sulphathiozole, chloramides, formaldehyde, glutaraldehyde), latex |
| Production | Antibiotics, piperazine, methyldopa, salbutamol, cimetidine |
| Sponge workers | Folmadehyde, ethylenediamine, phtalic anhydrides |
| Plastics industry | Toluene, diisocyanates, hexamethyldiisocyanates, phtalic anhydrides, triethylene tetraamine, hexamethyl tetramine, acrylates |

Adapted from Turkish Throacic Society Diagnosis and Treatment Guideline (2009)

been put forth, the exact mechanism of airway hyper reactivity is currently unknown.

## DESCRIPTION AND CLASSIFICATION

An asthma diagnosis is based on patient history and physical examination. Shortness of breath, wheezing, cough, pressure feeling on chest, which occurs in attacks, are some of the diagnostic features. Positive diagnostic tests support a diagnosis, however negative diagnostic tests are not cause for ruling out an asthma diagnosis. Variance in the symptoms within a single day, or seasons, triggering of the symptoms due to smoke, smells and exercise, an increase in symptoms at night, and response to treatment support an asthma diagnosis. Family history of asthma, and presence of other atopic diseases are also characteristics of this disease [19–21].

### Diagnosis of Asthma Phenotypes

Asthma can be present in differen phenotypes. Previously, asthma phenotypes were classified as extrinsic (allergic) and intrinsic (non-allergic) asthma, whereas today, other phenotypes such as late onset asthma, premenstrual asthma, nocturnal asthma, aspirin induced asthma, steroid resistant/dependent asthma, brittle asthma, occupational asthma have also been described.

## TESTS USED FOR DIAGNOSIS AND FOLLOW UP

### RESPIRATORY FUNCTION TESTS

Demonstrating the airway obstruction, reserve capacity and variability via respiratory function tests is supportive of a diagnosis. However, normal respiratory function tests are not sufficient to rule out a diagnosis. Spirometric measurements to demonstrate airway obstruction and variability in reserve capacity are recommended for a diagnosis. These tests are conducted for diagnostic purposes in the first presentation, however, throughout the treatment, they are repeated in order to identify the best values. >12% or >200 ml increase in Forced Expiratory Volume (FEV) value from the base value and 20% increase in Peak Expiratory Flow (PEF) value) 15 mintues after beta–2 agnonist inhalation in patients with airway obstruction shows the reversibility of airflow restriction.

PEF measurements obtained using a PEF metre is important for confirmation of an asthma diagnosis and follow up [21].

### ASTMA DRUGS

The purpose of asthma treatment is clinical control and maintenance. The drugs that are used for asthma treatment are classified into two groups as rescue medications and controller medications [22].

**Controller medications:** They help asthma remain under control with their anti inflammatory characteristics. They are used every day for long durations. This group includes; inhaled and systemic steroids, leukotrien antagonists, inhaled beta–2 agonists used in conjunction with inhaled steroids, slow release theophylline, chromones, and anti-IgE therapies. The most effective controller medications used currently are inhaled steroids.

**Rescue medications:** They are used in acute situations for symptom relief. Their effects, which include decreasing bronchospasm, begin immediately. This group includes fast acting inhaled β–2 agonists, short acting inhaled anticholinergic drugs, short acting theophylline and short acting oral β–2 agonists.

### Inhaled Steroids

Inhaled drugs that are used for asthma are available in adjustable dose inhaler (ADI), breath actuated ADI, dry powder inhaler and nebulizer forms.

Inhalers have different efficacies when it comes to delivering drugs to the lower respiratory airways, and this depends on the shape of the inhaler, drug formulation, particle size, aerosole size (depending on the inhaler) and ease of use. The use of ADI.s require training and skill. The use of ADI.s with spacers allow better transfer of drug to the patient, and decreases drug accumulation in the lung, hence local and systemic side effects [23].

**Side effects:** Among the reported side effects of inhaler steroids are oropharyngeal candidiasis, dysphonia, upper respiratory airway irritation due to cough. Washing the mouth after inhalation may decrease oral candidiasis. The use of drugs like ciclesonide which are inactive in the pharynx, but active in the lungs, formulas and equipment which decrease oropharyngeal accumulation of drugs, may decrease these side effects without the need of mouth washing [22]. A certain amount of inhaled steroids can cross into the systemic circulation, and can lead to side effects. This is dependent on the dose of the drug, potency, type of delivery unit used, systemic bioavailability, first pass metabolism, half life of the drug fraction present systemically [24]. As such, the systemic effects of inhalers vary a lot. Among the side effects that occur due to high dose, long duration usage are thinning of skin, ecchymoses [19], suppression of suprarenal glands [22–24] and lowering of bone mineral density [25,26]. Calcium and vitamin D supplementation is recommended especially in postmenopausal women. In cross sectional studies with inhaled steroids, an increase in the risk of cataract [22,23] and glaucoma [24] has been observed; however, this increase in risk has not been demonstrated in prospective studies [25–27]. There is no evidence that inhaled steroids can lead to increase of tuberculosis or any other lung infection, and inhaled steroids can be safely used in active tuberculosis [27].

### Leukotriene Antagonists

Of the leukotriene antagonists only montelukast and zafirlukast are present in Turkey. Clinical sudies have shown that leukotriene antagonists have a modest and variable bronchodilator effect, lessen the symptoms including coughing [28], improve lung function and decrease airway inflammation, whicn in turn leads to a decrease in asthma exacerbations [29,30].

**Side Effects:** Leukotriene antagonists are well tolerated. There are case reports, however, of Churg-Strauss syndrome occuring in conjunction with a decrease in the dose of systemic and/or inhaled steroids [31].

### Long acting inhaled β –2 agonists

Because long acting inhaled β –2 agonists like formoterol and salmeterol have no effect on airway inflammation, they must not be used alone. The best results are seen with concomitant use of inhaled steroids. Addition of long acting β –2 agonists to inhaled steroids, provides improvement in day/night symptoms, whereas, addition of fast-acting inhaled β –2 agonists, leads to a decrease in asthma attacks, improves lung fuction and allows clinical control of the disease [32].

**Side effects:** Inhaled β –2 agonists have less systemic side effects (cardiovascular stimulation, skeletal muscle teromor and hypokalemia) when compared to slow release oral forms. Regular use of β–2 agonists may cause tachyphylaxis (against bronchoprotective, bronchodilator and side effects). Due to mortality related to the use of salmeterol in a small group of patients, the American Food and Drug Administration (FDA) has recommended that salmeterol be used under physician control in conjunction with a steroid [33,34].

### Theophylline

Theophylline is a bronchodilator with slight anti-inflammatory properties in low doses. It does not have sufficient efficacy to be considered as a drug of first choice. It is generally put to use when control can not be established with inhaled steroids [35].

**Side effects:** The therapeutic index of this drug is very narrow, significant side effects can be seen especially in very high doses. The dose must be selected very carefully and the plasma levels of the drug must be followed up. The most frequently seen side effects are nausea/vomiting, gastrointestinal symptoms, and convulsion. While febrile diseases, pregnancy and tuberculosis drugs lower the plasma levels of the drug, liver diseases, congestive heart failure, cimetidine, quinolones and some macrolides may increase the plasma level of the drug [36].

### Anti-IgE

Anti-IgE (omalizumab), is indicated when the patients of the symptom cannot be controlled with inhaled steroids, or in patients who are not affected by perennial allergens. It has been shown to relieve the symptoms, decrease the frequency of exacerbations, hence, help in control of the disease.

**Side effecs:** Studies have shown that anti-IgE is relatively safe, however, since there is an anaphylaxis (1/1000) risk, the injections must be done in health centers, and the patients receiving the drug must be observed for two hours [37].

### Systemic Steroids

In very severe and uncontrollable asthma that lasts longer than 2 weeks, oral steroid treatment may be indicated, however the use is limited due to side effects. The therapeutic index of long duration systemic steroid therapy (effect/side effect) is lower than long duration inhaled steroids. If long systemic steroids are going to be administered for a long time, then precautions regarding the side effects must be taken.

**Side effects:** Osteoporosis, hypertension, diabetes, hypothalamo-hypophyseal-adrenal axis suppression, obesity, cataract, glaucoma, striations on the skin, thinning of the skin and muscle wasting. Although being rare, cessation of oral steroid drugs can lead to adrenal insufficiency or uncover an underlying disease such as Churg-Strauss Syndrome. Also, if the patient has tuberculosis, parasite infection, osteoporosis, glaucoma, diabetes, severe depression or peptic ulcer, the patient must be followed up closely [38].

## RESCUE MEDICATIONS

### Fast acting β–2 agonists

These drugs are used to releave the bronchospasm that occur during asthma attacks and exercise. They must be used only when necessary, and with the lowest possible dose. In our country, salbutamol, terbutaline and the long acting β–2 agonist formoterol are available. Formoterol can be used as a symptom reliever in a patient who is taking inhaled steroids regularly [22].

**Side effects:** Oral β–2 agonists cause more tremor and tachycardia when compared to inhaled β–2 agonists.

### Systemic Steroids

Systemic steroids are useful in the treatment of severe asthma attacks. It prevents the progression of the attack, decreases the number of emergency ward and hospital admission, recurrence of attack and morbidity. The therapeutic effect when used for acute asthma appears 4–6 hours after administration. This treatment is administered orally [39].

**Side effects:** Side effects of short duration high dose systemic treatment are rare. Possible side effects include glucose metabolism disturbances, increased appetite, fluid retention, moon face, psychological distrubances, peptic ulcer, aseptic necrosis of femur [22].

## Anticholinergic Drugs

The level of symptom relief achieved with the administration of the inhaled anticholinergic drug, ipratropium bromide, alone,is lower than that of inhaled β–2 agonists. The use of ipratropium bromide in an acute asthma attack provides additional improvement in the lung functions, and a decrease in hospital admissions [40].

**Side Effects:** Ipratropium Bromide inhalation can cause dry mouth, bitter taste, and prostatism [41].

## Theophylline

Short acting theophylline and aminophylline may be used in asthma as a symptom reliever. [42]. The role of theophylline in acute asthma attacks is not clearly establihed. While, short acting theophylline does not provide additional benefit to β–2 agonist's bronchodilator effects, possible benefits include, stimulation of respiration and elimination of diaphragm fatigue.

**Side effects:** Because administration of slow release theophylline may lead to unwanted side effects, if theophylline is going to be administered, plasma levels must be checked frequently [22].

**Short acting β -2 agonists**

Their use may be indicated in a small number of patients who cannot use inhaled drugs, however, the side effect prevalence with these drugs is much higher.

## REFERENCES


[1] **Demir AU, Karakaya G, Bozkurt B, Sekerel BE, Kalyoncu AF.** Asthma and allergic diseases in schoolchildren: third cross-sectional survey in the same primary school in Ankara, Turkey. Pediatr Allergy Immunol 2004; 15: 531-8.

[2] **Ones U, Akcay A, Tamay Z, Guler N, Zencir M.** Rising trend of asthma prevalence among Turkish schoolchildren (ISAAC phases I and III). Allergy 2006; 61: 1448-53.

[3] **Demir E, Tanac R, Can D, Gülen F, Yenigün A, Aksakal K.** Is there an increase in the prevalence of allergic diseases among schoolchildren from the Aegean region of Turkey? Allergy Asthma Proc 2005; 26: 410-4.

[4] **Bayram I, Guneser-Kendirli S, Yilmaz M, Altintaş DU, Alparslan N, Bingöl-Karakoç G.** The prevalence of asthma and allergic diseases in children of school age in Adana in southern Turkey. Turk J Pediatr 2004; 46: 221-5.

[5] **Saraclar Y, Kuyucu S, Tuncer A, Sekerel B, Saçkesen C, Kocabaş C.** Prevalence of asthmatic phenotypes and bronchial hyperresponsiveness in Turkish schoolchildren: an International Study of Asthma and Allergies in Childhood (ISAAC) phase 2 study. Ann Allergy Asthma Immunol. 2003; 91: 477-84.

[6] **GINA Report, Global Strategy for Asthma Management and Prevention (Changes Marked) 2007 Update: www.**ginasthma.org

[7] **Ober C.** Perspectives on the past decade of asthma genetics. J Allergy Clin Immunol 2005; 116: 274-8.

[8] **Holgate ST.** Genetic and environmental interaction in allergy and asthma. J Allergy Clin Immunol 1999; 104: 1139-46.

[9] **Braun-Fahrlander C.** Environmental exposure to endotoxin and other microbial products and the decreased risk of childhood atopy: evaluating developments since April 2002. Curr Opin Allergy Clin Immunol 2003; 3: 325-9.

[10] **Alper Z, Sapan N, Ercan I, Canitez Y, Bilgel N.** Risk factors for wheezing in primary school children in Bursa, Turkey. Am J Rhinol 2006; 20: 53-63.

[11] **Kalyoncu AF, Demir AU, Ozcakar B, Bozkurt B, Artvinli M.** Asthma and allergy in Turkish university students: Two cross-sectional surveys 5 years apart. Allergol Immunopathol (Madr) 2001; 29: 264-71.

[12] **Devereux G, Seaton A.** Diet as a risk factor for atopy and asthma. J Allergy Clin Immunol 2005; 115: 1109-17.

[13] **Çımrın AH.** Meslek Astımı-Türkiye Gerçeği. Toraks Dergisi 2000; 1: 87-89.

[14] **Akpinar-Elci M, Cimrin AH, Elci OC.** Prevalence and risk factors of occupational asthma among hairdressers in Turkey. J Occup Environ Med 2002; 44: 585-90.

[15] **Blanc PD, Toren K.** How much adult asthma can be attributed to occupational factors? Am J Med 1999; 107: 580-7.

[16] **Busse WW, Lemanske RF Jr.** Asthma. N Engl J Med 2001; 344: 350-62.

[17] **Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM.** Asthma. From bronchoconstriction to airways inflammation and remodeling. Am J Respir Crit Care Med 2000; 161: 1720-45.

[18] **Chung KF.** Airway smooth muscle cells: contributing to and regulating airway mucosal inflammation? Eur Respir J 2000; 15: 961-8.

[19] **Levy ML, Fletcher M, Price DB, Hausen T, Halbert RJ, Yawn BP.** International Primary Care Respiratory Group (IPCRG) Guidelines: diagnosis of respiratory diseases in primary care. Prim Care Respir J 2006; 15: 20-34.

[20] **Toraks Derneği Ulusal Astım Tanı ve Tedavi Rehberi.** Toraks Dergisi 2000; Ek 1.

[21] **Global Initiative for Asthma (GINA).** Global strategy for asthma management and prevention. 2008. www.ginasthma.org.

[22] **Global Strategy for Asthma Management and Prevention.** Global Initiative for Asthma (GINA), 2009. www.ginasthma.org.

[23] **Brown PH, Greening AP,Crompton GK.**Large volume spacer devices and the influence of high dose beclomethasone dipropionate on hypothalamo-pituitary-adrenal axis function. Thorax 1993; 48: 233-8.

[24] **Lipworth BJ.** Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med 1999; 159: 941-55.

[25] **Lung Health Study Research Group.** Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000; 343: 1902-9.

[26] **Pauwels RA, Yernault JC, Demedts MG, Geusens P.** Safetyand efficacy of fluticasone and beclomethasone in moderate to severe asthma. Belgian Multicenter Study Group. Am J Respir Crit Care Med 1998; 157: 827-32.

[27] **Garbe E, LeLorier J, Boivin JF, Suissa S.** Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. JAMA 1997; 277: 722-7.

[28] **Agertoft L, Larsen FE, Pedersen S.** Posterior subcapsular cataracts, bruises and hoarseness in children with asthma receiving long-term treatment with inhaled budesonide. Eur Respir J 1998; 12: 130-5.

[29] **Simons FE, Persaud MP, Gillespie CA, Cheang M, Shuckett EP.** Absence of posterior subcapsular cataracts in young patients treated with inhaled glucocorticoids. Lancet 1993; 342: 776-8.

[30] **Bahceciler NN, Nuhoglu Y, Nursoy MA, Kodalli N, Barlan IB, Başaran MM.** Inhaled corticosteroid therapy is safe in tuberculin-positive asthmatic children. Pediatr Infect Dis J 2000; 19: 215-8.

[31] **Dicpinigaitis PV, Dobkin JB, Reichel J.** Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. J Asthma 2002; 39: 291-7.

[32] **Lipworth BJ.** Leukotriene-receptor antagonists. Lancet 1999; 353: 57-62.

[33] **Drazen JM, Israel E, O'Byrne PM.** Treatment of asthma with drugs modifying the leukotriene pathway. N Engl J Med 1999; 340: 197-206.

[34] **Kalyoncu AF, Karakaya G, Sahin A, Artvinli M.** Experience of 10 years with Churg-Strauss syndrome: An accompaniment to or a transition from aspirin-induced asthma? Allergol Immunopathol 2001; 29: 185-90.

[35] **Lemanske RF Jr.**, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. JAMA 2001; 285: 2594-603.

[36] **Newnham DM, McDevitt DG, Lipworth BJ.** Bronchodilator subsensitivity after chronic dosing with eformoterol in patients with asthma. Am J Med 1994; 97: 29-37.

[37] **Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM.** The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006; 129: 15-26.

[38] **Barnes PJ.** Theophylline: new perspectives for an old drug Am J Respir Crit Care Med 2003; 167: 813-8.

[39] **Ahn HC, Lee YC.** The clearance of theophylline is increased during the initial period of tuberculosis treatment. Int JTuberc Lung Dis 2003; 7: 587-91.

[40] **Molimard M, de Blay F, Didier A, Le Gros V.** Effectiveness of omalizumab (Xolair) in the first patients treated in reallife practice in France. Respir Med 2008; 102: 71-6.

[41] **Recommendations for the prevention and treatment of glucocorticoid- induced osteoporosis.** American College of Rheumatology Task Force on Osteoporosis Guidelines. Arthritis Rheum 1996; 39: 1791-801.

[42] **Harrison BD, Stokes TC, Hart GJ, Vaughan DA, Ali NJ, Robinson AA.** Need for intravenous hydrocortisone in addition to oral prednisolone in patients admitted to hospital with severe asthma without ventilatory failure. Lancet 1986; 1: 181-4.

[43] **Rodrigo G, Rodrigo C, Burschtin O.** A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. Am J Med 1999; 107: 363-70.

[44] **Tamaoki J, Chiyotani A, Tagaya E, Sakai N, Konno K.** Effect of long term treatment with oxitropium bromide on airway secretion in chronic bronchitis and diffuse panbronchiolitis. Thorax 1994; 49: 545-8.

[45] **Weinberger M, Hendeles L.** Theophylline in asthma. N Engl J Med 1996; 334:1380-8.

 