Turkish Thoracic Society asthma management and prevention guideline: key points

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ÖZET

Türk Toraks Derneği astım tanı ve tedavi rehberi: Anahtar noktalar

Astım, dünyada ve ülkemizde patogenez, tanı ve tedavisinde tüm ilerlemelere rağmen morbiditesi ve maliyeti yüksek bir hastalıktır. Doğru tanı ve tedavi ile kontrol altına alınabilen bir hastalık olmasına rağmen dünyada ve ülkemizde belirlenen düşük kontrol oranları sadece hastalığın değişken seyrine ve hastaların psikososyal kronik hastalık davranışına bağlanamaz. Bu bağlamda, Türk Toraks Derneği de en son 2000 yılında yayınladığı "Astım Tanı ve Tedavi Rehberi"ni güncelleme kararı almıştır. Ülkemizin verileri toplanmış, konu ile ilgili eğitimcilerden oluşturulan yazarlar tarafından kanıta dayalı bilgiler derlenerek hazırlanmış ve Türk Toraks Derneği Astım ve Allerji Çalışma Grubu tarafından son şekli verilerek, danışman kişi ve kurumlara sunulmuştur. Haziran 2009 tarihinde Türk Toraks Derneği "Astım Tanı ve Tedavi Rehberi" Türkçe olarak yayınlanmıştır. Bu derlemede ulusal rehberin temel özellikleri ve diğerlerinden farkları İngilizce olarak sunulmaktadır.

Anahtar Kelimeler: *Astım, tanı, tedavi, rehber.*

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SUMMARY

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Asthma still has high morbidity and cost despite all advances in pathogenesis, diagnosis and treatment. Although asthma can be controlled with proper diagnosis and treatment, the low rates of control in our country and in the world can not be attributed to the variable course of the disease and patients' psycho-social behaviours for chronic disease. In this context, Turkish Thoracic Society (TTS) has decided to update Asthma Diagnosis and Management Guide latest published in 2000. National data were collected, compiled and prepared by authors, and final form given by the TTS Asthma and Allergy Study Group, after presenting to consultant individuals and institutions. In June 2009, the National Asthma Management and Prevention Guideline were published in Turkish. In this paper, we aimed to present the national guide in English with its basics and individual differences.

Key Words: *Asthma, diagnosis, treatment, guideline.*

DEFINITION and EPIDEMIOLOGY

Asthma is a chronic inflammatory disorder of the airways. 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 variable airflow obstruction which is often reversible either spontaneously or with treatment (1).

It is estimated that asthma affect 300 million individuals in worldwide. Hundreds of reports on the prevalence of asthma from different populations have shown wide range on asthma prevalence. The global prevalence of asthma ranged from 1% to 18% (1).

In Turkey, prevalence of asthma has important differences between cities and regions. Asthma prevalence is higher in coastal regions, urban areas, metropolitan cities and at lower socioeconomic conditions (2-6). There is an increase in global prevalence, mortality and morbidity of asthma in last 30 years, but some recent studies has showen that the prevalence of asthma tends to be stabilize or even to decrease (7-10). The prevalence of asthma both in childhood and adulthood in Turkey are shown in Table 1 and Table 2 (2,11-25). Results of national multicentered studies of Turkey are also shown in Table 3 (3,26-28).

Social and Economic Burden

Asthma effects the community not only economically but also socially. Asthma is an important cause of absence from school and days lost from work all around the world. Thus, mentioning the economic burden of asthma, it should cover both medical and non-medical costs. Unfortunately, there is lack of data on this issue in Turkey. In a prospective study including adult asthmatics from Ankara, the mean annual total

Table 1. Regional asthma prevalence studies in childhood.

City	Year	Prevalence	Method
Istanbul (12)	1996-1997	Cum, 17%	ISAAC
Adana (13)	1997	Cur, 12.6%	ISAAC
Edirne (14)	1997	Cum, 16.4%	Aberg
		Cur, 5.6%	
Afyon (15)	2000-2001	Cum, 7.5%	ECRHS
Diyarbakir (16)	2001	Cum, 14.1%	ISAAC
Ankara (3)	2002	Cur, 6.4%	Aberg
Bursa (17)	2006	Cur, 14.8%	ISAAC
Izmir (18)	2006	Cum,13.7%	ISAAC
		Cur, 7.2%	
Sanliurfa (19)	2006	Cur, 1.9%	ISAAC
Zonguldak (20)	2006	Cur, 4.9%	ISAAC

Cum: Cumulative, Cur: Current.

Table 2. Regional asthma prevalence studies in adulthood.

City	Year	Prevalence	Method
Eskisehir (21)	1997-1998	Cum, 17%	ECRHS
Ankara (22)	1999	Previous year, 3%	ECRHS
Elazig (23)	2002	Urban, 5.5%	ECRHS
		Rural, 3.1%	
Sivas (24)	2003	Previous year, 4.5%	ECRHS
Antalya (25)	2006	Cur, 9.4%	ECRHS
Manisa (26)	2006	Cum, 1%	ECRHS
		Cur, 1.2%	

Cum: Cumulative, Cur: Current.

Table 3. National multicenter asthma prevalence studies.

Study	Population	Year	Prevalence	Method
ROCHE (27)	Childhood	2001	Cum, 14.7% Cur, 2.8%	ISAAC
PARFAIT (28)	Childhood	2007	Cur, 13.3%	
PARFAIT (29)	Adulthood	2009	Cur, 8.1%	
AEGEAN REGION (4)	Childhood	2006	Cur, 6.4%	ISAAC

Cum: Cumulative, Cur: Current.

cost of asthma was found as 1467 ± 111.8 USD (29). Another study from Ankara including childhood asthma patients showed that mean annual total cost of asthma is 991.7 ± 73.2 USD (median: 688 USD) (30). A multicentered childhood study from Turkey found that mean annual total cost of asthma is 1597.4 ± 236.2 USD (31). The authors also reported that the annual cost of asthma is associated with unplanned doctor visits, hospitalization, asthma severity and days lost from school. Adulthood asthma study also found similar results (32).

RISK FACTORS

Factors influencing the development and expression of asthma are well known and include both host and environmental factors (1). In our published guide we mostly mentioned about the findings of national studies.

Genetic Factors

Asthma has complex heritable component. Multiple genes have roles in the pathogenesis of asthma (1,33). There are four major areas for the genetic intervention: production of allergen specific IgE antibodies, expression of airway hyperresponsiveness, generation of inflammatory mediators and determination of the ratio between Th1 and Th2 immune responses (1,34).

Obesity

Obesity is another risk factor for asthma. Leptin may involve in airway disfunction and developing of asthma (1,34,35).

Gender

In early childhood male sex is a risk factor for asthma. But as children get older the difference between genders decrease and in adulthood prevalence of asthma is greater in women than men (1,34-36).

Allergens

It is well known that both indoor and outdoor allergen exposure can lead increase in asthma symptoms, but their role in the development of asthma is still not clear (1,37,38). Some studies shown that exposure to house dust mite may be a causal factor in the development of asthma (39). It is also shown that exposure to cockroaches is an important cause of sensitization (40,41). Some epidemiologic studies found that early exposure to cats and dogs could protect against sensitization or the development of asthma, but others suggested that those kinds of exposure could increase the risk of sensitization (1). Children grown in rural areas have less prevelance of asthma which could be explained by hygene hypothesis (1,29,42).

Infections

The hygene hypothesis suggests that infections in early life influence the child's immune system along a "non-allergic" pathway, leading to a reduced risk of asthma and other allergic diseases (1). However, the interaction between viral infections and atopy is a complex situation.

Occupational Sensitizers

Many substances have been associated with occupational asthma. It is estimated that occupational sensitizers cause approximately 10% of adult asthma cases. Immunmediated occupational asthma with small molecules such as isocyanates has a latency period of months to years. Irritant induced asthma (previoulsy named reactive airways dysfunctional syndrome) occurs with intense exposure to irritants (1,34).

Smoking

Smoking and/or second hand smoke is associated with decline in lung function, increase in symptoms and medication requirements, triggers asthma attacks (14,34). Both prenatal and postnatal exposure to tobacco smoke lead asthma like symptoms in early childhood (17,43). Recently, it is found that 11.4% of asthmatic patients were smokers, which is lower than the percentage of smokers in the general population of Turkey (44%) (44).

Outdoor/Indoor Air Pollution

Although the role of outdoor air pollution in causing asthma is still controversial, it is obvious that asthma attacks increase with increased level of air pollution (45). Indoor pollutants e.g., smoke and fumes from gas and biomass fuels, molds, cockroach infestations are also related with triggered asthma symptoms (1).

Diet

Breast-feeding is the most studied subject in development of asthma. It is shown that infant fed formulas of intact cow's milk or soy protein have a higher incidence of wheezing illness in early childhood compared with those fed by breast milk (3). Some features of diet such as increased use of processed foods and decreased antioxidant, increased n-6 polyunsaturated fatty acid, and decreased n-3 polyunsaturated fatty acid intakes may be related to increase in asthma (1,46).

DIAGNOSIS of ASTHMA

The most important goal in order to be successful in asthma treatment is establishing a correct diagnosis (1). Clinical history is very important and diagnosis of asthma is prompted by episodic symptoms such as episodic breathlessness, wheezing and chest tightness (47). Daytime and seasonal variability of symptoms, triggering with fog, smoke, smell and exercise, increase at night and response to appropriate asthma treatment support asthma diagnosis (34). A positive family history of asthma and atopic diseases are also helpful diagnostic guides.

If the patient has no symptoms the physical examination of the respiratory system may be normal but asthma diagnosis can not be excluded. The most usual physical finding is wheezing and ronchi on auscultation. Coughing at the end of each inspiration during clinical and physical examination can be an indirect marker of bronchial hyperresponsiveness and may lead clinician to think asthma diagnosis. In severe asthma exacerbations wheezing and ronchi may be absent.

However, patients in this state usually have other physical signs reflecting severity, such as cyanosis, drowsiness, difficulty in speaking, tachycardia, hyperinflated chest, use of accessory muscles and intercostal retractions (1).

TESTS for DIAGNOSIS and FOLLOW UP

Asthma can often be diagnosed on the basis of symptoms. However, measurement of lung function supports the diagnosis by assessing the severity of airflow limitation, reversibility and variability in lung function. Lung function test results in normal ranges can not exclude the diagnosis of asthma. Although there was no strong correlation between symptoms and control parameters with lung function tests both in adults and children, these measurements provide descriptive information for asthma control (48,49).

A wide range of different methods to assess the level of airflow limitation exist, but two methods have found widespread acceptance in patients over 5 years age. These are the measurement of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and measurement of peak expiratory flow (PEF). Any FEV_1/ FVC value less than 75% are suggestive of airflow limitation (1,48). In a patient who has airflow obstruction a 12% or 200 mL improvement in FEV_1 in respect of basal value or a 20% improvement in PEF value after the inhalation of short acting beta2 agonists (4 puff salbutamol= 400 µg or 4 puff terbutaline = 1000 µg) indicates the early reversibility of airflow obstruction (1,49,50).

Some of the airflow obstructions have reversibility after 2-3 weeks oral corticosteroid (20-40 mg/day prednisolone) or 6-8 weeks appropriate dose inhaler corticosteroid treatment. If there is a 15% increase in FEV_1 value, this indicates the late reversibility. Reversibility can not be found in patients who are under treatment (1).

PEF is still considered as an important aid in the diagnosis and subsequent treatment of asthma (1). Ideally PEF should be first thing that measured in the morning when values are usually close their lowest and last thing at night after taking bronchodilator treatment when values are usually at their highest (1). A diurnal variation in PEF of more than 20% is considered to be diagnostic for asthma (1). Methods to measure PEF variablity are mentioned in the original document (34).

For patients with symptoms consistent with asthma, but with normal lung function, measurements of airway hyperresponsiveness to methacholine, histamine, or exercise challenge may help establishing a diagnosis of asthma (1,50-52).

The airway inflammation associated with asthma may be evaluated by examining spontaneously produced or induced sputum for total cell counts, eosinophils, neutrophils and mediators (1,50,53,54). In addition levels of exhaled nitric oxide (NO) or carbon monoxide (CO) have been suggested as non-invasive markers of airway inflammation in asthma (1,50,55).

Evaluation of allergic status in suspected patient from clinical history is skin prick test. The test results should correlate with history in order to carry clinical value. The standard allergens in a prick test examination are; positive/negative control, grass polen, dermatofagoides pteronyssinus, cat and alternaria allergens (38). Measurement of specific IgE is less sensitive and more expensive. Measurement of total IgE in serum has no value as a diagnostic test for atopy.

ASTHMA MEDICATIONS

The effectiveness of drug therapy in asthma has been established for many years. The goal of asthma treatment is to minimize symptoms with the fewest possible adverse effects. The pharmaceutical agents used for asthma can be classified into two main groups; relievers and controllers (1,34).

Available controller medications in Turkey are inhaled glucocorticosteroids, leukotriene receptor antagonists, long-acting β2-agonists, theophylline, anti-IgE and systemic glucocorticosteroids. Available reliever medications are rapid-acting inhaled β2-agonists, systemic glucocorticosteroids, anticholinergics, theophylline, short-acting oral β2-agonists. And the commonly available delivery systems are the metered dose inhaler (MDI), with or without the use of a spacer, dry powder inhalers and nebulizers (56,57).

Clinical effects and side effects for asthma medications are broadly given in Turkish Thoracic Society Asthma Guideline (34).

Controller Medications

Inhaler corticosteroids (ICS) are the most effective controller therapy and must be used continuously (58-64). Higher doses may be required for patients who smoke. Adding a second controller medication is prefered to increasing the dose of ICS (65,66). Common side effects of ICS are mentioned in the original document (34,67-78). There is no evidence that use of inhaled glucocorticosteroids increases the risk of pulmonary infections including tuberculosis (79,80). Daily

Table 4. Estimated equipotent daily dosage for inhaled glucocorticosteroids available in Turkey for adults.

Drug	Low dose (µg)	Medium dose (µg)	High dose (µg)
Beclomethasone	200-500	500-1000	1000-2000
Budesonide*	200-400	400-800	800-1600
Ciclesonide*	80-160	160-320	320-1280
Fluticasone	100-250	250-500	500-1000
Mometasone*	200	400	800

* Approved for once daily dosing in milder patients.

and equivalent doses of ICS available in Turkey are given in Table 4.

Leukotriene Receptor Antagonists (LTRA), are mild bronchodilator and anti-inflammatory drugs, used as an alternative treatment in mild persistent asthma, in some patients with aspirin-sensitive asthma and exercise induced asthma. They can be used as add-on therapy to reduce the dose of ICS required by patients with moderate to severe asthma (81-91). They are effective not only in asthma but also in patients with allergic rhinitis (92). Common side effects are mentioned in the original document (34). Churg-Strauss syndrome associated with LTRA treatment is accepted probably as the result of reductions in the doses of systemic and/or inhaled glucocorticosteroids (93-96).

Long Acting β2 Agonists (LABA), should not be used as monotherapy in asthma. Clinical control is achieved faster when they are added to ICS (97-102). Formoterol + budesonide combination can be used as both reliever and controller therapy (103-108). Common side effects are mentioned in the original document (34, 109-112).

Theophylline, it is a mild anti-inflammatory and mild bronchodilator agent. It can be added to ICS if adequate control cannot be achieved with ICS, but less effective than LABA (113-120). Common side effects are mentioned in the original document (34,121).

The principal indication for anti-IgE treatment is uncontrolled severe, allergic asthma cases under high doses of inhaled steroids and other controller therapies, with total IgE level between 30-700 IU (1,122). Anti-IgE has steroid sparing affect and improves asthma control in these selected group of asthmatics (123-126).

Long-term oral glucocorticosteroid therapy (longer than two weeks) may be required for severely uncontrolled asthma, but its use is limited by the risk of significant adverse effects. The therapeutic index (effect/side effect) of long-term inhaled glucocorticosteroids is always more favorable than long-term systemic glucocorticosteroid therapy in asthma. Oral preparations are preferred over parenteral (intramuscular or intravenous) for long-term therapy because of their lower mineralocorticoid effect, relatively short half-life, and lesser effects on striated muscle, and the greater flexibility of dosing that permits titration to the lowest acceptable dose that maintains control (1,127,128). Common side effects are well known and mentioned in the original document (34,96,129-133).

Allergen specific immunotherapy with clinically relevant allergens may be considered if disease activity is inadequately controlled by avoidance of the allergens and pharmacotherapy (1). Immunotherapy should be avoided when asthma is poorly controlled. Neither should immunotherapy be initiated nor the dosage increased during pregnancy. Common side effects are mentioned in the original document (34).

Reliever Medications

Rapid-acting inhaled β2-agonists are for relief of bronchospasm during acute exacerbations of asthma and for the pretreatment of exercise-induced asthma. They include salbutamol and terbutaline. Because of its rapid onset of action formoterol is also approved for symptom relief, but it should only be used for patients on regular maintenance therapy with inhaled glucocorticosteroids (1).

Systemic glucocorticosteroids are important in the treatment of severe acute exacerbations because they prevent progression of the asthma exacerbation, reduce the need for referral to emergency department and hospitalization, prevent early relapse after emergency treatment, and reduce the morbidity of the illness. Oral therapy is preferred and is as effective as intravenous hydrocortisone (1). The main effects of systemic glucocorticosteroids in acute asthma are evident after 4 to 6 hours. A typical short course of oral glucocorticosteroids for an exacerbation is 30 mg

prednisolone given daily for 5 to 10 days depending on the severity of the exacerbation.

Inhaled ipratropium bromide for relief of bronchospasm is less effective than rapid-acting inhaled β-agonists in asthma. But it can be used together with an inhaled β-agonist as it shows statistically significant improvement in pulmonary function, and significantly reduces the risk of hospital admission (1).

Short-acting theophylline or aminophilline may provide no additive bronchodilator effect over adequate doses of rapid-acting β-agonists, but it may benefical for stimulation of respiratory drive and diaphragmatic function (1).

The role of complementary and alternative medicine in adult asthma treatment has not been validated. They are not suggested for routine treatment of asthma in Turkey (1,34).

ASSESSMENT, TREATMENT and MONITORING of ASTHMA

Currently asthma treatment is focused on disease control (1,50,133-135). "Control" adjusted asthma treatment has three domains: assessment of asthma control, treatment to achieve control and monitoring to maintain control (1). In patients taking controller medications, the level of asthma control will guide decisions either to maintain or to adjust therapy (ie, step up if necessary, step down if possible Asthma control levels and control assessment parameters used in the national guideline are shown in Table 5 (1,34,136-140). In treatment naive patient we recommend to begin treatment according to asthma severity (34,50). Mild intermittent asthmatics should receive treatment from step 1 and as severetiy increases initiation step should increase respectively. However the follow-up should be done according to the asthma control (1,34,50).

Treatment steps to achieve asthma control

Step 1: As-needed reliever medication is used for occasional asthma symptoms. We recommend the use of rapid acting inhaled β2-agonist as the first choice (141).

Step 2: We recommend the use of regular controller medication from this step on. The first choice is low dose inhaler glucocorticosterids, alternative controller medication include leukotriene receptor antagonists. Controller medications should be combined with as needed reliever treatment (142-145).

Step 3: Low dose of inhaled glucocorticosterids combined with a long-acting β2 agonist is the first treatment option (1). Medium dose inhaled glucocorticosterids, low dose inhaled glucocorticosterids with a leukotriene receptor antagonist or sustained release theophylline are alternate regimens (135,146-150). All the regimens should be combined with as needed reliever treatment. If a combination inhaler containing formoterol and budesonide is selected, it may be used for both maintenance and reliever medication (1,151-154). We emphasize the importance of using long acting β2 agonists always with an inhaled glucocorticosteroids in asthma treatment.

Table 5. Levels of asthma control.

Characteristic	Totally controlled (all of the following)	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice a week	Three or more features of partly controlled asthma present in any week
Activity limitations	None	Any	
Nocturnal symptoms	None	Any	
Need for reliever medication	None (twice or less/week)	More than twice a week	
Lung functions (PEF or FEV_1)	Normal	< 80% predicted or personal best	
Exacerbations	None	One or more/year	One in any week
Questionnaires/tests	*ACT = 25	ACT = 20-24	ACT ≤ 19
	**ACQ ≤ 0.75	ACQ = 0.75-1.5	ACQ ≥ 1.5

* ACT: Asthma Control Test (Turkish validated version is available).

** ACQ: Asthma Control Questionnaire (Turkish validated version is available).

Step 4: Asthmatics who are not controlled on Step 3 should be referred to an experienced centre for asthma management. First treatment option is medium dose of inhaled glucocorticosterids combined with a long-acting β2 agonist (135,146,155,156). In patients whom control can not be achieved with this regimen a third drug like leukotriene receptor antagonist or sustained release theophylline could be added to the treatment (1,157-159). If control is still not achieved, then high dose of inhaled glucocorticosterids combined with a long-acting β2 agonist is another option.

Step 5: This step includes severe and hard to control asthmatics who need further evaluation in an experienced centre for asthma management. Oral glucocorticosterids and anti-IgE can help to achieve control in selected patients (160-164).

Ideally patients must be assessed in four weeks periods till the asthma control is achieved. Thereafter patients must be seen every three months (1). The medications should be reduced until "the minimum dose that maintains the control" is reached. Stepping down the treatment should be tailored according to the patient's combination of medications and doses that were needed to achieve control.

We recommend the following suggestions for stepping down the asthma therapy in whom the control is achieved for at least three months (1,34):

In patients using inhaled glucocorticosteroids alone, 50% dose reduction should be introduced at three months intervals (165-167). If the control is achieved with low dose inhaled glucocorticosteroids, once daily dosing can be administered (168,169). If the patient is using combination therapy, the stepping down strategy should begin with reducing the dose of inhaled glucocorticosteroids (170). When the minimum dose of glucocorticosteroids is reached than the long acting β2 agonist may be stopped. When the asthma remains controlled for one year with the minimum dose of controller medicine, controller therapy may be stopped. However patients must be closely monitored for the recurrence of symptoms.

Treatment should be stepped up in asthmatics that lose control. If repeated doses of rapid acting β2 agonists do not achieve control, short course of oral glucocorticosteroids or alternately four fold or greater increase in the dose of inhaled glucocorticosteroids (for one to two weeks) can be administered (171,172).

Difficult Asthma

Patients who do not have any factors that makes it difficult to control their asthma and who need two or more controller medications and high doses of inhaled glucocorticosteroids (step 4 therapy) and still can not achieve asthma control are considered as difficult asthmatics (1,173). These patients should be referred to an experienced centre for asthma management.

IDENTIFY and REDUCE EXPOSURE to RISK FACTORS

Pharmacologic intervention to treat asthma is highly effective in controlling symptoms and improving quality of life however measures to prevent the development of asthma or asthma symptoms by avoiding or reducing exposure to risk factors should be implemented when possible. Measures to prevent the development of asthma are named as "primary prevention", where as efforts focusing on prevention of asthma symptoms and attacks in patients with established asthma are called "secondary prevention" (34).

Few measures can be recommended for primary prevention of asthma because the development of the disease is complex and incompletely understood. The role of diet, prevention strategies against inhalant allergens, methods towards reducing exposure to house dust mites, exposure to cats, exposure to tobacco smoke, maternal smoking during pregnancy are widely discussed in the original document (34,174-185).

There are theoretical possibilities to avoid the development of asthma in subjects in whom allergic sensitization has already occurred. Whether antihistamines can prevent the development of asthma in children with atopic dermatitis remains an area of investigation (186). Allergen specific immunotherapy has been shown to decrease the risk of asthma development in later life in children with allergic rhinitis (187). However these interventions cannot be recommended for wide adoption in clinical practice at this time.

Asthma symptoms may be caused by many factors including allergens, viral infections, pollutants and drugs. Reducing a patient's exposure to some of these triggers improves the control of asthma and reduces medication needs. Allergens are important environmental factors that can cause symptoms in the sensitized patient (34). However there is conflicting evidence about whether measures to reduce exposure to indoor allergens are effective at reducing asthma symptoms (34,188-199).

Several studies have suggested that outdoor pollutants such as; ozone, nitrogen oxides, acidic aerosols and particulate matters aggravate asthma symptoms. For patients with asthma avoiding physical activity in cold

weather and high air pollution are practical recommendations for better control of the disease (200). The most important measure in controlling indoor air pollutants is to avoid passive and active smoking. A multicentered national study demonstrated a significant relation between exposure to tobacco smoke and asthma symptoms (28,201).

Occupational exposures account for a substantial proportion of adult asthma. The early identification of occupational sensitizers and the removal of sensitized patients from any further exposure are important aspects of the management of occupational asthma (202). Routine influenza vaccination of patients with asthma does not appear to protect them from exacerbations. The incidence of viral upper respiratory infections was not different between vaccined and non-vaccined asthmatic patients in a national study. However patients with moderate to severe asthma should be advised to receive an influenza vaccination every year or at least when vaccination of the general population is advised (203,204).

ASTHMA EXACERBATIONS in ADULTS

Asthma exacerbation is characterized by progressive increase in dyspnea, wheesing, chest tightness accompanied by worsening of pulmonary functions. Two main factors are responsible for an asthma exacerbation; inadequate antiinflammatory therapy and being exposed to triggering factors (1,205-210).

The severity of exacerbations can be determined according to the patient's clinical presentation, which includes breathlessness, talking pattern, alertness, respiratory rate, accessory muscle retractions, wheezing, pulsus paradoxus, PEF, PaO_2, $PaCO_2$ and SaO_2 values. Severity is classified into four categories: mild, moderate, severe and life threatening (1,211,212). We emphasized that severity of asthma should not be underestimated as it can be potentially life threatening. Patients who have risk factors for life threatening asthma exacerbations should be encouraged to admit to a physician without delay and should carefully be monitored in emergency setting. These are asthmatics shown in Table 6 (1,50,207,213-217).

Management of Exacerbations

We recommend home management in mild-moderate exacerbations. However, severe exacerbations should be managed in emergency settings (34).

Home management of exacerbations includes recurrent use of short acting β2 agonists (high doses preferably with a spacer) and systemic glucocorticosteroids (1,34,50,215,217-221).

Patient with a severe exacerbation admitted to emergency department should be evaluated promptly. Oxygen therapy (to achieve SaO_2> 90%), rapid acting β2 agonists (nebulized or given with a spacer) at regular and short intervals should be administered (1,34,50,213,215,219,221-223). Further bronchodilation can be achieved with combination of ipratropium with salbutamol (224-226). Systemic glucocorticosteroids should be administered orally or intravenously as they accelerate the resolution of exacerbation (0.5 mg/kg for 7-10 days) (1,34,50,227-229).

We recommend the use of intravenous magnesium sulphate infusion, intravenous theophylline infusion consecutively as further therapies (1,50,219,230,231). Detailed list and dosing of medications used in exacerbations are mentioned in the original document (34).

Intensive care unit therapy and mechanical ventilation: Indications for hospitalization in intensive care and mechanical ventilation are (1):

• Poor response to initial therapy at emergency care or worsening of exacerbation,

Table 6. Risk factors for life threatening asthma exacerbations.

• History of intubation and mechanical ventilation due to previous asthma exacerbation
• History of hospitalization or emergency care admission due to asthma exacerbation
• Who are currently using or have recently stopped using oral glucocorticosteroids
• Who are not using or has left using inhaler glucocorticosteroids
• Who are consuming excessive inhaled β2 agonist (> 1 canister/month)
• With a history of psychosocial problem or psychiatric disease
• Who are non-compliant with their therapy
• Who has low social and economic status
• Who has comorbid conditions (like cardiovascular or other lung diseases)

• Respiratory insufficiency despite oxygen support (PaO_2 < 60 mmHg and/or $PaCO_2$ > 45 mmHg),

• Confusion, cyanosis and severe symptoms,

• Cardiac and respiratory arrest.

Non-invasive mechanical ventilation can be administered in selected cases (1).

Patients can be discharged if their symptoms are under control in the last 24 hours with their prescribed home therapy. Inhaler glucocorticosteroids should not be discontinued during the exacerbation. If the patient was not on an inhaler glucocorticosteroid before exacerbation, it should be prescribed before discharge. Systemic glucocorticosteroids should not be discontinued before 7-10 days. Patients should be referred to an asthma specialist after discharge (1,211,221,232-236).

SPECIAL CONSIDERATIONS

Pregnancy; surgery; rhinitis, sinusitis and nasal polyps; occupational asthma, respiratory infections, gastroesophageal reflux and aspirin-induced asthma need to be considered as special considerations.

Asthma and Pregnancy

The most common respiratory system disorder during pregnancy is asthma (4-7%). Pregnancy effects the natural course of asthma as well as asthma can effect pregnancy and delivery. In approximately one-third of women asthma becomes worse; in one-third asthma becomes less severe; and in the other one-third it remains unchanged during pregnancy (1,237,238). Poorly controlled asthma can have an adverse effect on pregnancy may cause maternal and fetal complications (1,50,51,237,238). Asthma control during pregnancy is very important for both mother and the baby.

Using medications to obtain optimal control of asthma is justified even when their safety in pregnancy has not been proven. For most drugs used to treat asthma there is little evidence to suggest an increased risk to the fetus. Inhaled glucocorticosteroids (ICSs), β2-agonists, leukotriene receptor antagonists, specifically montelukast and appropriately monitored theophylline, are not associated with an increased incidence of fetal abnormalities. ICSs have been shown to prevent exacerbations of asthma in pregnancy. Acute exacerbations should be treated aggressively in order to avoid fetal hypoxia (34).

Delivery will not be different than the non-asthmatics, special consideration should be given to analgesia. Asthmatic mother could breat feed her baby while using her medications (51,238).

Surgery

Asthmatic patients are prone to intraoperative and postoperative respiratory complications due to their airway hyperresponsiveness, limitation, and mucus hypersecretion. These complications may change depending on the severity of asthma at the time of surgery, the type of surgery (thoracic and upper abdominal pose the greatest risks), and type of anesthesia (general anesthesia with endotracheal intubation carries the greatest risk). A careful and detailed evaluation should be undertaken several days prior to surgery and pulmonary function should be measured. If FEV_1 value is less than 80 percent of the patient's personal best, a short course of glucocorticosteroids should be considered. Furthermore, patients who have received systemic glucocorticosteroids within the past 6 months should have systemic coverage during the surgical period (100 mg hydrocortisone every 8 hours intravenously) and rapidly reduced 24 hours following surgery (1, 50,51,238).

Rhinitis, Sinusitis and Nasal Polyps

Upper airway diseases can influence lower airway function. Although the mechanisms associated with this relationship are not established, inflammation likely plays a similarly critical role in the pathogenesis of rhinitis, sinusitis, and nasal polyps, as seen in asthma.

Asthma and rhinitis often coexist in the same patient (50,92). The majority (like 75 %) of patients with asthma have a history or evidence of rhinitis and rhinitis frequently precedes the development of asthma (92). Treatment of rhinitis may improve asthma symptoms. Anti-inflammatory agents including glucocorticosteroids, leukotriene modifiers, and anticholinergics can be effective in both conditions (50,92,239).

Both acute and chronic sinusitis can worsen asthma. (92,240,241). Topical nasal decongestants or topical nasal or even systemic glucocorticosteroids should be used to reduce nasal congestion (1,50,92).

Nasal polyps associated with asthma and rhinitis are often accompanied with aspirin sensitivity (92). Between 36% and 96% of aspirin-intolerant patients have polyps and 29% to 70% percent of patients with nasal polyps may have asthma. Nasal polyps respond well to topical corticosteroids, surgery could be considered in non-responders (1,242-244).

Occupational Asthma

More than 400 causative agents for occupational asthma have been reported from developed countries (1,238). Recording on occupational diseases has been started in Turkey since 1970 and various occupational exposures have been reported (245-273). Symptoms and air flow limitation while at work and improvement outside the work will lead the diagnosis (34). Spirometric confirmation such as PEF meter follow-up is necessary for legal procedures with a sensitivity of 70-80% and specifity of 85-90%. Gold standard is specific bronchoprovocation but it could only be performed in special centers (50,51,238). Once diagnosed, complete avoidance of the relevant exposure is an important component of management. Continued exposure may lead to severe and potentially fatal asthma exacerbations and permanently impaired lung function. Medical treatment is not different than asthma (50,51,238).

Respiratory Infections

Viral and rarely bacterial infections of respiratory tract may increase symptoms and trigger exacerbations in asthmatics (274-276). As increased asthma symptoms often last for weeks beyond the infection, anti-inflammatory treatment should be continued for weeks to ensure adequate control (277-279).

Gastroesophageal reflux (GER), is nearly three times as prevalent in all patients with asthma in comparison to the general population (280,281). Most of these patients also have a hiatal hernia; furthermore, theophylline and oral β2-agonists may increase the likelihood of symptoms by relaxing the lower esophageal ring. Patients who are not well controlled with appropriate medical treatment should be evaluated and if necessary treated for GER (282-288).

Aspirin-Induced Asthma (AIA) is often together with rhinosinusitis, nasal polyp and aspirin intolerance (289). The majority of patients first experience symptoms during the third or fourth decade of life, which may include vasomotor rhinitis and profuse rhinorrhea. Chronic nasal congestion evolves, and physical examination often reveals nasal polyps. Asthma and intolerance to aspirin often develop subsequently. The intolerance itself presents a unique picture: within an hour following ingestion of aspirin, an acute, often severe asthma exacerbation develops, which may be accompanied by rhinorrhea, conjunctival irritation, and scarlet flush of the head and neck. Indeed, a single aspirin or other cyclooxygnease inhibitor can provoke violent bronchospasm, shock, loss of consciousness, and respiratory arrest (1,243,290-293). Although a patient's clinical history may raise suspicion of AIA, the diagnosis is only established by aspirin challenge, conducted in facilities where cardiopulmonary resuscitation capabilities exist. Patients with AIA should avoid aspirin, products containing it, and other analgesics that inhibit cyclooxygenase and hydrocortisone hemisuccinate. Glucocorticosteroids continue to be the mainstay of therapy, while leukotriene modifiers may be useful for additional control of the underlying disease (294-308).

CONFLICT of INTEREST

None declared.

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