

# Guidelines for Management of Asthma at Primary and Secondary Levels of Health Care in India (2005)



Program Development  
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Collaborative Programme  
(2004-2005)

Guidelines for Management of Asthma at Primary and Secondary Levels of Health Care in India (2005)

**A Consensus Statement Developed under the World Health Organization - Government of India Collaborative Programme (2004-2005)**

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## Preface

**N**umerous evidence based guidelines for diagnosis and management of bronchial asthma are available throughout the world. But there is a need for separate guidelines meant for the primary and secondary levels of health care in India. This is because of the differences in the overall health-care infrastructure, risk factors, disease prevalence and pattern. Also, a large prevalence of tuberculosis, which is an important cause of cough, adds to the difficulties of diagnosis and management in India.

These guidelines have been developed at the initiative of WHO (India) under the WHO-Government of India Collaborative programme (2004-2005). A workshop was held in February 2005 with representative participation from several national professional bodies, medical colleges, general health sector, and other institutes. The recommendations were subsequently compiled and reviewed by the participants and other experts. The document, based on the evidence available in literature, represents the consensus reached at the Workshop. The primary care physician looks after patients of both paediatric and adult age groups. This statement therefore applies also to children at the primary health care level. Detailed guidelines of the Indian Academy of Paediatrics for management of asthma in children are already available. Definitions used for different levels of evidence have been listed as an appendix to this document. A summary handout is also available for routine clinical use.

## Introduction

Asthma is a common disease worldwide with significant ethnic and regional variations. An increasing morbidity and mortality, as well as health care burden from asthma has been recognized lately.<sup>1</sup> There has been a change in the epidemiology and clinical spectrum of asthma with an apparent increase in the overall prevalence along with a rise in the incidence of 'difficult to treat' cases. Atopy, the production of abnormal amounts of IgE antibodies in response to common environmental allergens, is the strongest identifiable predisposing factor for developing asthma. Associations of asthma with infections, air pollution, tobacco smoke and other agents have been proposed but some of the risk factors are a subject of debate about their causal relationship with asthma.

## Definition

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 hyper-responsiveness 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.<sup>1</sup>

However for use in clinical practice, asthma may be defined as *a chronic inflammatory disorder of the airways characterized by recurrent episodes of wheezing, breathlessness, chest tightness and cough that is often reversible either spontaneously or with treatment.*

Epidemiologically, however asthma may need to be defined differently. Terms like 'current asthma' (prevalence of asthma symptoms in the last 12 months) and 'ever asthma' (prevalence of asthma symptoms anytime in the past or present) may need to be clarified during such a deliberation. The use of ambiguous terms like 'allergic bronchitis', 'asthmatic bronchitis', 'wheezing bronchitis' (etc.) should be avoided. For clinical purposes, classifying asthma as 'atopic and non-atopic', 'allergic and non-allergic' or 'intrinsic and extrinsic' does not alter the management in most patients.

## Epidemiology

Methodology used in determining the prevalence of asthma plays a very important role since differences in design of different studies can be associated with large differences in observed prevalence rates. The prevalence of asthma worldwide is around 200 million with a mortality of around 0.2 million per year.<sup>2</sup> Though the prevalence is more in the developed countries, the developing countries have a higher total burden of the disease due to differences in population. In India, the estimated burden of asthma is believed to be more than 15 million.<sup>2</sup> There has been a constant increase in asthma prevalence worldwide in the last 2 decades and the same is being observed in India. The population prevalence of asthma reported in different field studies is reported to be quite variable (Table 1)<sup>3-11</sup>. Similarly, different prevalence rates have been reported in many other specific population groups<sup>12-17</sup>.



**Table 1. Prevalence of asthma in adults and children in studies from India**

Region	No.	Age and setting	Method	Prevalence	Salient Features
Mumbai (Chowgule et al, 1998) <sup>3</sup>	2,313	2044 yrs Population based	ECRHS	3.5% by physician diagnosis	9-12% symptom prevalence without diagnosis of asthma
Chandigarh (Jindal et al, 2000) <sup>4</sup>	2,116	>18 yrs Population based	IUATLD based questionnaire Equal in urban and rural	3.9% (M) 1.3% (F)	Questionnaire standardized against physician diagnosis
Chandigarh (Gupta et al, 2001) <sup>5</sup>	9,090	9-20 yrs School based	IUATLD based questionnaire	2.6% (M) 1.9% (F)	Questionnaire standardized against physician diagnosis
Delhi (Chhabra et al, 1999) <sup>6</sup>	18,955	5-17 yrs School based	Questionnaire on wheeze	3.4% (Past wheeze) 11.9% (Current wheeze) 12.8% (M) 10.7% (F)	2.1% (Exercise Induced Asthma) 2.4% (Cold Associated Asthma)
Ludhiana (Singh et al, 2002) <sup>7</sup>	2,275	1-15 yrs Population based	Questionnaire on symptoms of asthma	2.6% (Rural)	Modified ATS criteria used for diagnosis
Lucknow (Awasthi et al, 2004) <sup>8</sup>	6,000	6-7 and 13-14 yrs School based	ISAAC Questionnaire	6.2% and 7.8% (Wheeze) 2.3% and 3.3% (Asthma)	Part of multicentric (ISAAC III) trial
Multicentric (ISAAC Steering Committee, 1998) <sup>9,10</sup>	37,171	6-7 and 13-14 yrs School Based	ISAAC Questionnaire	6.0% (Wheeze) 4.5% (Ever asthma)	Wide variations in different regions worldwide (including within India)
Multicentric (ICMR) (Jindal et al, In print) <sup>11</sup>	73,605	>15 yrs Population based	IUATLD based Questionnaire	2.4% (1.7-3.5% range)	Questionnaire standardized against physician diagnosis

ATS American Thoracic Society, ECRHS European Community Respiratory Health Survey, ICMR Indian Council of Medical Research, ISAAC International Study of Asthma and Allergies in Childhood, IUATLD International Union Against Tuberculosis and Lung Diseases.



## Morbidity and Socioeconomic Aspects

Poorly controlled asthma is associated with significant morbidity and socioeconomic problems such as the absenteeism from school/work, loss of productivity/wages, poor quality of life and economic burden. Poorly controlled asthma is also potentially fatal.

Poor control of asthma is the result of not just an increase in the severity of the disease itself but also because of the modifiable factors such as the inadequate usage of anti-inflammatory therapy (in particular inhaled corticosteroids) both in terms of the timing of initiation and the dosage of therapy. Effective treatment of asthma not only enables the affected person to lead a near normal lifestyle but also benefits the family economically since:

- Primary care is less expensive than the hospital care
- Emergency treatment is more expensive than planned treatment

## Natural History of Asthma

Onset of asthma can occur at any age but children and young adults are the commonly affected age groups. Both sexes are affected almost equally though slight differences in prevalence between males and females have been reported. Unlike what is commonly believed, children do not necessarily 'grow out of asthma' and almost two-third may continue to have symptoms in puberty and adulthood. Even in the remaining one-third who appear to have a clinical remission, there is persistence of lung function abnormalities. In fact, 5-10% of children with 'mild' asthma go on to develop severe asthma later in life.<sup>1</sup> Although asthma cannot be 'cured', clinical episodes can largely be prevented and controlled by proper management. Allergic rhinitis and skin allergy may coexist with or precede the onset of asthma.

## Risk Factors

The exact cause of asthma is not known. It could be partly genetic and partly environmental in origin.<sup>1</sup> Some of the factors which are important either to cause or to produce its clinical manifestations (or both) are listed as under:

### *Host Factors:*

1. Family history of asthma or atopy<sup>3,6,7,11,18</sup>
2. Atopy<sup>3,11</sup>
3. Airway hyper-responsiveness

### *Environmental Factors:*

#### **Indoor allergens:**

- House dust mites<sup>3</sup>
  - Insect allergens
  - Fungi, molds, yeasts



- Pet animal allergens
2. Outdoor allergens:
    - Pollens
    - Fungi, molds, yeasts
  3. Tobacco smoke (active and passive):<sup>5,6,7,11,19-21</sup>  
 Exposures to tobacco smoke lead to increase in severity of asthma, decreased response to treatment and accelerated decline in lung functions.<sup>1</sup>  
  
 The different ways in which tobacco smoke affects asthma are detailed in Table 2
  4. Air pollution (outdoor/indoor) Smoke and fumes especially use of biomass fuels for cooking are risk factors for asthma.<sup>11</sup> Poor ventilation in kitchens may worsen adverse effects of the latter.<sup>22-27</sup>
  5. Occupational exposures

**Table 2.** Role of tobacco smoke in asthma<sup>19</sup>

Active Smoking	Passive Smoking (environmental tobacco smoke exposure)
Increased bronchial responsiveness	Aggravation and occurrence of increased prevalence of respiratory symptoms
Frequent bronchial irritation symptoms	Bronchial hyper-responsiveness in adults
Increased sensitization to occupational agents	Aggravation of asthma symptoms
	Aggravation of acute episodes Precipitation of acute episodes
Association with asthma severity	Risk factor for development of asthma (both children and adults)
Risk factor for asthma?	Exaggerated decline in lung functions Role in development of fixed airway obstruction and chronic obstructive pulmonary disease?

## Triggers<sup>1</sup>

A trigger is defined as a factor or an exposure which precipitates an exacerbation in a stable or previously asymptomatic patient of asthma. Common triggers of asthma are:

1. Respiratory infections (usually viral)
2. Allergens (indoor/outdoor)
3. Air pollution (indoor/outdoor) including smoke and fumes (biomass fuel)
4. Tobacco smoke (active and passive)
5. Drugs Beta-blockers and NSAIDs (paracetamol and nimesulide are safe)
6. Additives and preservatives
7. Cold exposure exercise, psychological or other unaccustomed stress.



Foods are not common triggers of asthma but may occasionally be responsible in some patients. There is also some concern on indoor vapours from different incenses, anti-mosquito coils and repellents acting as triggers in some individuals. But there is no definitely documented evidence on this association.

## Pathogenesis and Pathophysiology<sup>1</sup>

Asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations. Chronic airway inflammation is associated in most cases with injury and repair of the bronchial epithelium, which results in structural and functional changes known as remodeling. Inflammation, remodeling, and altered neural control of the airways are responsible for both recurrent exacerbations of asthma and more permanent airflow obstruction. The major functional abnormality in asthma is the potential to develop excessive airway narrowing. The latter is caused by:

1. Altered smooth muscle behavior
2. Airway wall swelling
3. Parenchymal retractile forces
4. Intraluminal secretions.

Exacerbations are associated with an increase in airway inflammation. Unlike in COPD, respiratory failure in asthma is rare and results from severe airway obstruction, ventilation-perfusion mismatch and respiratory muscle exhaustion.

## Diagnosis

Diagnosis of bronchial asthma is essentially a clinical exercise, supplemented by results of supportive investigations and physiological tests, wherever available. Due to the myriad presentations of the disease, there is no single clinical rule of the thumb to make a positive diagnosis in a patient suspected to have this disease. A combination of information collected from clinical and laboratory parameters is important to make a diagnosis. Due to an overlap of respiratory symptoms between various common pulmonary disorders, it may not always be possible to clearly distinguish asthma from other diseases. Nevertheless, a detailed history and careful physical examination should enable the clinician to arrive at the correct diagnosis in most instances.

Diagnosis of bronchial asthma in any patient can be viewed as a two-step approach. In the first step, a clinician suspects the diagnosis and attempts to exclude common asthma mimics. In the next step, diagnosis is confirmed in equivocal cases based on the laboratory investigations. It is proposed that clinicians at all levels of health care should try to diagnose asthma based on information obtained at the first step (Fig 1). Facilities for laboratory investigations are generally available only at the secondary levels of health care or beyond. Therefore patients, in whom there is a difficulty in making a confident diagnosis, should be referred to those centers for further work-up.

## History

Careful history taking is the most important step in diagnosing asthma. A thorough enquiry should be made into four basic respiratory symptoms generally associated with asthma i.e. breathlessness, wheezing, cough, and chest tightness. Children usually



do not give a history of wheezing and instead a history of 'noisy breathing' should be elicited. Clinicians should remain aware that asthmatics can sometimes present with symptoms other than these four classical symptoms, and that none of these symptoms is specific for diagnosing asthma. A given patient may be entirely asymptomatic at the time of initial evaluation, or may present with a variable combination of one or more of these symptoms. When present, these symptoms typically tend to be variable, intermittent and recurrent. Presence of these symptoms in particular during night or early morning generally indicates the presence of asthma. These symptoms also tend to worsen after exposure to nonspecific triggers such as seasonal or temperature changes, exposure to noxious smells, smoke or other irritants, exercise, drugs or infections, (etc.). Additionally, symptoms suggestive of atopic conditions (such as sneezing, rhinorrhea, blocked nose, itchy eyes, or skin lesions) will support a diagnosis of asthma. Presence of asthma in the first-degree relatives also favors the diagnosis of asthma.

Specific enquiries should also be made regarding the presence of other symptoms that are helpful in ruling out disorders that can mimic asthma. In adults, presence of fever, weight loss, hemoptysis, or chest pain should alert the clinician to an alternative or a coexisting disease such as bronchiectasis, chronic obstructive pulmonary disease (COPD), tuberculosis, ischemic heart disease, left ventricular failure, lung cancer, etc. In children, the failure to thrive, presence of diarrhea, or the onset of symptoms since birth, may be important in identifying coexisting or alternative disease such as parasitic infestation, congenital cardiopulmonary disease or foreign body aspiration. At all levels of health care, patients presenting first time with symptoms of cough and expectoration for more than three weeks, should be evaluated for possible pulmonary tuberculosis through three sputum smear examination for the acid fast bacilli (as per recommendation under the Revised National Tuberculosis Control Programme).

### *Physical examination*

All patients suspected to have asthma should undergo a careful physical examination at the initial visit to the health care provider. Apart from a detailed respiratory evaluation, attention should also be paid to the skin and upper respiratory tract, as these can provide useful information on the atopic status of the individual. Examination of the chest may be entirely normal if patient presents during an asymptomatic phase of his illness. The commonest abnormal finding on chest examination of an asthmatic patient is the presence of rhonchi, which tend to be bilateral, diffuse and polyphonic, and are predominantly heard during expiration. Patients with long standing disease, especially children, may have a hyperinflated chest. Apart from these two findings, respiratory system examination is generally unrewarding in patients with stable disease. During exacerbations, however, one can elicit additional signs, especially if the exacerbation is severe. These patients may have tachypnea, tachycardia, use of accessory muscles of respiration, and cyanosis. Although diffuse rhonchi are well heard in most instances, patients with severe exacerbation may have a 'silent chest' related to severe airflow limitation and air trapping within the lungs.

### *Investigations*

The presence of characteristic symptoms and their pattern, along with findings on physical examination, should be sufficient to suspect a clinical diagnosis of asthma



in most instances at all levels of health care. Investigations are generally required only if the diagnosis of asthma is in doubt or other conditions are suspected to complicate asthma. This generally implies a referral to a secondary health care level. At the secondary health care level, symptoms and signs should be reassessed and further workup initiated in patients in whom it is deemed necessary and clearly indicated.

A battery of simple and widely available investigations should be sufficient to provide important clues to presence of cardiopulmonary diseases other than asthma, as well as comorbid conditions in patients highly suspected to have asthma. A hemogram should be obtained to look for anemia as a cause for respiratory symptoms. A baseline chest radiograph should be obtained. Although transient radiographic abnormalities may sometimes be seen in asthmatics, this investigation is very helpful in diagnosing disorders such as tuberculosis, bronchiectasis, lung cancer, interstitial parenchymal or other pulmonary diseases. An electrocardiogram is useful in diagnosing a cardiac disorder. Sputum should also be examined for acid-fast bacilli, wherever indicated.

### *Pulmonary function testing*

**S**pirometry helps to provide an objective measurement of the presence and severity of airflow limitation. Additionally, demonstration of bronchodilator reversibility on spirometry may be helpful in making a more confident diagnosis of asthma and excluding COPD as a cause of symptoms. Nevertheless, spirometry is not mandatory in the diagnostic workup but should be performed in situations where the clinical data is otherwise equivocal.

During spirometry, forced vital capacity (FVC) and forced expiratory volume in first second (FEV<sub>1</sub>) should be measured using standard guidelines.<sup>28</sup> Because the procedure is effort dependent, performance of the test should be supervised by an experienced technician or a clinician to enable correct interpretation of results. An obstructive defect on spirometry is generally interpreted if the FEV<sub>1</sub>/FVC ratio is reduced (typically to less than 70%).<sup>29</sup> However, the test may yield normal results if performed during asymptomatic periods. Regression equations for FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC ratio are available for use in Indian patients in several geographical settings, and can be used to determine if these values are reduced.<sup>30-35</sup> Patients with more severe disease have a greater reduction in observed values of these parameters.

Additionally, one can also quantify bronchodilator reversibility on spirometry. This involves performance of a baseline spirometry maneuver, followed by inhalation of 200-400 µg of salbutamol, and repetition of spirometry after 15-30 minutes. A greater than 12% relative, plus a greater than 200 mL absolute, increment in either FVC or FEV<sub>1</sub> over the baseline value is considered as being suggestive of bronchodilator reversibility, and strongly favors the diagnosis of bronchial asthma.<sup>28</sup>

Peak expiratory flow (PEF) meters are more widely available and simpler to use than the spirometers. In the absence of spirometry, a reduced PEF can be used as a surrogate to diagnose airflow limitation. But a high degree of variability and lack of reproducibility of PEF make it a weaker instrument than spirometry in this regard<sup>36-38</sup>. Overall, PEF measurements do not correlate well with FEV<sub>1</sub> values, and are not necessarily interchangeable in either diagnosing or staging airflow limitation.<sup>39</sup> A

reduction in PEF should therefore be considered as being highly suggestive, but not diagnostic, of airway obstruction. Similarly, an increase in PEF of 20% or more after bronchodilator administration with at least 60 L/min absolute increment, can be considered as being only a supportive evidence towards presence of bronchodilator reversibility.<sup>40</sup>

## Staging of disease

Once the diagnosis of asthma is made, it is important to categorize the disease based on its severity at time of initial evaluation. This not only helps in optimizing treatment for individual patients, but also helps in a more uniform explanation and understanding of the disease stage. All schemes to classify asthma severity are based on description of arbitrary compartments of symptoms, signs and physiologic parameters derived by consensus. It is desirable that the choice and reporting of various parameters included in any scheme of categorization should be simple, easily obtained, and indicative of common patient perception and activities in a given social and cultural setup. Extrapolation of a complicated system of disease categorization may not be feasible at the primary and secondary levels of health care in India. For successful incorporation into the basic health infrastructure in India, staging of asthma severity should rely on simple clinical criteria easily understood by both patients and clinicians.

Although it is generally advocated that pulmonary function testing should be used to categorize asthma severity, the same may not be feasible at primary and secondary levels of health care due to the limited availability of facilities for spirometry. Measurement of visual analog scale has been employed in a few studies but the results are not always reproducible<sup>41</sup>. Nevertheless, wherever available, results of lung function testing should be used to supplement clinical data in deciding the severity of asthma.

Asthma should be categorized as either mild, moderate and severe based on patient characteristics (Table 3). Clinicians should enquire about the frequency of (a) sleep disturbance associated with asthma-related symptoms, (b) symptoms during the daytime and (c) limitation of activities to which the patient is accustomed. In addition, patient should be asked about the dose and frequency of use of rescue medications. A rescue medication is defined as any oral or inhaled drug used by the patient for short-term relief of asthma-related symptoms. For uniformity and simplicity, requirement of rescue medications should be described in terms of nearly equivalent dose units e.g. 200 µg inhaled salbutamol, 250 µg inhaled terbutaline, 2 mg oral salbutamol, or 2.5 mg oral terbutaline provide similar bronchodilation and may be considered as equivalent dose units. Self-use of oral aminophylline, which is a weak bronchodilator, is not recommended as reliever medication, and should not be considered while calculating dose units of rescue medications required. For children, doses of rescue medications defining each unit are half those for adults. Presence of any of the features should be sufficient to place a patient in that category. When different features are placed in different grades of severity, the patient should be assigned to the most severe grade in which any feature occurs. Wherever facilities for spirometry or PEF estimation are available, their results should supplement the clinical information in deciding severity of asthma (Table 3).



**Table 3:** Categorization of severity of asthma

	Mild	Moderate	Severe
Symptoms disturbing sleep	< Once per week	> Once per week	Daily
Daytime symptoms	< Daily	Daily	Daily
Limitation of accustomed activities	Nil	<1 per week	>1 per week
Use of rescue medication *	<1 dose per day	1-2 doses per day	>2 doses per day
FEV1	Normal	60-80%	<60%
Peak expiratory flow	Normal	60-80%	<60%

A patient should be placed in the highest category of severity based on any one of the clinical features or lung function test.

FEV1 Forced expiratory flow in first second

\* Each rescue medication dose = 200 µg inhaled salbutamol = 500 µg terbutaline = 2 mg oral salbutamol = 2.5 mg oral terbutaline.

## Management of Asthma

Although there is no permanent cure for asthma, the disorder can be adequately controlled with drugs. With treatment, it is quite compatible with a normal life style and span. Underdiagnosis and/or inappropriate therapy remain the major cause of asthma morbidity and mortality. The aims of pharmacological management of asthma are: the control of day and night symptoms (including exercise-related symptoms), prevention of exacerbations, and achievement of normal (or near normal) lung function with minimal side effects. Rather than defining a fixed goal for all patients, it would be better to define the best possible goal for an individual patient since individual patients may have different goals and would like to balance these goals against the side-effects of drugs. In general, the goals as defined by the Global Initiative for Asthma (GINA) would include:

1. Minimal (ideally none) symptoms during day and night.
2. Minimal (ideally none) symptoms during exercise.
3. Minimal need for reliever medications.
4. No exacerbations.
5. No limitation of physical activity.
6. Maintaining pulmonary function as close to normal as possible.
7. Minimal side effects of asthma medications.
8. Prevent development of irreversible airflow obstruction.
9. Prevent asthma-related mortality.

Asthma is an inflammatory disorder, and the main aim of asthma treatment is to decrease inflammation by administration of anti-inflammatory agents and by decreasing exposure to triggers. Drugs used in asthma can be divided into two broad groups i.e. controllers and relievers.

**Controllers** are the drugs taken on a long-term basis to keep asthma under control and generally include drugs with anti-inflammatory properties. At present, inhaled glucocorticoids are the best available controller medications in terms of both efficacy and safety. The controller drugs include (in order of preference): inhaled corticosteroids, long-acting inhaled beta-2 agonists, sustained-release theophyllines, leukotriene modifiers, cromones, long-acting oral beta-2 agonists and oral glucocorticoids.

**Relievers** are the short and rapid acting bronchodilators, which relieve acute symptoms of asthma (like cough, dyspnea and wheeze). These include (in order of preference): short-acting inhaled beta-2 agonists, inhaled anticholinergics, short-acting oral beta-2 agonists and short-acting theophylline.

## Route of drug administration

**D**rugs for asthma can be administered either by the inhaled or the systemic route. The systemic route can be either oral or parenteral (subcutaneous, intravenous). The inhaled route is the preferred route of administration since large concentrations of the drugs can be rapidly delivered with minimal systemic side-effects.<sup>42,43</sup> Inhaled medications used for the treatment of asthma are available as pressurized metered dose inhalers (pMDI), dry powder inhalers (DPI) or as nebulizing solutions. Devices used for the delivery of inhaled drugs in asthma are equally efficacious (Level 1).<sup>44</sup>

When selecting an aerosol delivery device, the following points need to be considered: device/drug availability; clinical setting; patient's ability to use the selected device correctly; device use with multiple medications; convenience in both outpatient and inpatient settings; and physician and patient preference. Patients should be explained the usage of the inhaler device, and the technique should be reassessed regularly.

The major disadvantage of pMDI is the need for 'hand-mouth' coordination; considerable training and skill is required to master the technique. The use of a spacer chamber circumvents the need for this coordination and in fact improves the drug delivery from a pMDI (Level 1).<sup>45</sup> Spacers allow particles to remain suspended for 10-30 seconds after which they can be easily inhaled.<sup>46</sup> Moreover, they decrease oropharyngeal impaction of drug, and thus may decrease the incidence of cough (cold Freon effect) and oropharyngeal candidiasis (Level 1). Similarly, they also decrease the systemic absorption of drug and the risk of systemic side-effects.<sup>47</sup> In fact studies have shown that pMDI with spacers are as effective as nebulizers for the delivery of bronchodilators in the management of acute asthma in adults (Level 1), and are more advantageous in children (Level 2).<sup>47</sup> pMDIs employ chlorofluorocarbon (CFC) propellants which are responsible for depletion of the protective atmospheric ozone layer when released in the environment.

On the other hand, DPI does not utilize CFC propellants, and are more environment friendly. Also, they do not require hand-mouth coordination and are thus easy to use. However, a minimal flow rate is required to inhale from a DPI device, and thus many DPIs cannot be used during an exacerbation. It may also be difficult to store DPIs during humid conditions. Some DPIs deliver pure drug and some mixed with filler (e.g.



lactose). This fact must be remembered while prescribing DPIs and while shifting from pMDIs to DPIs.<sup>48</sup> DPIs are also costlier than pMDIs in the long run.

A common practice is to double the dose of medication while switching from pMDI to DPI. The CFCs in pMDIs are being replaced by hydrofluoroalkanes (HFAs), and the medication insert should be carefully reviewed while prescribing HFA inhalers or shifting from HFAs to CFCs. For bronchodilators, the dose of HFA and CFC inhalers appear to be equal, whereas the dose needs to be halved while shifting from CFC to HFA for some glucocorticoids.<sup>49,50</sup>

## Controller medications

### 1. *Inhaled glucocorticoids*

Inhaled corticosteroids (ICS) are currently the best available controller medication for use in persistent asthma. They have strong anti-inflammatory properties and their continued use also decreases bronchial hyperresponsiveness, improves lung function, improves the quality of life and decreases the frequency and severity of asthma exacerbations.<sup>51-53</sup> Inhaled corticosteroids differ in their potency and bioavailability, and comparisons are difficult because of the plateau effect of their dose-response characteristics. Table 4 shows the equipotent doses of different ICS administered via different inhalation devices for adults and children. It should be remembered that a flattening of dose-response curves for different outcomes (symptoms, lung function, hyperresponsiveness) is seen with a dose of 500 microgram of beclomethasone or its equivalent, and administration of higher doses increases the risk of side-effects without actually increasing the benefits of ICS.<sup>54</sup> However clear evidence does exist between the dose of ICS (quadrupling the dose of ICS) and prevention of severe acute exacerbations of asthma.<sup>44</sup> Addition of long-acting beta-2 agonists, rather than doubling the dose of ICS, therefore increases the efficacy.<sup>55-57</sup> A recent study also showed that a combination of formoterol and budesonide taken as controller therapy and on as-needed basis decreased the risk of asthma exacerbations. There is compelling evidence that addition of a long-acting inhaled  $\beta_2$ -agonist (LABA) to ICS gives better control in terms of reduced symptoms, improved lung function, and reduced exacerbations in patients with mild to moderate persistent asthma.<sup>55,56</sup> In a recent study, a combination of budesonide and formoterol was used both as a controller and a reliever medication.<sup>58</sup> Moreover, commencing with a moderate dose ICS is equivalent to commencing with a high dose ICS and down-titrating. The small benefits of commencing with a high ICS dose are not sufficient to warrant its use when compared to moderate or low dose ICS. However, initial moderate ICS dose appears to be more effective than initial low ICS dose.<sup>59</sup> Also ICS are somewhat more effective when taken twice rather than once daily with little evidence of benefit for dosage frequency more than twice daily. Once the asthma is well controlled, patient may be shifted to once-daily ICS.

The adverse effects of ICS include local oropharyngeal candidiasis and dysphonia. These effects may be prevented by the use of spacer devices,<sup>60</sup> and gargling (and spitting out) with water. All currently available ICS are absorbed from the lung with resultant systemic absorption and systemic side-effects which include easy bruising, osteoporosis, growth retardation in children, hypothalamo-pituitary adrenal axis



suppression, cataracts and glaucoma if taken for long-term in high doses. The adverse reactions also depend on the dose and the potency of the ICS and its systemic bioavailability, which in turn depends on the absorption from the gut, first-pass metabolism in the liver, and the half-life of its systemically absorbed fraction.<sup>61</sup> The systemic effects differ among the various ICS with budesonide and fluticasone having less systemic effects than beclomethasone.<sup>52,61</sup> The risk of systemic effects also depends on the delivery system. With spacers, the systemic bioavailability and the risk of systemic side effects are reduced for most ICS.<sup>62</sup> Moreover, in adults, systemic effects of ICS are not a problem at doses of 800 µg or less (400µg or less, in children) of beclomethasone or equivalent daily, although some patients may be susceptible to systemic effects at lower doses.

Inhaled steroids are the most effective available controller drugs for asthma, and their use in the treatment of persistent asthma should be balanced against the possible risk of systemic effects. The risks of uncontrolled asthma probably outweighs the risk of low incidence of systemic side effects.

## 2. *Systemic glucocorticoids*

Inhaled corticosteroids form the first choice for preventive treatment of asthma. Since they are expensive, and may not be affordable by a large number of patients in resource poor countries, oral prednisolone, which is much cheaper, continues to be in use. This practice however needs to be discouraged. On long term basis, ICS are not only safer but in fact more cost effective than oral corticosteroids. The mechanism of action of systemic glucocorticoids is same as that of ICS, except that they affect more cell types than ICS, and are obviously associated with far more side effects than ICS. In a review, it was found that, in the management of adults with chronic asthma, a daily dose of prednisolone 7.5 mg/day appears to be equivalent to a moderate to high dose of inhaled steroids (300-2000 µg/day).<sup>63</sup> However ICS at all doses were more effective than alternate day oral steroids.<sup>63</sup>

As side effects are common even with low doses of prednisolone, the lowest effective dose should be prescribed if there is no alternative to oral steroids. In the management of severe acute exacerbations, they prevent progression of the exacerbation, decrease the need for emergency department visits or hospitalizations, prevent early relapse after emergency treatment, and reduce the morbidity of the illness.<sup>64</sup> Oral therapy is preferred and is as effective as intravenous hydrocortisone (Level 2).<sup>65,66</sup> Prednisolone 40-60 mg is given daily for 7 to 10 days depending on the severity of exacerbation. When the symptoms have subsided and the lung function has approached the personal best value, the oral steroids can be stopped or tapered, and treatment with ICS continued.

The systemic side effects of long-term systemic glucocorticoids include osteoporosis, hypertension, diabetes mellitus, hypothalamic-pituitary-adrenal axis suppression, cataracts, glaucoma, obesity, cutaneous striae, easy bruisability and muscle weakness. Patients with asthma who are on long-term systemic glucocorticoids in any form should receive preventive treatment for osteoporosis. Adrenal failure may occur when a patient is withdrawn from long-term suppressive doses of oral steroids; therefore, caution and close medical supervision are recommended. One should be



careful when considering the use of systemic glucocorticoids in patients with asthma who also have tuberculosis, parasitic infections, osteoporosis, glaucoma, diabetes, severe depression, or peptic ulcers, and such patients should be referred to a higher level of care.

**Table 4.** Equivalent doses of inhaled corticosteroids (in micrograms/day)

Drug	Low-dose ICS		Medium-dose ICS		High-dose ICS	
	Adults	Children	Adults	Children	Adults	Children
Beclomethasone	200-400	100-200	400-1000	200-400	>1000	>400
Budesonide	200-400	100-200	400-800	200-400	>800	>400
Fluticasone	125-250	50-125	250-500	125-250	>500	>250

Medication inserts for hydrofluoroalkane (HFA) preparations should be carefully reviewed for the correct dosage level. In general, the dose of dry powder inhalers with filler (such as lactose) is double than that of pressurized metered dose inhalers.

### 3 Inhaled long-acting $\beta_2$ agonists

Inhaled long-acting  $\beta_2$  agonists (LABA), which include formoterol and salmeterol, by definition, have duration of action of at least 12 hours (in contrast to short acting  $\beta_2$  agonists which act for 4-6 hours). They cause smooth muscle relaxation, decrease mucosal permeability, enhance mucociliary clearance and decrease the release of inflammatory mediators from mast cells and eosinophils.<sup>67</sup> Their long term use is also associated with some anti-inflammatory effects.<sup>68,69</sup> Experimental, but not clinical, studies have shown that the duration of the bronchoprotective effect, provided by long-acting inhaled  $\beta_2$  agonists, decreases when these medications are used on a regular basis.<sup>70,71</sup>

Salmeterol achieves a prolonged duration of action because of the long aliphatic side chain that increases the lipophilicity of the molecule. The molecule diffuses laterally through the cell membrane to approach the auxiliary binding site (exo-site), a group of highly hydrophobic amino acids within the  $\beta_2$  adrenoceptors. Binding to the exo-site prevents dissociation of salmeterol from the adrenoceptors and allows the active saligenin head to repeatedly engage the active site of the receptor. This mechanism accounts for the long duration, but slow onset of action of salmeterol.<sup>72</sup> Formoterol is moderately lipophilic and is retained in the plasmalemma, and from this depot the molecule diffuses slowly to activate the  $\beta_2$  adrenoceptor over a prolonged period. Also, sufficient drug remains available in the aqueous biophase to allow immediate interaction with the active site of the receptor.<sup>73</sup>

Inhaled LABA should be considered when standard introductory doses of ICS fail to achieve control of asthma before raising the dose of ICS (Level 1). However, long-term treatment with inhaled LABA does not appear to influence the persistent inflammatory changes in asthma, and hence this therapy should **always** be combined with ICS (Level 1).<sup>74,75</sup> Addition of inhaled LABA to a daily regimen of ICS improves symptom scores, decreases nocturnal asthma, improves lung function, decreases the use of SABA,<sup>76,77</sup> and reduces the number of exacerbations.<sup>78,79</sup> As earlier stated, a combination of budesonide and formoterol was used both as controller and reliever medication in a recent study.<sup>57</sup> Moreover, it has been clearly shown in two landmark



studies that adding inhaled LABA to ICS, rather than doubling the dose of ICS is superior in terms of asthma control.<sup>80,81</sup> The efficacy of a combination of inhaled LABA with ICS has prompted the development of fixed dose combination inhalers of LABA and ICS. They are more convenient for patients, increase the patient compliance and also ensure that LABA is always accompanied by ICS. Giving the two drugs together is also usually less expensive than giving them separately.

#### 4. *Oral theophyllines*

Theophylline has been used to treat asthma for many years, but its mechanism of action has long been debated. The precise molecular mechanism by which theophylline exerts its pharmacological activity is not known, although alterations in intracellular calcium mobilization,<sup>82</sup> stimulation of endogenous catecholamine release,<sup>83</sup> prostaglandin antagonism,<sup>84</sup> adenosine receptor antagonism,<sup>85</sup> phosphodiesterase 4 inhibition,<sup>86</sup> increasing histone deacetylase activity,<sup>87</sup> and inhibiting phosphatidylinositol 3-kinase activity<sup>88</sup> have all been proposed. The bronchodilator action is usually seen at higher concentrations (>10mg/mL). At lower concentrations (5-10 µg/mL), theophylline is an immune system modulator, which prevents messengers of inflammation from triggering a cascade leading to bronchospasm. Theophylline also has a range of other pharmacological effects of potential therapeutic value in the treatment of patients with respiratory diseases that occur independently of its bronchodilator actions, including anti-inflammatory and immunomodulatory actions<sup>89,90</sup> and increased respiratory drive.<sup>91</sup> The clinical efficacy of theophylline is equivalent to that of inhaled LABA, although the risk of side effects is much higher with theophyllines.<sup>92</sup>

There is a considerable body of evidence documenting the anti-inflammatory actions of theophylline particularly at doses lower than those considered therapeutic, which may explain the beneficial effects observed with this orally active drug in the treatment of respiratory diseases like asthma. Recent studies have suggested a new mechanism to explain the pharmacological activity of this drug. Now that theophylline at low doses has been shown to be effective in asthma control in both adults and children, it may be used in patients with milder disease and as an add-on therapy to low or high doses of ICS when further asthma control is needed (Level 2).<sup>93-97</sup> Moreover, it is cheaper than the newer agents making it attractive for use in resource poor countries, and continues to be used as an ancillary treatment to steroids and beta agonists.

When given as a sustained-release preparation, it has a long duration of action and is thus useful in the control of nocturnal symptoms that persist despite the regular treatment with anti-inflammatory therapy. However sustained release preparations are far more expensive than ordinary preparations of theophylline, and thus one may use multiple doses of theophylline in control of asthma as no study has shown superiority of sustained release preparations over the ordinary ones.

Side effects are usually seen with doses exceeding 10 mg/kg body weight, and include gastrointestinal symptoms (nausea and vomiting). Higher doses in children and adults can result in seizures and even death, and these events may or may not be preceded by evidence of central nervous system stimulation. Cardiopulmonary effects include tachycardia and arrhythmias.



## 5. *Leukotriene-receptor antagonists (LTRA)*

The LTRA include drugs like montelukast, pranlukast, and zafirlukast, and block the cysteinyl LT1 receptors and thus the biological action of leukotrienes C4, D4, and E4. The role of LTRA is generally restricted to mild asthma as a substitute to ICS, or in severe asthma as an add-on therapy. The efficacy however varies from patient to patient. In mild to moderate asthma, ICS have been proven to be superior to LTRA (Level 1).<sup>98,99</sup> The addition of inhaled LABA is superior to LTRA in asthmatic adults inadequately controlled on low doses of ICS for preventing exacerbations requiring systemic steroids, for improving lung function, symptoms, and use of rescue short acting  $\beta_2$  agonists (Level 1).<sup>100</sup> Also, addition of LTRAs as add-on therapy to ICS, brings about only modest improvement in lung function. Although addition of LTRAs to ICS appears comparable to increasing the dose of inhaled steroids, it is again inferior to the addition of inhaled LABA as add-on agent. Addition of LTRAs is associated with modest glucocorticoid-sparing effect with superior asthma control after glucocorticoid tapering.<sup>100,101</sup> Thus, at present the role of LTRAs in the routine management of asthma is limited.

## 6 *Cromones*

Cromones (sodium cromoglycate and nedocromil) act by inhibiting IgE mediated mast cell release of mediators, and probably also act on other inflammatory cells to prevent mediator release. Although they are effective in mild asthma, they are inferior to ICS in asthma control. Hence like LTRAs, their role in asthma is also limited (Level 2).<sup>102</sup>

## 7. *Oral long-acting $\beta_2$ agonists*

Oral LABA include slow release forms of salbutamol and terbutaline, and bambuterol (a prodrug of terbutaline). They are bronchodilators and act by relaxing bronchial smooth muscle, decreasing vascular permeability, enhancing mucociliary clearance and probably also by modulating release of mediators from mast cells and basophils. They have minimal, if any, anti-inflammatory action, and are thus adjuncts to ICS. Their role in asthma therapy is similar to inhaled LABA except that they may be associated with significantly more side effects. In two studies, bambuterol was found to be as effective as salmeterol in controlling asthma in patients not controlled on low doses of ICS alone, although it was associated with more frequent side effects.<sup>103,104</sup>

# Reliever medications

## 1. *Rapid-acting inhaled $\beta_2$ agonists*

Rapid acting inhaled  $\beta_2$  agonists provide rapid relief of symptoms and include salbutamol and terbutaline. They are the best available medications for the rapid control of asthma. Formoterol is a new inhaled LABA, which also has a rapid onset of action. The mechanism of action is similar to that of inhaled LABA. Also they are comparable in efficacy to oral  $\beta_2$  agonists except that they are associated with lesser side effects. There have been fears that the regular use of inhaled  $\beta_2$  agonists could have a detrimental effect on airway diameter and asthma control<sup>105-107</sup>. Such concerns were



alleviated by placebo-controlled trials which showed no worsening of expiratory airflow or asthma control.<sup>108,109</sup> However, regular treatment with rapid acting inhaled  $\beta_2$ -agonists has largely been superseded by the use of inhaled LABA.

Retrospective studies have suggested that polymorphism at the 16th amino acid residue of the  $\beta_2$ -adrenergic receptor is associated with adverse effects of  $\beta_2$ -agonist use in asthmatic patients.<sup>110,111</sup> In one prospective study, patients were stratified by genotype, and it was found that those with the Arg/Arg genotype improved when  $\beta_2$ -agonist therapy was withdrawn and replaced with ipratropium bromide, whereas in those with the Gly/Gly genotype, they were better with regular  $\beta_2$ -agonist therapy than when it was withdrawn. These improvements were seen in morning PEF, other physiological indices, symptoms, and rescue medication use.<sup>112</sup> There is at least some evidence that the levo isomer of salbutamol is better in efficacy, and has a better side effect profile than the racemic mixture.<sup>113-117</sup>

The use of rapid acting inhaled  $\beta_2$ -agonists as required for symptom control is recommended and provides a good indication of the need for further therapy. An increasing requirement for rapid-acting inhaled  $\beta_2$ -agonists is a warning of deteriorating asthma control, and indicates the need to institute or intensify regular anti-inflammatory therapy. Similarly, failure to achieve a quick and sustained response to  $\beta_2$ -agonist treatment during an exacerbation indicates the need for short-term treatment with oral glucocorticoids.

Formoterol has a well-documented role as controller therapy in asthma, and some studies have identified its role as a reliever therapy. But, it is more expensive than salbutamol, and its superiority over salbutamol has not been demonstrated.

## 2 *Oral glucocorticoids*

See section on controller therapy

## 3. *Inhaled Anticholinergics*

Inhaled anticholinergics (ipratropium) competitively inhibit the muscarinic receptors, and thus block the effect of acetylcholine, which is released from cholinergic nerve endings. When compared to inhaled bronchodilators, they have a slower onset of action (30-60 minutes), and are less effective than inhaled  $\beta_2$ -agonists. The benefit of ipratropium in chronic asthma is not clear (Level 2),<sup>118</sup> although it is occasionally used in some patients who develop significant side effects, such as tachycardia, tremors or arrhythmia, with the use of inhaled  $\beta_2$ -agonists, or as recently suggested in some genetic polymorphisms of asthma.<sup>112</sup> On the contrary, there is a clear role of anticholinergics in acute asthma. There is considerable evidence that anticholinergic agents are not effective for the treatment of mild and moderate exacerbations. However, the use of multiple doses of anticholinergics in addition to  $\beta_2$ -agonists is safe, improves lung function and decreases hospital admissions by 30 to 60%. The use of single-dose protocols of inhaled ipratropium with  $\beta_2$ -agonist treatment causes a modest improvement in pulmonary function without reduction in hospital admissions; in adults, the data showed a similar increase in pulmonary function with an approximately 35% reduction in the hospital admission rate (Level 2).<sup>119,120</sup>



#### 4. Oral short acting $\beta_2$ agonists

They are bronchodilators and act by relaxing bronchial smooth muscle. They are used in patients who cannot use inhaled medications. Although they are as efficacious as inhaled rapid acting  $\beta_2$  agonists, they have a high propensity for side effects like tremors, tachycardia, irritability etc.

There are quite a few short reports from India on use of different drugs for asthma.<sup>121-140</sup> Most of them represent useful experience of a particular centre with a known anti-asthma drug.

#### Stage-wise control of asthma

The presence of one of the features of severity is sufficient to place a patient in that category. A patient should be assigned to the most severe grade in which any feature occurs (Table 3). The characteristics noted in the table are general and may overlap. Furthermore, an individual's classification may change over time. Moreover, patients at any level of severity can have mild, moderate, or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms. Also, progression to the next step is indicated when adequate control is not achieved with the current treatment. Importantly, compliance of medications should be assured before moving to the next step. The medications at each step of asthma are indicated in Table 5. Dosages of some commonly used drugs are separately listed (Table 6). Some important points for managing patients with asthma are:

1. If the patient has day-time symptoms < 1/week and night-time symptoms 2/month, then the patient can be managed with reliever medications alone. Use of reliever medications more than 1/week indicates the need for long-term controller medications.
2. In addition to daily controller therapy, reliever medications should be taken as needed to prevent symptoms but not more than 3/day. If required more than 3/day, visit to health-care facility is needed.
3. Requirement of reliever medications more than 2/week indicates poor control and reassessment of treatment at health-care facility.
4. Once the goals for asthma have been achieved and maintained for at least three months, a gradual reduction of maintenance therapy is required i.e. 25% reduction in dose of controller medications every three months.
5. Once the patient is off all asthma medications, the patient should be followed up every six months and a lung function test (spirometry with bronchodilator reversibility) performed every one to two years.
6. The dose of DPI has to be doubled in case of DPI having lactose as carrier, whereas it is the same in case of 'pure' DPI.
7. A pediatrician or a physician with particular interest in treating asthma in children should ideally be consulted before starting treatment in children.



## Mild asthma

The preferred medication for treatment of mild asthma is low dose ICS (Tables 4-6). Low dose ICS treatment is superior to all other medications including theophyllines, cromones and LTRAs (Level 1). Patients with daytime symptoms quantified as less than 1 episode/week and night-time symptoms less than three per month can be managed with reliever medications alone. However, the use of reliever medications more than once a week indicates the need for long-term controller medications. The alternate drugs for mild asthma are listed in Table 5.

**Table 5.** Management of asthma in different stages

Stage	Daily controller medications	Other treatment options
Mild	Low-dose ICS*	Sustained-release theophylline or Cromones
Moderate	Moderate dose ICS + inhaled LABA** and/or LTRA	-Moderate dose ICS + either sustained-release theophylline or LTRA or oral LABA - High-dose ICS
Severe	High dose ICS + inhaled LABA plus one or more of the following if needed: sustained-release theophylline, leukotriene modifiers, oral LABA, oral glucocorticoid.	

\* Inhaled LABA optional; \*\* Optional in children

ICS Inhaled corticosteroids; LABA Long-acting beta-2 agonist; LTRA Leukotriene receptor antagonists

## Moderate asthma

The treatment of choice for moderate asthma is a combination of moderate dose ICS plus inhaled LABA (Level 1). Alternative choices include moderate dose ICS with either sustained-release theophylline or leukotriene modifier or oral LABA or high-dose ICS.

## Severe asthma:

The aim in severe asthma is to achieve the best possible results with minimal side effects. The treatment approach is multifaceted (Table 4). Primary therapy includes high dose ICS plus inhaled LABA taken at least twice a day. In this regard, a dose of ICS taken four times a day is better than a dose taken twice a day.<sup>141</sup>

## Reduction of maintenance therapy

Once the control of asthma is achieved and maintained for at least 3 months, one can start the process of reduction of maintenance therapy. This should be individualized from patient to patient. In general, a reduction in the maintenance dose of at least 25% should be done once asthma is well controlled for at least 3 months. Importantly, one should always perform lung function tests prior to reduction of maintenance therapy, as there is a wide miscorrelation between the symptoms reported by the patient and lung function tests. During this period, patient should be closely monitored for any



**Table 6.** Dosages of different anti-asthma drugs

	Adult	Children
<b>Long-acting beta-2 agonists</b>		
pMDI/DPI		
Salmeterol	50-100 µg/day	50-100 µg/day (>5 years)
Formoterol	12-24 µg/day	12-24 µg/day (>5 years)
Oral		
Bambuterol	10-20 mg/day	-
<b>Systemic steroids</b>		
Prednisolone		
For acute exacerbations	40-60 mg/day for 7-10 days in single or divided doses	1-2 mg/kg/day for 3-10 days in single or divided doses
For long-term control	Administer lowest dose required to control symptoms Preferably single a.m. dose; alternate day if possible	Administer lowest dose required to control symptoms Preferably single a.m. dose; alternate day if possible
Intravenous Hydrocortisone		
For acute exacerbations	100 mg stat and 50 mg q6 hourly	4-8 mg/kg/day
<b>Theophyllines</b>	Starting dose 10mg/kg/day (max. 300 mg/day); usual maximum 600-800 mg/day	Starting dose 10mg/kg/day; usual maximum dose age 1 year- 16 mg/kg/day age < 1 year- [0.2 (age in weeks) + 5] mg/kg/day
<b>Leukotriene modifiers</b>		
Montelukast	10 mg/day	2-5 years 4 mg/day 6-14 years 5 mg/day
<b>Short-acting beta-2 agonists</b>		
Salbutamol		
pMDI/DPI	100-200 µg/dose	100 µg/dose
Nebulized	2.5 to 5 mg q 4-6 hourly	0.05 mg/kg/dose, (min. 1.25 mg, max. 2.5 mg) q 4-6 hourly
Oral	2-8 mg q 6-8 hourly	1-4 mg q 6-8 hourly
Intravenous	3-20 µg/minute adjusted to bronchospasm and heart rate	0.1-0.2 µg/kg/minute adjusted to bronchospasm and heart rate
Subcutaneous	8 µg/kg	Not recommended
Terbutaline		
pMDI/DPI	250 µg/dose	250 µg/dose
Nebulized	10 mg q 4-6 hourly	0.3 mg/kg/dose, (max. 10 mg/dose) q 4-6 hourly
Oral	2.5 mg q 6-8 hourly	0.25µg/kg/dose q 6-8 hourly (Not recommended below 2 y of age)
Intravenous/Subcutaneous/Intramuscular	0.25-0.5 mg q 4-6 hourly	10µg/kg/dose (max. 300µg)
<b>Anticholinergic drugs</b>		
Ipratropium		
pMDI/DPI	20 µg/dose	20 µg/dose
Nebulized	0.25 mg q 4-6 hourly	0.25 mg q 4-6 hourly
Tiotropium (pMDI/DPI)	12 µg/day	

*DPI Dry powder inhaler; pMDI Pressurized metered dose inhaler*

worsening of symptoms or lung function tests. Reduction of therapy should follow the reverse order of initiation of therapy, i.e. the drugs added last should be withdrawn first.

In patients who have symptoms during a particular season only, treatment may be started just before the expected onset of the season or upon the first symptoms, and can be stopped at the end of the season when symptoms or lung function abnormalities are no longer present.

## Exacerbations of asthma

**E**xacerbations of asthma are characterized by the worsening of symptoms with increase in dyspnea, cough and wheeze. These can range from mild to life threatening exacerbations. There is also a decline in lung function, which can be quantitated with measurements of PEF or FEV<sub>1</sub>. The exacerbations are categorized as severe or non-severe.

*Severe exacerbation of asthma are characterized by*

- Increase in dyspnea, with patient unable to complete one sentence in one breath (In children: interrupted feeding, agitation)
- Respiratory rate > 30/minute
- Heart rate > 120/minute
- Use of accessory muscles of respiration
- Pulsus paradoxus > 25 mm Hg
- PEF < 60% personal best or < 100L/minute (in adults)

In case of children, the normal respiratory and pulse rates are different from adults (Table 7), and values exceeding these normal limits should be considered abnormal.

**Table 7.** Normal respiratory and pulse rates in awake children

<i>Age</i>	<i>Normal respiratory rate</i>
< 2 months	< 60/min
2-12 months	< 50/min
1-5 years	< 40/min
6-8 years	< 30/min
<i>Age</i>	<i>Normal pulse rate</i>
2-12 months	< 160/min
1-2 years	< 120/min
2-8 years	< 110/min

These guidelines are meant only to guide the physician, and not to replace the clinical judgment, which is an art of medicine. If a physician feels that the patient is sick and needs admission, he can manage the episode as severe. Patient with severe exacerbations should be managed at the health care facility, and if the episode does not remit within two hours, should be referred to a tertiary health care centre. Patient not meeting the criteria for severe exacerbations are categorized as non-severe, and can be managed, in most instances, on an outpatient basis.



## Management of non-severe exacerbations

Patients with non-severe exacerbations can be usually managed on an outpatient basis, with repeated administration of rapid-acting inhaled  $\beta_2$ -agonists (2 puffs every 20 minutes for the first hour), which is the best and most cost-effective method to achieve rapid reversal of airflow limitation. In this regard, pMDI with holding chambers have outcomes that are almost equivalent to nebulizer delivery.<sup>45</sup> Oral glucocorticoids (1 mg/kg prednisolone daily for 7-10 days) should be used in all but the mildest exacerbations as they significantly reduce the number of relapses and decreases beta-agonist use without an apparent increase in side effects.<sup>141</sup> A rough guide is to use oral steroids if response to the rapid acting inhaled  $\beta_2$ -agonist alone is not prompt or sustained (PEF > 80 % personal best) after 1 hour. However, no additional medication is necessary if the rapid acting inhaled  $\beta_2$ -agonist produces a complete response (PEF returns to greater than 80 percent of personal best), and the response lasts for at least 3 to 4 hours.

## Management of severe exacerbations

Severe exacerbations of asthma can be life-threatening, and should be managed on an emergency basis. Certain points which are important in management of acute severe asthma, are summarized below:

1. A hand-held chamber is as effective as a nebulizer for the delivery of drugs used in acute asthma.<sup>45</sup>
2. The use of intravenous aminophylline does not result in any additional bronchodilation compared to inhaled beta-agonists. But, the frequency of adverse effects is higher with aminophylline. Thus it should be used only if patient is not able to cooperate for any form of inhaled therapy, or if inhaled therapy is ineffective.<sup>142</sup>
3. A combination of ipratropium plus salbutamol is better than salbutamol alone in the management of severe exacerbations.<sup>119,120</sup>
4. The use of continuous beta-agonists (defined as truly continuous aerosol delivery of beta-agonist medication using a large-volume nebulizer or sufficiently frequent nebulisations that medication delivery was effectively continuous i.e. 1 nebulisation every 15 minutes or 4 / hour) in patients with severe acute asthma improves their pulmonary functions and reduces hospitalization in patients who present to the emergency department.<sup>143</sup>
5. Glucocorticoids are the mainstay of therapy. The use of corticosteroids within 1 hour of presentation to an emergency department significantly reduces the need for hospital admission in patients with acute asthma.<sup>144</sup> There is no advantage of parenteral over oral glucocorticoids except in some exceptional circumstances. There is also no advantage of a particular preparation of glucocorticoids in acute asthma, and a maximum dose of 40-60 mg/day of prednisolone is effective in most cases.<sup>145</sup> Prednisolone (40-60 mg daily) is given and continued for at least 7-10 days or until recovery.
6. Inhaled corticosteroids have no added benefit when used in addition to oral



steroids.<sup>146</sup>

7. Slow intravenous aminophylline infusion is helpful, but toxicity is common, especially in patients who are already on maintenance oral theophylline therapy. It should therefore be used with caution.
8. There is no evidence to support the use of intravenous beta2-agonists in patients with acute severe asthma. Where and when possible, these drugs should be given by inhalation.<sup>147</sup>
9. In patients with acute severe asthma who have not had a good initial response, administration of a single dose of intravenous magnesium sulfate (2 gm over 20 minutes) improves pulmonary function when used as an adjunct to standard therapy.<sup>148</sup> The treatment should however be used with great caution under proper monitoring.
10. There is no role of routine use of antibiotics except if patient has fever, leucocytosis, purulent sputum or radiographic infiltrates suggestive of an infection.
11. A proper written discharge should be given, specifically mentioning the drugs, their dosages, frequency and requirement for follow-up visits. Patient must be clearly informed and explained the importance of continuation of therapy.

The **stepwise management of acute severe asthma** is described below.

- **Hour 1-** (i) Oxygen administration, (ii) hydration (intravenous fluids), (iii) upto four doses of inhaled salbutamol with ipratropium, (iv) intravenous hydrocortisone (100 mg) or oral prednisolone (40-60 mg).
- **Hour 2-** (i) Four more doses of inhaled salbutamol with ipratropium, (ii) intravenous aminophylline, (iii) intravenous magnesium sulfate 2 gm, (iv) subcutaneous terbutaline/ adrenaline 0.3-0.5 mg (0.01 mg/kg- child) q 3 doses,

*Patient not responding within 2 hr of treatment or deteriorating-* **REFER IMMEDIATELY**

## Patient referral

**G**eneral indications for referral of a patient with suspected/established asthma to an advanced center include:

1. Diagnosis unclear or in doubt.
2. Atypical signs or symptoms (significant expectoration > 60 mL/day, hemoptysis, monophonic wheeze).
3. Failure to respond to treatment for over 1 month.
4. Other conditions complicating asthma or its diagnosis necessitating additional work-up.
5. Severe persistent asthma.
6. Life threatening asthma (cyanosis, mental obtundation).
7. Acute severe asthma not responding within two hours of intensive therapy.



## Prevention of Asthma

Although pharmacological intervention to treat established asthma is highly effective in controlling symptoms and improving quality of life, every attention should be paid to the measures to prevent this chronic disease. As for all other diseases, three levels of prevention have been described for asthma.<sup>1</sup>

### *Primary prevention*

This is introduced before the occurrence of exposure to risk factors known to be associated with a disease. The goal is to prevent the onset of disease in susceptible individuals. This is not yet possible in asthma. Increasing evidence indicates that allergic sensitization is the most common precursor to the development of asthma. Since sensitization can occur antenatally<sup>149,150</sup>. Primary prevention is likely to focus on perinatal interventions in future.

Prescription of a food-allergen-avoidance diet to a high-risk woman during pregnancy is unlikely to reduce the risk of an atopic infant and may have an adverse effect on maternal and/or fetal nutrition.<sup>151</sup> Breast-feeding does not appear to have any protective action in reducing asthma symptoms.<sup>152</sup> There are no measures applied prenatally, that can be recommended for primary prevention.<sup>1</sup>

Allergen avoidance during infancy has focused on feeding practices and avoidance of cow's milk protein, eggs, fish, and nuts. There is evidence that early dietary manipulation may create a risk of impaired growth and hence are not recommended in resource poor countries. In the future primary prevention to strategies applied postnatally will include immunomodulation using immunoadjuvants, DNA vaccines, antigens, cytokines (IL-12 or IFN gamma) and oral administration of relevant gut microorganisms. Currently, all these strategies remain investigational.<sup>1</sup>

Aeroallergen avoidance has been promoted in order to avoid sensitization, and a correlation between the level of allergen exposure in infants and sensitization to allergens has been shown in some studies.<sup>153</sup> Recent studies show that an early contact with cats and dogs may in fact prevent allergy more effectively than avoidance of these pets.<sup>154,155</sup>

These controversial results have led to the suggestion that, in the future, primary prevention strategies will be designed to redirect the newborn infant's immune response toward a T-helper 1(Th1), nonallergic response. Efforts to establish a proper Th1/Th2 balance might be achieved by high-dose exposure to relevant allergens and cytokines Interleukin IL-12.<sup>120</sup> These approaches have gained considerable credibility in relation to the "hygiene hypothesis," which has identified associations between early microbial experience and subsequent reduced allergic disease.<sup>157</sup> Repeated viral infections other than lower respiratory tract infections early in life may reduce the risk of developing asthma up to school age.<sup>158</sup>

Studies of lung function immediately after birth have shown that smoking during pregnancy has an influence on lung development,<sup>159</sup> and such infants are four times more likely to develop wheezing illnesses in the first year of life.<sup>160</sup> Smoking during pregnancy has an impact on lung development, which increases the frequency of



nonallergic wheezing illnesses in infancy. Environmental tobacco smoke exposure both prenatally and postnatally has an adverse influence on lung development and wheezing illnesses in infants and should be strongly discouraged.

### *Secondary prevention*

This is employed after primary sensitization to allergen has occurred. The aim is to prevent the establishment of chronic disease in people who are susceptible and who have early signs of the disease. This approach is currently being investigated in asthma. Secondary prevention of asthma is likely to focus on the first year or two of life.

Occupational asthma studies have shown that early cessation of exposure to an offending allergen, is more likely to lead to a total resolution of symptoms than if the exposure continues.

The greatest benefit of Allergen Specific Immunotherapy (SIT) has occurred when administered to patients with allergic rhinitis that has been unresponsive to conventional pharmacotherapy or specific environmental control or in circumstances in which patients do not wish to use medications for prolonged periods of time. Several studies have demonstrated that SIT using extracts of common aeroallergens may have some benefit in patients with allergic asthma. Limited experience on immunotherapy is also available from India<sup>161-163</sup>. A Cochrane review that examined 54 randomized controlled trials of SIT in asthma confirmed the efficacy of this therapy in asthma.<sup>164</sup> The clinically useful outcomes which were used included: decreased symptom scores and medication requirements, as well as improved allergen-specific and nonspecific airway hyperresponsiveness. Despite this evidence, a number of questions remain to be addressed regarding the role of SIT in asthma therapy. The relatively modest effect of SIT in asthma especially compared to the use of inhaled glucocorticoids, the risk of adverse effects and the inconvenience of the prolonged course of injection therapy, SIT should be considered only after strict environmental-avoidance and pharmacologic intervention, including inhaled glucocorticoids, have failed to control a patient's asthma.<sup>165</sup> There are no studies that compare SIT with pharmacological therapy for asthma. SIT is not recommended at primary and secondary levels and wherever indicated should be carried out only at tertiary care centers.

### *Tertiary prevention*

This involves avoidance of allergens and nonspecific triggers when asthma is established. The goal is to prevent exacerbations or illnesses that would otherwise occur on exposure to identified allergens or irritants. Tertiary prevention should be introduced when the first signs of asthma have occurred.

The occurrence and severity of asthma symptoms are related to environmental allergens.<sup>166</sup> The indoor allergens are domestic mites, animal allergens, cockroach allergens, and fungi. Some of the measures to control the growth of dust mites are: i. use impermeable covers for mattresses; ii. Washing of all bedding in the hot water (55-60° C) weekly; iii. replace carpets with linoleum or wood flooring; iv. minimize upholstered furniture and replace with leather furniture; v. replace curtains with blinds or easily washable curtains.<sup>1</sup>



Removal of pet animals from the home is not always possible but even after permanent removal of the animal it can be many months before allergen levels decrease. In patients who are allergic to cats or dogs and persist in keeping their pet, exposure-reduction measures may be considered.<sup>1</sup> However, the clinical effectiveness of these measures remains unproven and there are many conflicting data on this subject.

To minimize fungal allergen indoors, maintaining a low humidity (less than 50 percent) is important. Air conditioners and dehumidifiers reduce humidity and filter large fungal spores, lowering the mold and yeast count indoors, although their benefit in reducing asthma symptoms is controversial. In tropical and subtropical climates, fungi may grow on the walls of the house due to water seepage and humidity and can be prevented by regular cleaning. Outdoor allergens such as pollens and molds are almost impossible to completely avoid. Closing windows and doors, remaining indoors when pollen and mold counts are high, and using air conditioners, may reduce exposure during peak seasons.<sup>1</sup>

Another important measure is to avoid exposure to passive and active smoking. Passive smoking increases the risk of allergic sensitization in children.<sup>167</sup> It also increases the frequency and severity of symptoms in asthmatic subjects. Active cigarette smoking reduces treatment efficacy of inhaled and systemic glucocorticoids.<sup>168</sup> Smoking cessation needs to be vigorously encouraged in all asthmatics.

The major air pollutants are respirable particles, nitric oxide, nitrogen oxides, carbon monoxide, carbon dioxide, and sulfur dioxide, produced by combustion of cooking fuel, vehicular emission and industrial exhausts. Studies have shown that exposure to combustion of all types of fuels have detrimental effects on lung function, liquid petroleum gas, fossil fuels and biomass fuel produce similar effects. Preventing exposure to air pollution and preservation of lung function is best achieved by effective ventilation of the kitchen.<sup>22</sup>

A large number of substances have been identified as occupational allergens that can cause asthma. Once a patient has been sensitized, the level of exposure necessary to induce symptoms may be extremely low, and resulting exacerbations may become increasingly severe. Ideally, the patient should be advised a change of occupation if feasible. Those cases where this is not feasible, measures to reduce occupational exposure (occupational hygiene) have been successful in reducing asthma symptoms.<sup>1</sup> These measures may be used along with conventional pharmacotherapy to obtain relief from symptomatic episodes.

Food allergy, as an exacerbating factor for asthma, is uncommon and occurs primarily in young children. Sulfites found in processed foods, alcoholic beverages such as beer and wines have often been implicated in causing severe asthma exacerbations and occasional deaths. Proof for the involvement of other dietary substances, tartrazine, benzoate, and monosodium glutamate is lacking. Confirmation of food allergy requires double blind challenge before making specific dietary restrictions.

Some medications can exacerbate asthma. Aspirin and other nonsteroidal anti-inflammatory agents can cause severe exacerbations and should be avoided in patients



with a history of hypersensitivity to these agents. Beta-blocker drugs including cardio-selective beta-blockers may exacerbate bronchospasm and should not be used by patients with asthma. Other drugs such as the opiates, iodinated contrast agents and nitrofurantoin have been found to precipitate asthma and should be avoided.<sup>1</sup>

There are two other components for asthma control, i.e. patient (and family) education, and lifestyle modification. The two together constitute the crucial arm of all plans to both manage and prevent asthma.

## Patient Education

The aim of patient and family education is to develop an ongoing partnership with the patient, and to provide suitable information and training so that the patient can keep well and adjust treatment according to a medication plan developed in advance with the physician. Health education should include simple information about the types of treatment available, the rationale for the inhaled drugs, different inhaler devices and techniques. Patients should be advised about preventive measures including avoidance of allergen exposure and air pollution. Patients should be given adequate opportunity to express their expectations. The patient and his family should be encouraged to make note of any questions that may arise and should be clarified on subsequent visits on a continual basis to gain their confidence and improve compliance<sup>169</sup>. Efficacy of patient education and parental awareness has been also shown in reports from India<sup>170-173</sup>.

During the patient education sessions, the concept of peak expiratory flow (PEF) monitoring should be considered as appropriate to the patient's age, education, and socioeconomic status. Patients with moderate to severe disease should receive training to measure and record PEF.<sup>1</sup> Patient should record and interpret their PEF. This helps to monitor the effectiveness of therapy and gives early warning of deterioration of asthma, so self-management plan can be promptly implemented. A recent systematic review by the Cochrane Airways group compared self-management plan with usual care and showed significant benefits in the intervention groups in terms of reduced morbidity and reduced use of health services. The effects were greatest where the intervention involved the issuing of written self-management action plans.<sup>174</sup>

Significant improvement in knowledge, symptom score and emotion score was found at 1 year with the use of a self care manual (SCM) irrespective of demographics and disease severity<sup>133</sup>. Subjects with better education, higher income, urban residence and longer disease duration had better knowledge of the disease. There was a significant reduction in number of severe attacks, emergency visits, need for injections in both groups, which was more marked in SCM group.<sup>175</sup>

Awareness of the disease is an important aspect of asthma management. It is not only the patient and their family members but also the general practitioners at the peripheral care levels who need to continuously keep themselves updated on asthma<sup>176-178</sup>.

## Lifestyle Modifications

All asthmatic individuals should adopt a healthy life style and should receive adequate guidance by their physician in this regard. This should include regular



balanced diet and avoidance of obesity. The restriction of physical exercise is not advisable. Rather asthmatics should be encouraged to participate in exercises. Short acting beta-2 agonists should be used prior to anticipated exercise in a patient with exercise-induced asthma to alleviate symptoms.

## Asthma in special situations

### *Pregnancy*

Asthma control is essential for the well being of both the mother and the fetus. Most drugs used to control asthma are safe in pregnancy. LTRAs are better avoided. Similarly, systemic glucocorticoids should be avoided, especially during the first and second trimesters. But severe exacerbations should be managed aggressively with systemic steroids, wherever indicated. Caution should be exercised during the use of PGF2 alpha during labor, as it may precipitate asthma.

### *Surgery*

Minor surgery (without general anesthesia) can be performed without any modification of asthma treatment. For major surgery, asthma control and lung function should be optimized prior to surgery to minimize the postoperative morbidity and mortality. If preoperative FEV<sub>1</sub> < 80% predicted, short course of oral steroid is advised to improve airflow obstruction prior to surgery. Systemic steroids should be used in patients who have history of steroid use or acute severe asthma in the previous 6 months and those with moderate and severe persistent asthma. The recommended schedule is to administer Hydrocortisone 100mg IV 8 hourly and tapered after 24 hours of surgery, as per clinical status.

### *Allergic rhinitis, Nasal polyps and Sinusitis*

Allergic rhinitis, nasal polyps and sinusitis must be treated as per standard treatment guidelines as the ongoing upper airway inflammation may worsen asthma. The traditional practices of using indigenous nasal drops containing petroleum products, oils and ghee must be discouraged for the fear of lipid pneumonia.

### *Gastroesophageal reflux disease (GERD)*

Prevalence of GERD is three times more in asthma patients than the general population<sup>179,180</sup>. This should be suspected in difficult to control asthma cases especially with nocturnal symptoms. Diagnosis is based on simultaneous measurements of esophageal pH and lung function tests and is not widely available. Symptomatic patients should be adequately treated and a subgroup of asthma patients do benefit from anti reflux treatment.

### *Cardiovascular diseases*

Short acting beta 2 agonists (SABA) and theophylline use in patients with coronary artery disease can be associated with arrhythmias and must be carefully used. Beta-blockers (even topical preparations) and aspirin can precipitate acute attack and must be used with great care in asthmatic subjects. One must be very careful while using theophylline along with macrolide and fluoroquinolone antibiotics (cytochrome enzyme inhibitors) since their interactions may lead to fatal cardiac arrhythmias.

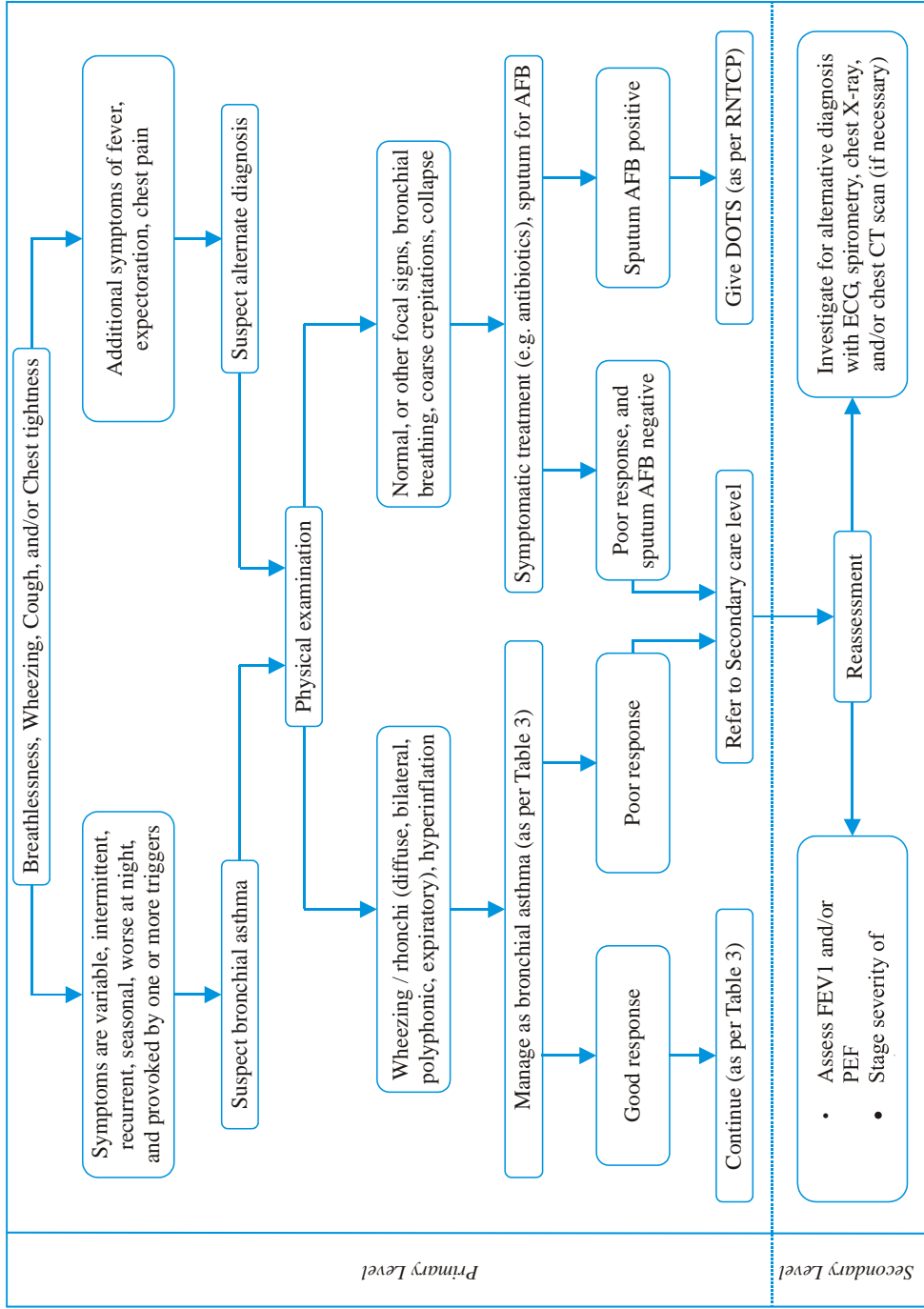


## Alternative Systems of Medicine

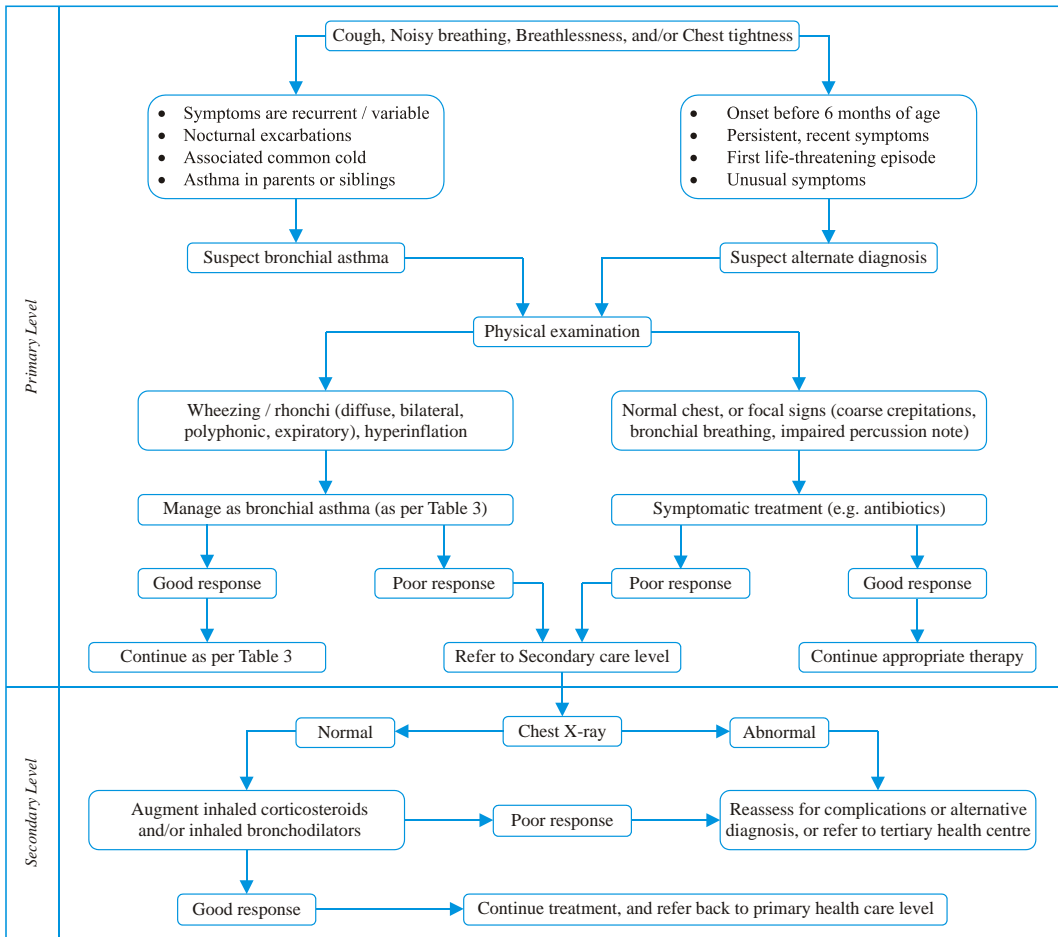
Although alternative and complimentary medicines are popular with some patients, they have not yet been compared with standard therapy, and their effectiveness is unproven. In some countries, traditional methods of healing are a primary way of treatment. These traditional therapies are not validated by conventional standards, and it is difficult to evaluate traditional healing methods in randomized controlled trials. At present there is no evidence to show any beneficial effects of any other alternate system of Medicine<sup>1</sup> on asthma control as compared to standard pharmacotherapy.

Ayurvedic medicine, an ancient Indian science includes herbal medications, meditation and Yoga. A yogic breathing exercise technique, Pranayama, was studied in a double-blind controlled trial. There was small but significant reduction in histamine reactivity in the Pranayama group after two weeks<sup>181</sup>. Many of these remedies especially the use of foods such as the fresh green vegetables and fruits, yogic and relaxation exercises improve the quality of life and can be incorporated as healthy life style measures. Further studies are required before these can be incorporated as routine management of asthma.





**Figure 1 :** Algorithm for diagnosis and management of bronchial asthma in adults at primary and secondary levels of health care. AFB Acid-fast bacilli, DOTS Directly-observed treatment (short course), ECG Electrocardiogram, FEV1 Forced expiratory flow in first second, PEF Peak expiratory flow, RNTCP Revised National Tuberculosis Control Programme



**Figure 2 :** Algorithm for diagnosis and management of bronchial asthma in children at primary and secondary levels of health care.



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**Appendix:** Levels of evidence used for classification in this document

<b>Description</b>	
<b>Level 1</b>	Randomized controlled trials with statistically significant results
<b>Level 2</b>	Randomized controlled trials with substantial threats to validity (small numbers, inadequate blinding, weak methodology)
<b>Level 3</b>	Observational study with a concurrent control group
<b>Level 4</b>	Observational study with a historical control group; consensus opinion
<b>Level 5</b>	Bench study, animal study, case series



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## Errata

1. Please read the sign  $\hat{a}$  as  $\hat{2}$  on pages 11, 13, 15-17 and 21.
2. Read the dosages of inhaled salmeterol, formoterol, salbutamol, terbutaline, ipratropium and tiotropium in  $\mu\text{g}/\text{day}$  (and not  $\text{g}/\text{day}$ ) in Table 6.



