



## Asthma: Achievements and Questions in Front

Jamshid Salamzadeh\*

*Pharmaceutical Sciences Research Center, Shaheed Beheshti University of Medical Sciences,  
Tehran, Iran*

---

### Abstract

Asthma, which is mainly distinguished by airway inflammation and bronchial hyper-responsiveness, is known as one of the most common chronic diseases worldwide. It also is the most frequent chronic respiratory disorder amongst all age groups. On one side of the asthma story, there are massive investment of time, effort and money, a large number of pharmaceutical and academic research studies, health service modifications and revised guidelines. On the other side, there are unacceptably high, but mostly preventable, morbidity and mortality rates, socio-economic burdens and psychological problems due to asthma. A considerable proportion of doctor's workload, hospital resources, health utilization costs, days off from school and work are caused by asthma. Our knowledge about this disorder and its complications is still on demand. There are significant questions regarding asthma and its pathophysiology which should be answered. National, regional and local initiatives are needed to be established to help health systems to overcome socio-economic burdens due to this disease. These could only be done if a clear picture of this respiratory disorder and its management achievements are available. This review article is an approach to present an image about asthma and its management based on the current understandings of the nature of this disorder.

*Keywords:* Asthma; Epidemiology; Risk factors; Classification; Management.

*Received:* April 6, 2005; *Accepted:* June 12, 2005

---

### 1. Definition of asthma

Recent understanding of different medical fields including allergy and immunology, molecular and cell biology, histology, pharmacology and epidemiology have led to a better understanding about asthma and its management. It has been recognized that

inflammatory processes are important characteristics of asthma leading to airway obstruction and bronchial hyperresponsiveness. However, there is still a lack of information about natural history, pathophysiology and the understanding of specific causes and marker(s) of asthma [1, 2]. This could be because of the complex pathophysiology of asthma, which engages series of events in the cytokine network. Findings obtained in the last decade, shows that the cysteinyl

---

\*Corresponding author: Jamshid Salamzadeh, Pharmacy, Shaheed Beheshti University of Medical Sciences, Tehran, Iran. P.O. Box: 14155-3817.,  
Tel (+98)21-88773521-5, Fax (+98)21-88775008  
E-mail: jsalamzadeh@gmail.com

leukotrienes (C<sub>4</sub>, D<sub>4</sub> and E<sub>4</sub>) are among the important mediators involved in the pathogenesis of asthma. In addition, pathogenesis of asthma has been linked to the production of type 2 cytokines. Current animal and human studies have highlighted a major role for CD4(+) and CD8(+) T lymphocytes in the development of allergen induced airway responses. However, there is increasing evidence of Th1/Tc1-mediated processes in the aetiopathology of asthma [3-7].

In a joint workshop held by the National Heart, Lung and Blood Institute (NHLBI) and World Health Organization (WHO) [8], an operational description of asthma based on the inflammatory nature of this disorder was defined:

*“Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in 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 that is often reversible either spontaneously or with treatment.”*

## 2. Epidemiology of asthma

Asthma occurs in all countries regardless of the level of development. In general, epidemiological studies have shown that its prevalence is higher in affluent and western populations compared to non-affluent countries. In some areas of the UK, Australia, New Zealand and Ireland there is a 40% prevalence rate of asthma in children, whilst in less affluent countries such as Indonesia, China, India and Ethiopia values as low as 3% have been reported [1]. Unfortunately, there is no precise statistical information about this disease and its social and economic impact in Iran. This would mainly be a result of poor

database and recording systems available in Iran. Nevertheless, reports confirm that the prevalence of asthma is increasing in all over the world [9]. Factors underlying this increase are unclear. However, it may be related to environmental factors including increasing exposure to allergens, pollutants and their synergistic interaction with allergic sensitization [1, 8]. For example passive smoking during infancy may be associated with an allergic sensitization to common aero-allergens [10]. Urbanization (related to higher pollution rates) [11] and dietary factors [12, 13] are also reported to be associated with asthma prevalence. However, their role has not been clearly confirmed. In England no significant tendency has been found for asthma to be diagnosed more often in urban compared with rural areas [9].

It seems that in addition to the prevalence of asthma, its severity (and the related morbidity) has also increased. This increase is suggested by the rise in hospital admissions as well as a higher usage of anti-asthma medications [1]. The socio-economic status may be involved in the increased severity that may be related to problems in obtaining adequate medical care and to poor housing environment. Other factors underlying the increased asthma morbidity may be attributed to the following factors [8, 14-21]:

Under-prescribing of anti-inflammatory drugs and over-reliance on bronchodilators.

Absence of monitoring the lung function using serial measurements of Peak Expiratory Flow Rate (PEFR).

Delay in seeking medical help during an exacerbation and difficulty in access to medicinal care.

Non-concordance/compliance with therapy and management plans.

These factors could be worsen by patient (e.g. language, psychosocial factors, poor knowledge and poor understanding of the

condition) and physician (e.g. time limited, poor communication and performance skills) barriers. All these may have a negative impact on asthma educational interventions [22- 27].

### 3. Risk factors and triggers of asthma

Risk factors and triggers are involved in the onset and development of asthma as well as the development of asthma exacerbations. These risk factors can be classified into three main groups [8]:

*Predisposing factors* that give rise to a susceptibility for the disease. These include atopy and gender. Atopy, demonstrated by increased serum IgE, appears to be the strongest identifiable predisposing factor for asthma. In addition, it has been shown that patients with the worst asthma could be the most atopic, too. Atopic diseases occur in families and thus it could be concluded that atopy is at least partly under genetic control. Furthermore, asthma and airway hyper-responsiveness has been reported to occur in families, but for asthma the evidence of a genetic control is less convincing. Gender is a predominant factor in childhood asthma (usually under age of 10), when asthma is more prevalent in boys than girls mostly because of the narrower airways and increased airways' tone in boys in this age group. In addition, gender differences in childhood asthma could be partly explained by gender differences in allergen sensitivities.

*Causal factors* sensitize the airways and cause asthma. Allergens and chemical agents are the most important risk factors for the onset of asthma. These include indoor and outdoor allergens (environmental factors). Examples of these allergens are domestic mites, animal allergens, cockroach allergens, fungi, pollens, drugs such as aspirin and other non-steroidal anti-inflammatory drugs, and occupational sensitizers for instance flour, coffee bean dust, grain or wood dust, cotton dust, proteins and enzymes.

Asthma triggers include a further exposure

to the causal factors that have already sensitized the airways of an asthmatic patient. These can cause recurrent asthma exacerbations by inducing airway inflammation together with immediate and/or delayed broncho-constriction. Triggers also include exercise and hyperventilation, exposure to cold air, irritant gases such as sulfur dioxide, weather changes, extreme emotional stress and food additives. These factors can not cause asthma to develop, but once it is present, they can lead to asthma exacerbation.

*Contributing factors* that either enhance the likelihood of asthma deterioration upon exposure to a causal factor or may even increase the susceptibility to asthma. These factors include respiratory infections, small size at birth, diet, air pollution (outdoor and indoor pollutants), and smoking (passive or active).

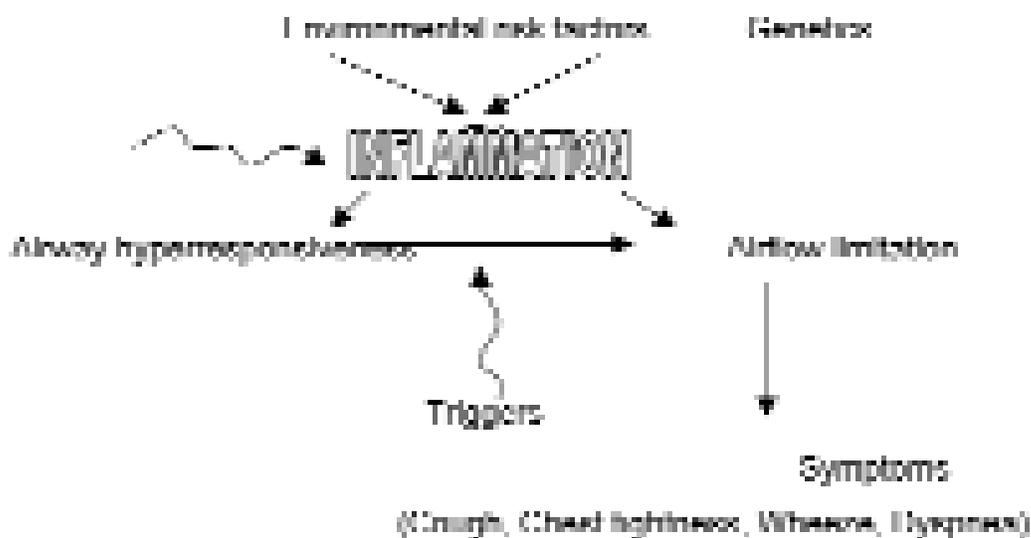
Figure 1 illustrates the interaction between environmental (causal and trigger factors) and genetic factors (predisposing) that can contribute to chronic respiratory inflammation.

### 4. Covariates and explanatory factors associated with asthma morbidity

In addition to the risk factors which are directly related with asthma incidence and prevalence, there are several parameters recognized as covariates for asthma morbidity. Some of these factors are described below:

*Socioeconomic status:* A strong link between deprivation, lower social class and many common chronic diseases e.g. chronic respiratory disorders, diabetes, arthritis and heart disorders has been reported [28]. A direct significant correlation between asthma morbidity and socioeconomic variables is also documented by several studies [29-32].

*Ethnicity:* Some studies have revealed that there could be a relationship between ethnicity and the pattern of anti-asthma drugs



**Figure 1.** The interaction between environmental and genetic factors that give rise to respiratory inflammation.

usage [32-35]. Others have reported a relationship between ethnicity and the morbidity or mortality rate of asthmatics. The diversity which exists in ethnicity groups could be a source of different lifestyles, health beliefs and response to health care programs [36-38].

*Workload of doctors at the primary care level:* A higher workload on the services offered by doctors could be associated with a lower quality of asthma prescribing and therefore resulting in a poor asthma control along with a higher morbidity rate [39-43].

*Gender:* There is evidence that there could be gender-related morbidity, mortality and health inequalities because of socioeconomic differences confounded by age, employment status, cultural and biological factors [44]. There are reports confirming a higher consultation rate and steroid usage (inhaled and oral) by asthmatic women [45, 46]. Female gender is also reported as a risk factor for asthma hospitalization [42, 43, 47-49].

*Smoking:* It is confirmed that smoking

could increase the frequency and severity of symptoms in asthmatics [50, 51]. The same findings are reported for environmental tobacco smoke exposure, i.e. passive smoking [52, 53].

*History of allergy:* Allergen exposure has been identified as a risk factor for asthma severity, acute attacks and hospital admissions [42, 43, 54, 55]. It has been reported that children with continuous exposure to higher concentrations of house dust mite allergens could be at a greater risk of readmission to hospital [56], or suffer from increased asthma symptoms [57].

*Age of asthma onset:* The age of asthma symptoms onset is one of the factors that could adversely influence the normal physiology of distal, parenchymal and proximal airways. Uncontrolled asthma over a long time can cause a remodelling of the airways which is reflected by reduced airflow rates and increased airway responsiveness [58-60]. In addition, patient with a longer history of asthma may have higher morbidity [61].

**Table 1.** Asthma classification based on the severity of airways obstruction [70].

Symptoms	Mild	Moderate	Severe
Wheeze, tightness, cough, dyspnea	Occasional e.g. with viral infection or exercise	Most days	Every day
Nocturnal asthma	Absent	<once/week	>once/week
Asthma on wakening	Absent	Usually not	Usually
Hospital admission or emergency room visit in the past year (for adults)	Absent	Usually not	Usually
Previous life-threatening attack	Absent	Usually not	May have a history
Bronchodilator use in adults	Infrequent	Needed most days	Needed >3-4 times/day
FEV <sub>1</sub> <sup>a</sup> (%predicted)	>80%	60-80%	<60%
Mean peak flow variability* over 2 weeks	6-10%	11-25%	>25%
Minimum waking PEFR <sup>b</sup>	>85% best	70-85% best	<70% best

a: Forced Expiratory Volume in the first second

b: Peak Expiratory Flow Rate

$$\text{*Daily mean PEFR variability \%} = \frac{\text{Highest PEFR} - \text{Lowest PEFR}}{\text{Highest PEFR}} \times 100$$

*Respiratory infection:* The large number of infectious organisms reaching the airways, including viruses and bacteria, along with the susceptibility of asthmatic patients to respiratory tract infections (RTIs) could explain the high rate of the respiratory infections in asthmatic patients [62, 63]. Studies have also reported these infections as triggers associated with asthma morbidity [64-66].

*Seasonal covariates:* Studies with different settings and study populations have reported various seasonal patterns associated with anti-asthma drugs usage, asthma morbidity and mortality [67-69]. No precise relationship has been found.

## 5. Classification of asthma based on the severity

A classification of the degree of airways obstruction in asthmatic subjects is important for guiding therapeutic recommendations. The Australian National Asthma Campaign

group has classified asthma into three groups (mild, moderate, and severe) according to the signs and symptoms as shown in Table 1. In this classification if a patient is using regular inhaled corticosteroids, he/she should not be categorized as mild [70]. A similar classification has been presented by the Global Initiatives for Asthma. In this classification, asthma severity is divided into four groups of intermittent, mild persistent, moderate persistent and severe persistent. However, the British Thoracic Society (BTS) guidelines for asthma management have a different definition of asthma severity. In this guideline, severity is defined based on the treatment stage. It states: “in treated patients the current operational definition of severity should be the treatment step needed to maintain good, or best possible control in terms of symptoms, lifestyle and lung function” [71]. In the BTS guidelines a four step-by-step approach for the management of chronic asthma in children under 5 years of age as well as a five step-by-step protocol for adults and school children have been recommended. Table 2 represents

**Table 2** Step-by-step approach for the management of chronic asthma in adults and schoolchildren (>5 years old) according to the BTS guidelines [72]

**STEP 1: Occasional use of relief bronchodilators.**  
Inhaled, short acting beta<sub>2</sub> stimulant as required, up to once a day.

**Note:** Move to step 2 if needed 3 times a week or more, or if night-time symptoms more than once a week or if exacerbation in the last 2 years requiring systemic corticosteroid or nebulised bronchodilator; check compliance and inhaler technique.

**Step 2: Regular inhaled anti-inflammatory agents.**  
As for step 1 plus:  
regular standard dose inhaled corticosteroid\*  
(alternatives\*\* are considerably less effective)

**Step 3:** As for Step 1 plus:  
regular standard-dose inhaled corticosteroids; plus long acting beta<sub>2</sub> stimulant (e.g. salmeterol) but discontinue in the absence of response.

*If asthma not controlled:*  
Use high dose inhaled corticosteroids\*\*\*

*If asthma still not controlled:*  
Add one of:  
Leukotrien receptor antagonist  
Modified release oral theophylline  
Modified release oral beta-2 agonist

**Step 4: High dose inhaled steroids and regular bronchodilators.**  
As for Step 1 plus high dose inhaled corticosteroid\*\*\* plus inhaled long-acting beta-2 agonist plus (in adults) 6-week sequential therapeutic trial of one or more of other long-acting bronchodilators \*\*\*\* with or without a leukotrien receptor antagonist.

**Step 5: Addition of regular corticosteroid tablets.**  
As for Step 1 plus regular high dose inhaled corticosteroid\*\*\* and one or more long-acting bronchodilator\*\*\*\* plus regular prednisolone tablets in a single daily dose.

**Note:** In addition to regular prednisolone, continue high-dose inhaled corticosteroid (in exceptional cases may exceed licensed doses); these patients should normally be referred to an asthma clinic.

**Stepping down:** review treatment every 3 months. If control is achieved stepwise reduction may be possible. Use lowest possible dose of corticosteroid. Reduce dose of inhaled corticosteroid slowly (consider reduction every 3 months, decreasing dose by up to 50% each time) to the lowest dose which controls asthma.

**\* Standard dose inhaled corticosteroids:**  
Beclomethasone dipropionate or budesonide  
100-400 mcg twice daily  
Fluticasone propionate 50-200 mcg twice daily

**\*\* Alternatives to inhaled corticosteroids:**  
Leukotrien receptor antagonists  
Theophylline  
In adults, regular cromoglycate; and in children, regular nedocromil

**\*\*\* High dose inhaled corticosteroids:**  
Beclomethasone dipropionate or budesonide  
800-2000 mcg daily (in divided doses)  
Fluticasone propionate 400-1000 mcg daily (in divided doses)  
Use a large volume spacer.

**\*\*\*\* Long-acting bronchodilators:**  
Inhaled long-acting beta<sub>2</sub> stimulant  
Sustained release theophylline  
Inhaled ipratropium or oxitropium (adults only)  
Modified release beta<sub>2</sub> agonist tablets  
High dose inhaled bronchodilators

the treatment plan introduced for asthmatics > 5 years of age. For children under 5 years of age, except some minor changes, the step-by-step protocol is similar to that of over five years.

The BTS guidelines have four main categories for the severity of asthma exacerbations at the accident and emergency department level. In this classification, the severity of an attack is based on the immediate measurement of the PEFr and comparing this measurement with the best or predicted PEFr for each individual patient. In this regard, four main categories have been identified:

- Mild: >75% of the best/predicted PEFr
- Moderate: 50-75% of the best/predicted PEFr
- Severe: 33-50% of the best/predicted PEFr
- Life threatening: <33% of the best/predicted PEFr

## 6. Asthma management: Goals and medical treatment

Many interventions have attempted to establish or modify treatment protocols for asthma. A good asthma service should lead to the following outcomes:

- Prevention of asthma attacks
- Reduction of asthma morbidity
- Limitation of asthma mortality

To achieve these goals, it is recommended that the delivery of care must include primary care, hospital (secondary) care as well as health and educational authorities. Good communications between the specialist centers and the other groups involved are considered necessary [71].

The final aim of asthma therapy is to obtain a normal pulmonary function and abolish symptoms. The main target, therefore, is to improve the condition so that asthmatic patients could live as normal and as active a life as possible with a minimum physical and psychosocial disruption. Asthma treatment is symptomatic and directed at maximizing the reversibility of the airway obstruction and

minimizing adverse effects. The risks of each individualized treatment plan must, therefore, be considered against the risks of the disease [2, 19].

It is recommended that asthma management to be conducted in three main directions:

*a-Patient education and self-management:* Patient education and self-management plans are a major part of the current asthma management initiatives. Patients should be informed about the nature of their problem, medication(s), appropriate inhaler technique, self-monitoring of their asthma (e.g. using a Peak Expiratory Flow Meter), exacerbation symptoms and action plans needed to apply at the time of an asthma attack. This is very important in patient-oriented management protocols and in creating a two-way relationship between patients and health professionals (concordance) towards a better control on their asthma.

*b-Non-pharmacological treatment:* An avoidance from different risk factors and triggers, which are involved in asthma development or exacerbation, is a major goal of the current management protocols [71].

*c- Pharmacological treatment:* There are two main physiological problems associated with asthma, *inflammation* and *bronchoconstriction*. Consequently, there are two main therapeutic groups of drugs which are used, bronchodilators and anti-inflammatory agents. Considering the inflammatory nature of asthma, corticosteroids are known as the key drug in the treatment of asthma. Table 3 represents asthma medications and their mechanisms of action [8, 72].

Xanthines (theophylline and its salt aminophylline) as another group of bronchodilators are used in the management of asthma. Present guidelines recommend the use of oral theophylline as an additional bronchodilator in patients who remain

**Table 3.** Medications used commonly for the pharmacological treatment of asthma [8, 72].

Preparation		Mechanism of Action
<u>Corticosteroids</u>		
<i>Inhaler</i>	<i>Oral</i>	Anti-inflammatory agent: Prevent and suppress activation and migration of inflammatory cells; reduces airway swelling, mucus production, and micro-vascular leakage; increases responsiveness of smooth muscle beta-receptors.
Beclomethasone	Prednisolone	
Budesonide	Prednisone	
Flunisolide	Methylprednisolone	
Fluticasone		
Triamcinolone		
<u>Glycates</u>		
Sodium cromoglycate		Anti-inflammatory agent: Inhibit activation of, and mediator release from, inflammatory cells.
Nedocromil sodium		
<u>Short-acting beta2-agonists</u>		
Salbutamol	Orciprenaline	Bronchodilator: Open airways by relaxing airway smooth muscle, enhancing muco-ciliary clearance, and decreasing vascular permeability.
Terbutaline	Fenoterol	
Isoetharine	Pirbuterol	
Bambuterol		
<u>Long-acting beta2-agonists</u>		
<i>Inhaler</i>	<i>Oral (long-acting forms)</i>	Bronchodilator: Open airways by relaxing airway smooth muscle, enhancing muco-ciliary clearance, and decreasing vascular permeability (not to be used to treat attacks).
Salmeterol	Terbutaline	
Eformoterol	Salbutamol	
<u>Anticholinergics</u>		
<i>Inhaler</i>		Bronchodilator: Reduce vagal tone of airways (slower onset of action than short-acting beta2-agonists).
Ipratropium bromide		
Oxitropium bromide		
<u>Xanthines</u>		
<i>Oral</i>	<i>Injection</i>	Bronchodilator: Open airways by relaxing airway smooth muscle. Anti-inflammatory effects???
Theophylline	Aminophylline	
Aminophylline		
<b>NOTE:</b> Do not change the brand-name that patient is stabilized on. Useful on controlling nocturnal asthma and morning wheezing. Modified-release forms are preferred. In patients on oral preparations who are going to receive aminophylline i.v., measurement of plasma concentration is essential.		
<u>Leukotriene modifiers</u>		
<u>a. Leukotriene receptor antagonists (LTRAs)</u>		
Montelukast sodium		Anti-inflammatory agent: Inhibit the action of the inflammatory mediators (leukotrienes C <sub>4</sub> and D <sub>4</sub> )
Zafirlukast		
Pranlukast		
<u>b. 5-lipoxygenase inhibitor</u>		
Zileuton		
<u>Ketotifen</u>		
		Antihistamine: Inhibit activation of, and mediator release from, inflammatory cells. Efficacy???

symptomatic with moderate to high-dose of inhaled corticosteroids (stages 3 and 4 of the BTS guidelines). Currently, usage of this group is restricted. This mainly is due to a very narrow therapeutic index of theophylline and its potentially serious side effects. In addition, limited access to facilities required for theophylline therapeutic drug monitoring (TDM) forces the doctors to be cautious in prescribing this drug, in particular for newly diagnosed asthmatic patients. Although theophylline has shown some anti-inflammatory effects, this remains to be confirmed by further studies [71, 73]. Aminophylline could be given as an intravenous injection in the treatment of severe asthma attacks when there is no rapid response to nebulized beta-2 agonists [72].

Leukotriene modifiers including leukotriene receptor antagonists (LTRAs), e.g. montelukast sodium, pranlukast and zafirlukast, and a 5-lipoxygenase inhibitor i.e. zileuton, are a new class of medications for the treatment of asthma. They specifically inhibit the action of the inflammatory mediators (leukotrienes C<sub>4</sub> and D<sub>4</sub>). These mediators have a potent broncho-constrictive effect and can increase mucus production. Leukotrienes can also attract eosinophils into the tissues and deteriorate the inflammatory process. The precise role of the LTRAs in asthma is still to be determined. However, they are likely to be useful as a preventive treatment in asthma. Their recommended indications are: prevention of day and night-time symptoms, treatment of aspirin-sensitive asthma patients, prevention of exercise-induced broncho-constriction and in patients not responding to other therapies [70].

Ketotifen (and other H<sub>1</sub> blockers from the same group of anti-histamines) is also an anti-allergic agent, which may inhibit mast cell activation or mast cell mediator release (similar to that of cromoglycates). However, its efficacy in asthma has not been sufficiently

documented [8, 72].

During the recent years, difficult-to-treat asthma which is mainly dependent to maximal topical and additional systemic glucocorticoid therapy has been tried to be treated with other T cell immunomodulatory agents as adjuvant therapies. Gold salts have had a modest but significant glucocorticoid-sparing effect in severe asthma, however, lung function was not improved and not all patients respond. Meta-analysis of trials of methotrexate has revealed that concomitant weekly methotrexate for a minimum of 3 to 6 months enables significant (approximately 20%) overall reduction in oral glucocorticoid requirements, although only approximately 60% of patients showed a significant response. There was little effect on lung function. Cyclosporine, administered for at least 3 months, could be effective in only a proportion of patients with oral glucocorticoid-dependent asthma, where it may improve disease severity and/or enable oral glucocorticoid dosage reductions. The macrolides tacrolimus (FK506) and sirolimus (rapamycin) have shown final effects similar to those of cyclosporine. Presently, the evidence that intravenous immunoglobulin (Ig) is effective in patients with glucocorticoid-dependent asthma is ambiguous. Brequinar sodium, mycophenolate mofetil and leflunomide, newly-synthesised inhibitors of synthesis of pyrimidines and purines, theoretically may be beneficial for therapy of patients with oral glucocorticoid-dependent asthma. Humanized anti-CD4, anti-IgE and anti-interleukin (IL)-5 monoclonal antibodies, and other cytokine inhibitors such as soluble IL-4 receptor are still on trials.

The worth of the immunomodulatory drugs, explained above, is limited since: (i) not all patients respond and response cannot be predicted; (ii) the high incidence of unwanted effects makes it difficult to assess overall benefit/risk ratios. There are increased risk of opportunistic potentially fatal infection and (in

theory) neoplasia as well as other serious unwanted effects e. g. dermatitis, hepatic and renal dysfunction, proteinuria, interstitial pneumonitis, fever, aseptic meningitis and urticaria; (iii) there are many relative and absolute contraindications to therapy; and (iv) there is lack of knowledge about the long-term effects, beneficial or damaging, of therapy [74-77].

### **7. New inhaler devices and delivery systems**

Chloro-fluoro-carbones (CFCs) are known as one of the chemicals responsible for damages to the ozone layer. At the Montreal Convention in 1987, it was decided to limit usage of CFCs [78]. In this respect, pharmaceutical companies have been encouraged to look for environmentally friendly preparations to substitute the current CFC-inhalers. In the recent years two main groups of preparations i.e. hydro-fluoro-alkane (HFA) inhalers and dry powder inhalers (DPIs) were introduced to the market. These new systems are going to be used instead of the traditional metered dose inhalers (MDIs), which are the most frequently prescribed delivery systems [79, 80]. This means that in the near future, there will be no CFC inhaler available and that all patients using them will have to transfer to HFA (CFC-free) inhalers and/or DPIs. Most HFA inhalers are reformulated at the same potency as their CFC equivalent. However, they look, feel, weigh, and taste slightly different and therefore patients and doctors should be aware of these differences [78]. On the other hand, the new inhalers may have different clinical effects or efficacy compared to existing CFC inhalers. For example, it is documented that when switching from a CFC-beclomethasone product to a HFA-beclomethasone, dose of the corticosteroid should be halved, because HFA product achieves the same effect at half the dose as the CFC preparation [81].

Dry powder inhalers are another group of new delivery systems used for inhalation.

DPIs can be divided into two groups: powder inhalers which use accurate factory-dispensed dose of medication sealed in individual units, including Spinhaler (available as Intal), Rotahaler, Diskhaler, Inhalator, Accuhaler (Discus), and Easi-Breath inhalers; the second group of DPIs includes reservoir powder inhalers such as Turbuhaler and Clickhaler. Since DPIs are actuated by the patient's own inhalation and do not need shaking before use then they are generally considered easy to use correctly (unlike MDIs that should be shaken before use and patients need to coordinate inhalation with actuation). However, in DPIs internal resistance of the device is a problem. Patients that cannot achieve the recommended inhalation flow may not gain maximum benefit from their medicine. Studies have shown that a higher inspiratory flow through a DPI could increase drug delivery to the lungs and therefore could result in a better clinical response [82]. Because not all asthmatics could achieve the minimal inspiration flow rate, therefore it is necessary to identify the appropriate device for each individual patient before deciding to prescribe a DPI. This could be determined using an inspiratory flow meter e.g. In-Check Dial<sup>®</sup>. This instrument is a low-range inspiratory flow meter that has a selectable resistance. It is calibrated to enable the measurement of airflow as the patient using a DPI.

### **8. Conclusion**

Asthma is a complex disorder and its management and treatment outcomes are multi-dimensional concepts. The relationship between disease management and clinical outcomes, therefore, could be considerably affected by potential confounding factors. Although not perfectly, considerable progress has been made in understanding asthma pathophysiology and aetiology. Despite knowledge currently available, day-by-day exciting new reports are published. Today, even genetic factors have been reported to have an impact

on the extent of the therapeutic response to anti-asthma medications [83]. However, there are still some unknown and dark corners which need to be revealed:

Who are more likely to suffer from asthma (high-risk groups)?

Which characteristics/factors make some patients more susceptible to asthma morbidity?

How are these characteristics/factors related to higher morbidity rates?

What should be done and what newer medication/formulations or management protocols should be introduced to minimize the suffering due to asthma?

Which patients are going to have the most benefit from the newly introduced protocols/medications and how?

At present there are no precise answers to these questions.

## References

- [1] Chung KF, Adcock I. *Asthma mechanisms and protocols*. New Jersey: Humana Press, 2000; pp.1-29.
- [2] Kelly HW. Asthma. In: Koda-Kimbel MA, Young LY, (editors). *Applied therapeutics: the clinical use of drugs*. 5<sup>th</sup> ed. Washington: Applied Therapeutics Inc., 1992; pp.15.1 – 15.24.
- [3] Hartl D, Greise M, Nicolai T, Zissel G, Prell C, Konstantopoulos N, Gruber R, Reinhardt D, Schendel DJ, Krauss-Etschmann S. Pulmonary chemokines and their receptors differentiate children with asthma and chronic cough. *J Aallergy Clin Immunol* 2005; 115: 728-36.
- [4] Kuepper M, Bratke K, Julius P, Ogawa K, Nagata K, Luttmann W, Virchow JC Jr. Increase in killer-specific secretory protein of 37 kDa in bronchoalveolar lavage fluid of allergen-challenged patients with atopic asthma. *Clin Exp llergy* 2005; 35: 643-9.
- [5] Muratov V, Barck C, Bylin G, Kallstorm E, Hallden G, van Hage M, Elvin K, Lundahl J. Aallergen challenge alters intracellular cytokine expression. *Scan J Immunol* 2005; 62: 161-7.
- [6] Schaller MA, Lundy SK, Hhuffnagle GB, Lukacs NW. CD8<sup>+</sup> T cell contributions to allergen induced pulmonary inflammation and airway hyperreactivity. *Eur J Immunol* 2005; 35: 2061-70.
- [7] Evans JF. Cysteinyl leukotriene receptors. *Prostaglandins Other Lipid Mediat.* 2002; 68-69: 587-97.
- [8] National Hearth, Lung and Blood Institute and World Health Organisation Workshop report: global strategy for asthma management and prevention [Online], 2004 [Accessed 2005 April 04]; aAvailable from: URL: <http://www.ginasthma.com/Guidelineitem.asp?i1=2&i2=1&intId=60>.
- [9] *National Asthma Campaign. The national asthma audit*. London; 1999/2000.
- [10] Murray AB, Morrison BJ. Effect of passive smoking on asthmatic children who have and who have not had atopic dermatitis. *Chest* 1992; 101: 16-8.
- [11] von Mutius E, Fritzsche C, Weiland SK, Roll G, Magnussen H. Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison. *Br Med J* 1992; 305: 1395-9.
- [12] Black PN, Sharpe S. Dietary fat and asthma: is there a connection? *Eur Respir J* 1997; 10: 6-12.
- [13] Burney PG, Neild JE, Twort CH, Chinn S, Jones TD, Mitchell WD, Bateman C, Cameron IR. Effect of changing dietary sodium on the airway response to histamine. *Thorax* 1989; 44: 36-41.
- [14] Salamzadeh J, Wong ICK., Hosker H, Chrystyn H. The relationship between the quality of prescribing and practice appointment rates with asthma management data in those admitted to hospital due to an acute exacerbation. *Respir Med* 2005; 99: 735-41.
- [15] Adams RJ, Smith BJ, Ruffin, RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. *Thorax* 2000; 55: 566-73.
- [16] Salamzadeh J, Habibi M, Fahimi F, Boroumand B. A study of possible predictors associated with hospitalization in 198 asthmatic outpatients referred to the Labbafi-nezhad university hospital in Tehran. In: Valizadeh H, Azarmi Sh, Ghobe Zarrin N, (editors). *9th Iranian Seminar of Pharmaceutical Sciences*. Abstracts of contributions; Tabriz, Iran, 2004 August 23-26; Tabriz, Iran.: Tabriz University of Medical Sciences; 2004; p. 282.
- [17] Coakley AL, Johnson AJ. Inhaled steroids for asthma: a qualitative study exploring patients' views and the meeting of educational needs within inhaler packaging. *Asthma J* 1999; 4: 175-8.
- [18] O'Callaghan C, Barry P. Delivering inhaled corticosteroids to patients: if side effects are important, why are we so ignorant of the dose inhaled? *Br Med J* 1999; 318: 410-1.
- [19] Clark NM, Gong M. Management of chronic

- disease by practitioners and patients: are we teaching the wrong things? *Br Med J* 2000; 320: 572-5.
- [20] Stevenson FA. The strategies used by general practitioners when providing information about medicines. *Patient Educ Couns* 2001; 43: 97-104.
- [21] Ordonez GA, Phelan PD, Olinsky A, Robertson CF. Preventable factors in hospital admissions for asthma. *Arch Dis Child* 1998; 78: 143-7.
- [22] Bosley CM, Fosbury JA, Cochrane GM. The psychological factors associated with poor compliance with treatment in asthma. *Eur Respir J* 1995; 8: 899-904.
- [23] FitzGerald JM, Turner MO. Delivering asthma education to special high risk group. *Patient Educ Couns* 1997; 32: S77-S86.
- [24] Gruffydd-Jones K. *Compliance: the challenge in asthma management.*; London: Miller Freeman UK Ltd. 1998; pp.1-8.
- [25] Raheerison C, Tunon-De-Lara JM, Vernejoux JM, Taytard A. Practical evaluation of asthma exacerbation self-management in children and adolescents. *Respir Med* 2000; 94: 1047- 52.
- [26] Salamzadeh J, Fahimi F, Habibi M, Boroumand B. A study of inhaler technique in asthmatics and its explanatory parameters. In: Valizadeh H, Azarmi Sh, Ghobe Zarrin N, eds. *9<sup>th</sup> Iranian Seminar of Pharmaceutical Sciences. Abstracts of contributions*; 2004 August 23-26; Tabriz, Iran. Tabriz university of Medical Sciences; 2004; pp. 283. In: Valizadeh H, Azarmi S, Ghobe Zarrin N, (editors). *9<sup>th</sup> Iranian Seminar of Pharmaceutical Sciences. Abstracts of contributions*; Tabriz, Iran, 2004 August 23-26: Tabriz University of Medical Sciences; p. 283.
- [27] Salamzadeh J, Habibi M, Boroumand B. Peak Expiratory Flow Rate (PEFR) in asthmatic patients: what are possible predictors? In: Valizadeh H, Azarmi Sh, Ghobe Zarrin N, eds. *9<sup>th</sup> Iranian Seminar of Pharmaceutical Sciences. Abstracts of contributions*; 2004 August 23-26; Tabriz, Iran. Tabriz university of Medical Sciences; 2004; p. 278.
- [28] Eachus J, Williams M, Chan P, Smith GD, Grainge M, Donovan J, Frankle S. Deprivation and cause specific morbidity: evidence from the Somerset and Avon survey of health. *Br Med J* 1996; 312, 287-92.
- [29] Minkovitz CS, Andrews JS, Serwint JR. Rehospitalization of children with asthma. *Arch Pediatr Adolesc Med* 1999; 153: 727-30.
- [30] Majeed A, Bardsley M, Morgan D, O'Sullivan C, Bindman AB. Cross sectional study of primary care groups in London: association of measures of socioeconomic and health status with hospital admission rates. *Br Med J* 2000; 321, 1057-60.
- [31] Watson JP, Cowen P, Lewis RA. The relationship between asthma admission rates, routes of admission, and socioeconomic deprivation. *Eru Respir J* 1996; 9: 2087-93.
- [32] Salamzadeh J, Patel MG, Wong ICK, Wright DJ, Chrystyn H. Characteristics of general practices with different asthma prescribing. *Pharma J (suppl)* 2000, 265: R52.
- [33] Gottlieb D J, Beiser AS, O'Connor GT. Poverty, race, and medication use are correlates of asthma hospitalization rates. *Chest* 1995; 108: 28-35.
- [34] Finkelstein JA, Brown RW, Schneider LC, Weiss ST, Quintana JM, Goldmann DA, Homer CJ. Quality of care for pre-school children with asthma: the role of social factors and practice setting. *Pediatrics* 1995; 95: 389-94.
- [35] Duran-Tauleria E, Rona RJ, Chinn S, Burney P. Influence of ethnic group on asthma treatment in children in 1990-1: national cross sectional study. *Br Med J* 1996; 313: 148-52.
- [36] Apter AJ, Reisine ST, Affleck G, Barrows E, ZuWallack RL. The influence of demographic and socioeconomic factors on health-related quality of life in asthma. *J Allergy Clin Immunol* 1999; 103: 72-8.
- [37] Gilthorpe MS, Lay-Yee R, Wilson RC, Griffiths RK, Bedi R. Variations in hospitalization rates for asthma among Black and minority ethnic communities. *Respir Med* 1998; 92: 642-8.
- [38] Moudgil, H., Marshall, T. and Honeybourne, T. Asthma education and quality of life in the community: a randomized controlled study to evaluate the impact on white European and Indian subcontinent ethnic groups from socioeconomically deprived areas in Birmingham, UK. *Thorax* 2000; 55: 177-183.
- [39] Salamzadeh J, Patel M, Wong I, Wright D, Chrystyn H. Analysis of the impact of practice characteristics and social deprivation on prescribing quality for asthma. *Thorax (suppl.)* 1999; 54: A54.
- [40] Law MR, Morris JK. Why is mortality higher in poorer areas and in more Northern areas of England and Wales? *J Epidemiol Community Health* 1998; 52: 344-52.
- [41] Hippisley-Cox J, Hardy C, Pringle M, Fielding K, Carlisle R, Chilvers C. The effect of deprivation on variations in general practitioners' referral rates: cross sectional study of computerized data on new medical and surgical outpatient referrals in Nottinghamshire. *Br Med J* 1997; 314: 1458 - 61.
- [42] Salamzadeh J, Wong ICK, Hosker HSR, Chrystyn

- H. A logistic regression analysis of predictors for asthma hospital re-admissions. *Iranian J Pharma Res (IJPR)* 2003; 2: 5-9.
- [43] Salamzadeh J, Wong ICK, Hosker HSR, Chrystyn H. A cox regression analysis of covariates for asthma hospital readmissions. *J Asthma* 2003; 40: 645-52.
- [44] Matthews S, Manor O, Power C. Social inequalities in health: are there gender differences? *Soc Sci Med* 1999; 48: 49-60.
- [45] Sexton M, Althuis MD, Santanello N, Hyndman S, Williams R, Schmeidler D. Sex differences in the use of asthma drugs: cross sectional study. *Br Med J* 1998; 317: 1434-37.
- [46] Yuksel N, Ginther S, Man P, Tsuyuki RT. Underuse of inhaled corticosteroids in adults with asthma. *Pharmacother* 2000; 20: 387-93.
- [47] Heard AR, Campbell DA, Ruffin RE, Smith B, Luke CG, Roder DM. Rehospitalization for asthma within 12 months: unequal rates on the basis of gender at two hospitals. *Aust N Z J Med* 1997; 27: 669-71.
- [48] Mitchell EA, Bland JM, Thompson JMD. Risk factors for readmission to hospital for asthma in childhood. *Thorax* 1994; 49: 33-6.
- [49] Prescott E, Lange P, Vestbo J, Jensen G, Schnohr P, Appleyard M, Nyboe J, Grenbaeck M, Nordestgaard B. Effect of gender on hospital admissions for asthma and prevalence of self-reported asthma: a prospective study based on a sample of the general population. *Thorax* 1997; 52: 287-9.
- [50] Langhammer A, Johnsen R, Holmen J, Gulsvik A, Bjermer L. Cigarette smoking gives more respiratory symptoms among women than among men: The Nord-Trøndelag health study (HUNT). *J Epidemiol Community Health* 2000; 54: 917-22.
- [51] Siroux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F. Relationship of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the genetics and environment of asthma. *Eur Respir J* 2000; 15: 470-7.
- [52] Eisner MD, Yelin EH, Henke J, Shiboski SC, Blanc PD. Environmental tobacco smoke and adult asthma: the impact of changing exposure status on health outcomes. *Am J Respir Crit Care Med* 1998; 158: 170-5.
- [53] Gurkan F, Ece A, Haspolat K, Derman O, Bosnak M. Predictors for multiple hospital admissions in children with asthma. *Can Respir J* 2000; 7: 163-6.
- [54] Rosas I, McCartney HA, Payne RW, Calderon C, Lacey J, Chapela R, Ruiz-Velazco S. Analysis of the relationship between environmental factors (aeroallergens, air pollution, and weather) and asthma emergency admissions to a hospital in Mexico City. *Eur J Allergy Clin Immunol* 1998; 53: 394-401.
- [55] Miles J, Cayton R, Ayres J. Atopic status in patients with brittle and non-brittle asthma: a case-control study. *Clin Exp Allergy* 1995; 25: 1074-82.
- [56] Sporik R, Platts-Mills TAE, Cogswell JJ. Exposure to house dust mite allergen of children admitted to hospital with asthma. *Clin Exp Allergy* 1993; 23: 740-6.
- [57] Warner JA, Warner JO. Allergen avoidance in childhood asthma. *Respir Med* 1991; 85: 101-5.
- [58] Cassino C, Berger KI, Goldring RMIA, Narmann RG, Kammerman S, Ciotoli C, Reibman J. Duration of asthma and physiologic outcomes in elderly non-smokers. *Am J Respir Crit Care Med* 2000; 162: 1423-8.
- [59] Sears MR. Consequences of long-term inflammation: the natural history of asthma. *Clin Chest Med* 2000; 21: 315-29.
- [60] Zeiger RS, Dawson C, Weiss S. Relationship between duration of asthma and asthma severity among children in the childhood asthma management programme. *J Allergy Clin Immunol* 1999; 103: 376-87.
- [61] Foroutan N, Habibi M, Salamzadeh J. Designing a new questionnaire to evaluate asthma morbidity. Canadian Society for Pharmaceutical Sciences. *8th Annual Symposium of Canadian Society for Pharmaceutical Sciences: accelerating drug discovery and development*. Toronto, Canada; 2005, May 30- June 2, p.64.
- [62] Jebrak G, Brugiere O, Uffredi ML. Impact of infections a chlamydia pneumonia infections on asthma. *Presse Med* 2000; 29: 1425-32.
- [63] Reddel H, Ware S, Marks G, Salome C, Jenkins C, Woolcock A. Differences between asthma exacerbations and poor asthma control. *Lancet* 1999; 353: 364-9.
- [64] Smith A, Nicholson K. Psychosocial factors, respiratory viruses and exacerbation of asthma. *Psychoneuroendocrinology* 2001; 26: 411-20.
- [65] Gern JE, Busse WW. The role of viral infections in the natural history of asthma. *J Allergy Clin Immunol* 2000; 106: 201-12.
- [66] Micillo E, Bianco A, D'Auria D, Mazzarella G, Abbate GF. Respiratory infections and asthma. *Eur J Allergy Clin Immunol (suppl)* 2000; 55: 42-5.
- [67] Salamzadeh J, Kebriayeezadeh A, Shalchi M. Drug utilization review of anti-asthma drugs using Defined Daily Doses (DDD) in 28 provinces of Iran during the years 2000-2002. In: Valizadeh H, Azarmi S, Ghobe Zarrin N, (editors). *9th Iranian Seminar of Pharmaceutical Sciences*.

- Abstracts of contributions; Tabriz, Iran, 2004 August 23-26: Tabriz University of Medical Sciences; p. 284.
- [68] Fleming DM, Cross KW, Sunderland R, Ross, AM. Comparison of the seasonal patterns of asthma identified in general practitioners episodes, hospital admissions, and deaths. *Thorax* 2000; 55: 662-5.
- [69] Stedman JR, Anderson HR, Atkinson RW, Maynard RL. Emergency hospital admissions for respiratory disorders attributable to summer time ozone episodes in Great Britain. *Thorax* 1997; 52: 958-63.
- [70] National asthma council Australia (2005) *Asthma management handbook* [Online], 2002, [accessed April 4, 2005]. [Online] Available from URL: <<http://www.nationalasthma.org.au>>.
- [71] British Thoracic Society, National Asthma Campaign, Royal College of Physicians of London, General Practitioner in Asthma Group, British Association of Accident and Emergency Medicine, British Paediatric Respiratory Society and Royal College of Paediatrics and Child Health; The British guidelines on asthma management: 1995 review and position statement. *Thorax (suppl 1)*, 1997; 52: S1-S21.
- [72] *British Medical Association and Royal Pharmaceutical Society of Great Britain (2005) British National Formulary (Number 49)*. Oxon: The Pharmaceutical Press, 2005.
- [73] Tavakkoli A, Rees PJ. Drug treatment of asthma in the 1990s: Achievement and new strategies. *Drugs* 1999; 57: 1-8.
- [74] Corrigan CJ. Asthma refractory to glucocorticoids: the role of newer immunosuppressants. *Am J Respir Med* 2002; 1; 47-54.
- [75] Corrigan CJ, Shiner RJ, Shakur BH, Ind PW. Methotrexate therapy of oral corticosteroid-dependent asthmatics reduces serum immunoglobulins: correlation with clinical response to therapy. *Clin Exp Allergy* 2005; 35: 579-84.
- [76] Karagiannidis C, Ruckert B, Hense G, Willer G, Menz G, Blaser K, Schmidt-Weber CB. Distinct leukocyte redistribution after glucocorticoid treatment among difficult-to treat asthmatic patients. *Scand J Immunol* 2005; 61: 187-96.
- [77] Girgis SI, Nwokeji A, Shakur BH, Ind PW, Shiner RJ. The effect of steroid-sparing response to low-dose methotrexate on bone metabolism in glucocorticoid-dependent asthmatics. *Clin Chim Acta* 2004; 341: 157-63.
- [78] General practitioners in asthma group. GPIAG opinion sheet no. 3. CFC to HFA: the transition [Online], 2001 [accessed 2002 May 1, 2002]. Available from: URL: [http:// www.gpiag-asthma.org/Opinions/opinion3.htm](http://www.gpiag-asthma.org/Opinions/opinion3.htm).
- [79] Schlaeppi M, Edwards K, Fuller RW, Sharma Ret al. Patient perception of the Diskus inhaler: a comparison with the Turbuhaler inhaler. *Br J Clin Pract* 1996; 50: 14-9.
- [80] Sharma RK, Edwards K, Hallet C, Fuller RW. Perception among paediatric patients of the Discus inhaler, a novel multidose powder inhaler for use in the treatment of asthma: comparison with the Turbuhaler inhaler. *Clin Drug Invest* 1996; 11:145-53.
- [81] Levy M, Hilton S, Barnes G. *Asthma at your fingertips*. 3<sup>rd</sup> ed. London: National Asthma and Respiratory Training Centre; 2000. pp.14, 164, 169, 180, 212.
- [82] Persson G, Olsson B, Soliman S. The impact of inspiratory effort on inspiratory flow through Turbuhaler in asthmatic patients. *Eur Respir J* 1997; 10: 681-4.
- [83] Gottlieb S. Personalized medicine comes one step closer for asthma. *Br Med J* 2000; 321: 724.