# Diagnosis and Management of Adult Asthma: Excerpts from 'National Asthma Guidelines for Medical Practitioners'

***Dr. Md. Rashidul Hassan,*** *MBBS, MCPS, FCPS (Med), MD (Chest), Physician & Pulmonologist, Associate Professor, Department of Chest Medicine, Institute of Diseases of the Chest & Hospital, Mohakhali, Dhaka*
***Dr. Asif Mujtaba Mahmud,*** *DTCD, PhD (Respiratory Medicine), Asst. Prof., Institute of Diseases of the Chest & Hospital, Mohakhali, Dhaka*
***Dr. Md. Ali Hossain,*** *FCPS (Med), MD (Chest), Associate Professor, Institute of Diseases of the Chest & Hospital, Mohakhali, Dhaka*
***Dr. Kazi Saifuddin Bennoor,*** *DTCD, Medical Officer, National Institute of Cancer Research & Hospital, Mohakhali, Dhaka*

## Foreword

The Asthma Association, Bangladesh, has published the revised and updated version of "National Asthma Guidelines for Medical Practitioners" recently. It is a comprehensive handbook covering almost all aspects of asthma. Here, we present excerpts from the book regarding the diagnosis and management of asthma in adult patients.

## Introduction

Asthma is an important disorder of the airways with significant morbidity and mortality. Globally it affects about 100 million people. According to the first National Asthma Prevalence Study (NAPS)[1] conducted throughout Bangladesh in 1999, about 7 million people (5.2% of the population) are suffering from current asthma. In the United States, asthma affects more than 14 million individuals and asthma prevalence increased by 75% from 1980 to 1995, with similar trends seen in most developed countries.[2] Rising environmental pollution has been implicated for the increase in asthma prevalence. Contrary to popular belief, the NAPS has shown that occurrence of asthma is lesser in metropolitan areas in relation to other urban (districts) and rural areas (villages); environmental pollution is therefore considered to be a trigger rather than an inducer. In spite of better understanding of the patho-physiological processes underlying the disease, which has led to apparently improved treatment, mortality from asthma has remained unchanged and in some countries has increased.

## Definition

Asthma is a chronic inflammatory disorder causing hyper-responsiveness of airways to certain stimuli resulting in recurrent variable airflow limitation, at least partly reversible, presenting as wheezing, breathlessness, chest tightness and coughing.[3]

## Asthma is characterized as having 5 distinct features:

1. *Bronchial inflammation:* Asthma is an inflammatory disease with an eosinophil-rich infiltrate within the bronchial mucosa. Other features of asthma, such as airway obstruction, bronchial hyper-responsiveness and mucus hypersecretion are a consequence of this inflammatory response. The recruitment of inflammatory cells, including eosinophils and T cells, in asthmatic airways clearly plays a role in the pathogenesis of the disease.[4,5]
2. *Cardinal features:* In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning.
3. *Reversible airway obstruction:* The obvious feature of asthma is the presence of decreased airflow during expiration. This is most commonly measured using either the forced expiratory volume in 1st second ($FEV_1$) or the peak expiratory flow rate (PEFR). Reversibility refers to the fact that, in contrast to chronic obstructive pulmonary disease (COPD), the obstruction in asthma usually improves after bronchodilator therapy.
4. *Bronchial hyper-responsiveness:* Irritant stimuli such as tobacco smoke, fumes, cold dry air and exercise provoke bronchospasm in asthmatic airways at lower levels than that required in healthy controls.
5. *Sub-basement membrane fibrosis:* Moreover recent evidence indicates that sub-basement membrane fibrosis may occur in some patients with asthma and that these changes contribute to persistent abnormalities in lung function.

## Pathogenesis

The relatively recent understanding of the major role of inflammation in the pathogenesis of asthma has led to an emphasis on anti-inflammatory medications in treatment.

The *immediate asthmatic response* consists of a decrease in airflow within several minutes after bronchial allergen exposure. This is attributed to mast cell activation and the release and generation of a number of mediators, including leukotrienes, histamins, proteases, and prostaglandins. Six to ten hours later, there is often a second decrease in airflow, called the *pulmonary late-phase response*, which is associated with inflammatory cell infiltration into the bronchial mucosa. The pulmonary late-phase response shares a number of features with chronic asthma, including a prominent eosinophilic infiltrate and the presence of bronchial hyperresponsiveness. During this late-phase response, T cells are observed in the bronchial mucosa, releasing additional mediators including cytokines such as interleukin 4 (IL-4), IL-5 and IL-13. Additionally, eosinophils migrate to the lung and release a number of highly toxic granule proteins including major basic protein and eosinophil cationic protein.

## Diagnosis

In most cases, the diagnosis of asthma is relatively simple. Patients report the classic symptoms of wheezing, chest

tightness, shortness of breath or cough all of which improve after bronchodilator therapy. A thorough history should detail the type, frequency and chronicity of asthma symptoms and their precipitating or aggravating factors (Table-1). A patient's requirement for short acting β2-agonists may be an independent indicator of asthma severity. Assessment of previous outcomes of asthma exacerbations, including emergency room visits and hospitalizations indicates the patient's potential for severe exacerbations.

**Table 1: Initial history of asthmatic patients**

| |
|---|
| 1. Symptoms: Cough, wheezing, shortness of breath, chest tightness, sputum production, nocturnal symptoms |
| 2. Frequency of short acting β2-agonist use |
| 3. Precipitating factors: Upper respiratory infections, allergen or irritant exposure, exercise, environment, medications |
| 4. Pattern of typical exacerbation |
| 5. Severity of asthma exacerbations: Emergency room visits, hospitalizations, history of intubation |
| 6. Disease development: Age of onset, progress of disease (better or worse) |
| 7. Family history |
| 8. Social history |
| 9. Impact of asthma on the patient and family |

Newly diagnosed asthma patients should undergo pulmonary function testing (spirometry) with values obtained before and after the inhalation of a short acting β2-agonist. Although physicians can generally make the diagnosis of an obstructive lung disease by history and physical examination, spirometry is necessary to quantitate the magnitude of obstruction and the degree of reversibility. For diagnosis and initial evaluation, spirometry is preferred over peak flow meters because of the wide variation in readings between peak flow meters. A post-bronchodilator increase in $FEV_1$ of 200 ml and 12% or more is evidence of reversibility consistent with the diagnosis of asthma. That together with a history and physical examination indicating asthma, should be sufficient to make the diagnosis.

## Clinical Classification

1. **Intermittent asthma:** Between the attacks, patient is symptom free and PFT is normal.
2. **Persistent asthma:** Frequent attack i.e. patient has coughing, wheezing, or shortness of breath at night or early morning at least more than two occasions in a month. In between the attack patient may or may not be symptom free and PFT is abnormal except in mild persistent variety.
   a) Mild Persistent Asthma: Usually patients have nocturnal attack of dyspnoea more than 2 times per month and baseline PEFR or $FEV_1$ is usually <80% to 65%. Occasionally PFT may be normal in between attacks.
   b) Moderate Persistent Asthma: Usually patients have almost daily attack of dyspnoea and baseline PEFR or $FEV_1$ is <65%to 50%.
   c) Severe Persistent Asthma: Usually patients have dyspnoea to some extent continuously for 6 months or more and baseline PEFR or $FEV_1$ is less than 50% of predicted value.
3. **Acute exacerbation:** Loss of control of any class or variant of asthma, which may cause mild to life threatening attack.
   a) Mild: Patient is dyspnoeic but can talk in sentences.
   b) Moderate: Patients is more dyspnoeic and can not complete sentences in one breath.
   c) Severe (status asthmaticus): Patient is severely dyspnoeic, talks in words and may be restless, even unconscious.
4. **Special Variants:** There are 5 special variants of asthma:
   a) Seasonal asthma
   b) Exercise induced asthma (EIA)
   c) Drug induced asthma
   d) Cough variant asthma
   e) Occupational asthma

## Asthma Medications

There are basically three kinds of medicines:

1) Relievers (bronchodilators) are medicines that relax smooth muscles that have tightened around the airways. They relieve asthma symptoms. Short acting β2-agonists, short acting aminophylline, and ipratropium are bronchodilators or relievers.
2) Preventers (anti-inflammatory medicines) are medicines that reduce or reverse the swelling in the airways of an asthmatic. These medicines also prevent the initiation of inflammation after exposure to trigger factors. Thereby they prevent asthma episodes. Sodium cromoglycate, nedocromil sodium, inhaled corticosteroids and oral corticosteroids are anti-inflammatory medicines or preventers. They are used as per need in 2nd to 5th steps of 'Step Care Management'. Aminophylline and theophylline also have some weak anti-inflammatory effects. Antileukotrienes are newer preventer medicines.
3) Protectors (symptom controllers) are long acting bronchodilator medicines, which prevent recurrence of attack particularly nocturnal symptoms. Salmeterol, long acting theophylline, sustained release salbutamol are protector medicines.

### *Inhaled Corticosteroids*

Inhaled corticosteroids are the most potent anti-inflammatory medicine e.g., Triamcinolone acetonide (Azmacort®) inhaler. They inhibit inflammatory cell migration to the bronchi and decrease the release of cytokines and other inflammatory mediators. Inhaled corticosteroids improve airflow and quality of life measurements while decreasing bronchial hyper-responsiveness and rescue bronchodilator use. Most importantly, inhaled corticosteroids prevent exacerbations of asthma. Additionally, data suggest that inhaled corticosteroids may prevent the development of irreversible airflow obstruction.[6,7]

### *Cromones*

Cromolyn and nedocromil share a similar mechanism of action by inhibiting mast cell degranulation. Nedocromil sodium

(Tilade®) is indicated for prevention of extrinsic and exercise induced asthma. The initial and maintenance therapy is with four and two actuations (each yielding 2 mg of nedocromil sodium) respectively twice daily. They are mostly used in children and in situations where long-term toxicity of inhaled corticosteroids is a threat.

**Table 2: Comparative dose ranges for inhaled corticosteroids in adults**

| Drugs | Low Dose | Moderate Dose | High Dose |
|---|---|---|---|
| Beclomethasone dipropionate | 168-504 µg/day | 504-840 µg/day | >840 µg/day |
| Budesonide | 200-400 µg/day | 400-600 µg/day | >600 µg/day |
| Flunisolide | 500-1000 µg/day | 1000-2000 µg/day | >2000 µg/day |
| Fluticasone | 88-264 µg/day | 264-660 µg/day | > 660 µg/day |
| Triamcinolone acetonide (Azmacort®) | 400-1000 µg/day | 1000-2000 µg/day | >2000 µg/day |

### *Methylxanthines*

Theophylline was the central component of asthma therapy in the 1970s and 1980s, before the development of inhaled β2-agonists and corticosteroids. It has moderate bronchodilator activity being rarely used as a single agent in asthma but may have a role as adjunctive therapy in severe asthmatic patients. In view of it's weak anti-inflammatory properties, it has been proposed as the fundamental component of the 'economic schedule' for poor patients in our guidelines.

### *Leukotriene Antagonists*

The newest approved class of asthma drugs is the leukotriene antagonists (LTA). These include zafirlukast, montelukast and zileuton. The LTAs represent a major milestone in asthma therapy being the first licensed asthma medication to target a specific inflammatory pathway. All LTAs are administered orally. The 'kast' drugs (zafirlukast and montelukast) are specific antagonists of the cysteinyl leukotriene receptor 1 (CysLT1), thus blocking the action of LTC4, LTD4 and LTE4. These drugs have an extremely high affinity for the CysLT1 receptor and are able to completely block the bronchospastic effect of inhaled leukotrienes.[8]

### *β2- Adrenergic Agonists*

Reliever medications are used to provide as needed relief of asthma symptoms, typically through their action as bronchodilators. The most effective quick relief medications are the inhaled short-acting β2 adrenergic agonists, including salbutamol, albuterol, pirbuterol and tolubeterol. All have similar efficacy and side effect profiles. These drugs provide both bronchodilatation and protection against bronchoconstrictive stimuli such as allergen exposure, exercise and methacholine challenge.

### *Salmeterol*

Salmeterol is a long-acting β2-agonist that has an effective duration of action of 12 hours. It is typically used as a twice-daily medication, and therefore is classified as a protector medication. Salmeterol is particularly useful for patients with moderate to severe asthma requiring frequent β2-agoinst therapy. Patients with nocturnal asthma may also benefit from the extended duration of action.

### *Ipratropium Bromide*

Ipratropium is a cholinergic antagonist that has moderate bronchodilatory activity but is less effective than β2-agonists. Ipratropium may provide some additional bronchodilation for patients already receiving β2-agonists therapy. It is also helpful in smokers.

## Treatment

The general goals of asthma therapy are to attain the following points:

1. Patient is almost asymptomatic.
2. Patient can perform near normal activities.
3. Use of reliever bronchodilator is once or less per day.
4. Diurnal variability of peak flow is 10% or less.
5. No nocturnal symptoms, if occurs, less than two times per month.
6. No emergency visit to doctors or hospitals.
7. No or minimal side effects of medication.

Initially, the symptoms of asthma are treated with reliever medications, typically short-acting inhaled β2-agonists. The frequent (more than twice per week) use of short-acting β2-agonists suggests that the patient's asthma is not well controlled on the current anti-inflammatory regimen and should be re-evaluated. Consideration should be given to adding or increasing the dose of inhaled corticosteroids.

### *Intermittent Asthma*

Patients with mild intermittent asthma often have little to no evidence of asthma on pulmonary function tests or examination, but they demonstrate bronchoconstriction when their asthma is provoked by stimuli such as allergen exposure, exercise and viral infections. Short-acting ß2-agonists are indicated as monotherapy for these patients. Typically, no long-term control medication is needed. These patients may benefit from periodic treatment with inhaled corticosteroids during asthma exacerbations.

### *Mild Persistent Asthma*

In patients with mild persistent asthma, low-dose inhaled corticosteroids are the long-term control drug of choice and provide greater benefits than LTAs,[9] cromolyn, or nedocromil.[10] The value of daily preventative long-term control medication in maximizing quality of life[11] and minimizing the occurrence of asthma exacerbations[12,13] should be stressed to the patients to increase compliance.

### *Moderate Persistent Asthma*

Patients with moderate persistent asthma have daily asthma symptoms and demonstrate a decreased $FEV_1$ at all times. High dose inhaled corticosteroids are indicated as the long-term control therapy. In addition, patients with nocturnal asthma may benefit from nightly salmeterol.

***Severe Persistent Asthma***

Patients with severe asthma are defined as having continuous symptoms for more than six months and an $FEV_1$ of ≤60% of predicted value. These patients typically require multiple medications to manage their asthma, and even after treatment, will demonstrate considerable obstruction. Most patients with severe asthma will require frequent bursts or long-term therapy with oral corticosteroids to maintain an acceptable level of function. The use of high potency inhaled corticosteroids such as triamcinolone acetonide (Azmacort®) is preferred. The usual recommended dosage is two inhalations (200 µg) given three to four times a day or four inhalations (400 µg) given twice daily. Clinical studies have shown that Azmacort® inhalation may be effective in the management of asthmatics dependant or maintained on systemic corticosteroids, which may permit replacement or significant reduction in the dosage of systemic corticosteroids. The use of the long-acting $\beta_2$-agonist salmeterol decreases the frequency of drug administration in patients who require round-the-clock bronchodilators. Additional adjunct medications that may be of value include the LTAs and theophylline.

## THE STAIRCASE OF STEP CARE MANAGEMENT

(for children ≥5 years to adults)

| STEP | Treatment to be given | | | |
|---|---|---|---|---|
| **Step-v** ϕ | Oral Steroid (Prednisolone) Single Morning dose (5-20 mg) | PLUS All medications of Step IVB | PLUS Step I | |
| **Step-IV** ♣ ϕ | **IVB** | Long acting $\beta_2$ agonist inhaler (Salmeterol) PLUS Sustained release Aminophylline/Theophylline (Both) | PLUS High dose Corticosteroid (Option:Z) | PLUS Step I |
| | **IVA** | Long acting $\beta_2$ agonist inhaler (Salmeterol) OR Sustained release Aminophylline/Theophylline (Alone) | | |
| **Step-III** ♦ ϕ | **Option: Z** High dose Corticosteroid Inhaler (Dose: for ≥5-18 yrs - > 400-800 µg or more; for Adults->800-2000 µg) | | | PLUS Step I |
| | **Option: Y** Low dose Corticosteroid (Option: b) PLUS Long acting $\beta_2$ agonist (Salmeterol) or Sustained release Aminophylline/ Theophylline or slow release Salbutamol | | | |
| | **Option: X** Full dose Cromone Inhaler (Option a) PLUS Low dose Corticosteroid Inhaler (Option b) | | | |
| **Step-II** • ϕ | **Option: C** Leukotrienes antagonists (Zafirlukast - 20 mg bd, 1hr before or 2hrs after meal. Montelukast-6-12 yrs:5mg, >12yrs:10 mg at bed time) | | | PLUS Step I |
| | **Option: b** Low dose of Corticosteroid Inhaler (Triamcindone/Beclomethasone) (Dose: for ≥5-18 yrs-upto 400 µg; for Adults-upto 800 µg) | | | |
| | **Option: a** Full dose of Cromone Inhaler (Sodium Cromoglycate/ Nedocromil Sodium) (Dose: 10 mg 4 times daily) | | | |
| **Step-I** ϕ | Short acting $\beta_2$ agonist inhaler (Salbutamol) as required (when patient feels even mild cough, wheeze and chest tightness, he should take inhaled Salbutamol, up to 4-6 times/day). Additional inhalation prior to exercise may be required. | | | |

**NOTE**

- • Step II comprises three options: a, b & c
- ♦ Step III comprises three options: X, Y & Z
- ♣ Step IV comprises two divisions: IVA & IVB
- ϕ Leukotrienes antagonist is a option in Step II. It can be added in any step from Step III to Step V

## Step Care Management

The step care management system should be practiced in managing asthma optimally. Step Care Management is like a staircase. Treatment is started at the appropriate step. Then *step up* is indicated along the stairs if asthma is not controlled or becomes more severe and *step down* is required when patient's asthma is fully controlled for 3 months or more.

***Scoring System for Step Care Management***

It is important to learn and practice step care management. At the same time it is essential to learn which step is appropriate for a particular patient. 'Asthma Centre', Mohakhali, Dhaka has developed a scoring system for determination of appropriate step for a patient.

Five important criteria for each patient have to be considered. First four are direct questions to the patients and the last one is assessment of PEFR by the physician. There is a score for every criterion. The appropriate step of management can be determined accordingly after calculating the total score.

***Rescue Steroid Therapy***

During step care management, patient may suddenly lose asthma control at any step, for example due to a viral respiratory tract infection. At that time oral rescue steroid (prednisolone) 30-60mg/day for adult and 1-2 mg/kg body weight/day for children in single morning dose or two divided doses for 3-14 days is usually prescribed.

| Criteria | Score |
|---|---|
| 1. Do you have dyspnoea everyday? | Yes=1 No=0 |
| 2. Do you have nocturnal attack of dyspnoea more than two times per month? | Yes=1 No=0 |
| 3. Have you suffered from dyspnoeic attacks which were severe enough to necessitate - Steroid tablets, Nebulizer therapy, Aminophylline Injection or Hospital admission? | Yes=1 No=0 |
| 4. Do you have persistent dyspnoea for last six months or more OR are you taking steroid tablets (Betnelan/Prednisolone/Deltasone) for one year or more? | Yes=3 No=0 |
| 5. Is patients' baseline (during asymptomatic stage) PEFR <60% of predicted value? | Yes=1 No=0 |
| | **Total Score = 7 - 0** |

**Recommended Step**

| Score | |
|---|---|
| 0 | Step–I |
| 1 | Step–II |
| 2 | Step–III |
| 3 | Step–IVA |
| 4 | Step–IVB |
| 5-7 | Step–V |

This rescue course of steroid tablets may be needed to control exacerbation of asthma at any step. Indications for this course are listed below. No stepping up is required prior to it. Patient should follow the existing step after ending the rescue course.

The indications for rescue steroid therapy are-

- Symptoms and PEFR progressively worsening day by day
- PEFR falls below 60% of patient's best
- Sleep is disturbed by asthma
- Morning symptoms persist till midday
- Appearance of diminishing response to inhaled bronchodilators
- Nebulized or injected bronchodilators are needed for emergency use.

## Patients Follow-up

Patient is advised to come for follow-up at monthly interval till control is achieved. After achievement of control, patient should come every three months for review of treatment. Control means:

a) Patient can perform near normal daily activities.

b) Patient requires Salbutamol inhalation <1 time/day.

c) Patient does not feel any disturbance during sleep.

d) PEFR is >80% of personal best result.

e) Diurnal variability in Peak Flow Chart, if available is <20%.

Once control is achieved and sustained for 3 months a reduction of drug therapy i.e. step down is appropriate and helpful to determine the minimum therapy for maintaining the control. Reduction of therapy should be slow and gradual. Patient should be advised to come for follow-up even if he is completely asymptomatic.

If patient's asthma is under control, then at every 3 months interval, the dose of inhaled corticosteroid has to be reduced by 25% from total dose up to minimum low dose. Then protector drugs (salmeterol/theophyllin SR) are withdrawn at 3 months interval. Patient may relapse when inhaled corticosteroids are completely discontinued.

If patient's asthma is not adequately controlled even after 1 month's intensive medications, at first any pitfalls on the part of the patient or the physician have to be checked. Any such loopholes, if present, have to be corrected. If control is not achieved after that, then an increase in medication i.e. step up is indicated. Medicines of the immediate higher step have to be employed. Simply, addition of the new drug and/or increasing the dose of the existing drug will suffice. No gradual increase of dosage is required as stipulated in step down procedure.

## Future Therapies

The recent advancement of the immunologic basis of asthma is currently being translated into a new generation of asthma therapies that target specific inflammatory mediators and pathways. The LTAs represent the first of many new classes of such specific antagonists. The advantage of these drugs is fewer unintended side effects, resulting in a greater therapeutic index. Multiple immunologic therapeutics are in the early phases of clinical development. These include antagonists of cytokines (IL-5, IL-13, eotaxin), adhesion molecules (VCAM-1, VLA-4) and costimulator molecules (CD23, CD28, CD40). Clearly, some of these approaches will be of limited value. However, the information gained about which inflammatory pathways are required for the generation of asthmatic inflammation will be of critical importance in the development of the next generation of immunologically specific asthma therapies.

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