CHAPTER 1

INTRODUCTION

1.1 ASTHMA - AN OVERVIEW

World Health Organization (WHO) recognizes asthma as a disease of major public health importance. In 1992, WHO joined with the National Heart, Lung and Blood Institute (NHLBI) to form Global Initiative for Asthma (GINA) to implement an optimal strategy for asthma management and prevention [1].

GINA program defined asthma as a chronic persistent inflammatory disease of the airways characterized by recurrent attacks of breathlessness and wheezing due to chronic airway inflammation, reversible airway obstruction and hyperresponsiveness to a variety of specific and nonspecific stimuli [2]. The severity and frequency of asthma vary from person to person. In an individual, they may occur from hour to hour and day to day. Failure to recognize and avoid triggers may result in an asthma attack, respiratory distress and even death [3].

Asthma is a complex disease condition in which the risk factors are not absolutely understood [4]. However, the risk factors for asthma can be divided as follows

- Causal factors - eg. Host factors such as genetic, gender and obesity, which influence the development of the disease [5, 6] and
- Triggers - eg. Environmental factors such as, allergens, infections, occupational irritants, indoor or outdoor air pollution, tobacco smoking, diet, drugs, strong emotions, etc., which affect the expression of asthma [7, 8].
1.2 STATEMENT OF PROBLEM

Asthma has affected 300 million people worldwide and 255,000 people died of asthma in 2005 [9]. Each decade prevalence of asthma increases by 50% [10, 11]. The disease is predicted to affect an additional 100 million population by 2025 [12]. Asthma is not only a public health problem for developed countries, but also to developing countries like India, China, etc. At least one person dies from asthma in Ireland every week. In India, estimates indicate a prevalence of 15 - 20 million asthmatics [13]. Worldwide, the economic costs associated with asthma are estimated to exceed those of tuberculosis and HIV/AIDS combined. The number of disability-adjusted life years (DALYs) lost due to asthma worldwide is estimated to be 15 million per year, which is similar to that for diabetes, liver cirrhosis and schizophrenia. It is estimated that asthma accounts for one in every 250 deaths worldwide [14]. Many of these deaths are preventable and are due to suboptimal long-term medical care and delay in obtaining help during the final attack.

1.3 PATHOPHYSIOLOGY OF ASTHMA

Asthma is an inflammatory disorder of the airways, which involves several inflammatory cells and multiple mediators that result in characteristic pathophysiological changes. Inflammatory cells like mast cells, eosinophils and Th2 cells are released during inflammatory process of asthma. These cells release mediators such as chemokine, cysteinyl leukotrienes, cytokines, histamine, nitric oxide and prostaglandin D-2 (PGD$_2$), which contribute to the symptoms of asthma. Structural cells of the airways also produce inflammatory mediators and contribute to the persistence of inflammation in various ways [15].

As the disease becomes more persistent and progressive, other factors such as edema, inflammation, mucus hypersecretion and the formation of mucus plugs, as well as structural changes, including hypertrophy and hyperplasia of the airway smooth muscle further limit the bronchial air flow [16]. Mucus hypersecretion results
from increased numbers of goblet cells in the airway epithelium and increased size of submucosal glands. These latter changes may not respond to usual treatment [17].

Bronchial hyper responsiveness (BHR) is an exaggerated bronchoconstriction response to a wide variety of stimuli. It is a major feature of asthma. The mechanisms influencing BHR are inflammation, dysfunctional neuroregulation and structural changes. Inflammation appears to be a major factor in determining the degree of BHR. Treatment directed towards reducing the inflammation can reduce BHR and improve asthma control [18].

In some patients, permanent structural changes may occur in the airway, which leads to progressive loss of lung function. It could be neither prevented nor reversible by current therapy. Airway remodeling leads to structural changes such as thickening of the sub-basement membrane, sub-epithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, mucous gland hyperplasia and hypersecretion [19, 20].

1.4 CLASSIFICATION OF ASTHMA

The National Asthma Education and Prevention Program (NAEPP) have classified asthma into intermittent, mild persistent, moderate persistent and severe persistent [21]. This classification is based on severity, which is determined by symptoms and lung function. Asthma severity is the intrinsic intensity of the disease process and useful at initial visit before prescribing controller therapy.
Table 1.1 Classification of asthma based on severity

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Intermittent persistent</th>
<th>Mild persistent</th>
<th>Moderate persistent</th>
<th>Severe persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day-time symptoms</td>
<td>Less than 2 days a week</td>
<td>More than 2 days a week, but do not occur daily</td>
<td>Daily</td>
<td>Throughout each day</td>
</tr>
<tr>
<td>Nocturnal symptoms</td>
<td>Less than 2 days per month</td>
<td>More than 2 per month, but not weekly</td>
<td>More than 1 times a week, but do not happen daily</td>
<td>Often and sometimes every night</td>
</tr>
<tr>
<td>Lung function</td>
<td>&gt;80%</td>
<td>&gt;80%</td>
<td>60 - 80%</td>
<td>≤60%</td>
</tr>
<tr>
<td>Normal activities</td>
<td>Do not interfere</td>
<td>Attacks may affect daily activity</td>
<td>Attacks may affect daily activity or sleep</td>
<td>Severely limit daily physical activities</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>Infrequent</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

From the above classification of asthma, it is very difficult to predict the treatment required for patients and the patient’s response to treatment. Therefore, GINA classified asthma not only by the severity of its underlying disease but also its responsiveness to therapy.

According to GINA’s level of control, asthma is classified as controlled, partially controlled and uncontrolled as illustrated in table 1.2. Asthma control is the degree to which the goals of therapy are met and are used at every subsequent visit to determine response to therapy [2]. However, classification of asthma by severity is used for research purposes and for initial assessment of a patient.
Table 1.2 Classification of asthma based on level of control

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controlled (All of the following)</th>
<th>Partly controlled (Any measure present in a week)</th>
<th>Uncontrolled</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Day-time symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Twice or less per week</td>
<td>More than twice per week</td>
<td>Three or more features of partly controlled asthma in a week</td>
</tr>
<tr>
<td></td>
<td>Nocturnal symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung function</td>
<td>Normal</td>
<td>&lt;80 % predicted</td>
</tr>
<tr>
<td></td>
<td>Normal activities</td>
<td></td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Exacerbations</td>
<td>None</td>
<td>One or more per year</td>
</tr>
</tbody>
</table>

1.5 DIAGNOSIS OF ASTHMA

Under diagnosis, delayed diagnosis and misdiagnosis of asthma are common problems, that needs to be addressed, as early detection and treatment of asthma may improve the long term prognosis of the disease [21].

1.5.1 Symptoms

A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough and chest tightness. Episodic symptoms after an incidental allergen exposure, seasonal variability of symptoms and a positive family history of asthma and atopic disease are also helpful diagnostic guides [22].

1.5.2 Physical Examination

The most usual abnormal physical finding is wheezing on auscultation, a finding that confirms the presence of airflow limitation. However, in some people with asthma, wheezing may be absent or only detected when the person exhales.
forcibly, even in the presence of significant airflow limitation. Occasionally, in severe asthma exacerbations, wheezing may be absent owing to severely reduced airflow and ventilation [23]. However, patients in this state usually have other physical signs reflecting the exacerbation and its severity, such as cyanosis, drowsiness, difficulty in speaking, tachycardia, hyper inflated chest, use of accessory muscles and intercostal recession [24].

1.5.3 Measurements of lung function

Generally, patients with asthma have poor recognition of their symptoms and poor perception of symptom severity, especially if asthma is long standing. Measurement of lung function provides an assessment of the severity of airflow limitation, its reversibility and its variability and provides confirmation of the diagnosis of asthma [25]. Spirometry is the most recommended method of measuring airflow limitation and reversibility.

In spirometer, the % predicted value of Forced Expiratory Volume in 1 second (FEV₁) is obtained. The degree of reversibility in FEV₁, which indicates a diagnosis of asthma is generally accepted as ≥ 12% (or ≥ 200 ml) from the pre-bronchodilator value [26]. Spirometry is reproducible, but effort dependent. Therefore, proper instructions to perform the forced expiratory maneuver must be given to patients and the highest value of three recordings to be taken.

Spirometry requires maximal effort from the patient. The volume and flow parameters measured are defined in terms of maximal effort and maximal exhaled volume. The performance of spirometry, while seated upright in a chair is preferable to standing as this is the most stable position should the patient experience dizziness during the test. The seated position is also preferable for patients with urinary incontinence who may otherwise limit the expiratory effort.
The key steps are urging the patient to:

- Breathe in fully (the lungs must be absolutely full)
- Seal the lips around the mouthpiece and immediately (while it is not mandatory to use nose clips to prevent loss of measured volume through the nose, their use is sometimes of benefit)
- Exhale the air out as fast and as far as possible until the lungs are completely empty
- Repeat the test until three acceptable and reproducible results are obtained
- The highest FEV₁ should be reported, even if they come from separate blows

1.5.4 Measurement of allergic status

Measurement of allergic status, such as IgE and skin allergy tests can help in identifying the risk factors that cause asthma symptoms in individual patients. Measurement of specific IgE in serum does not exceed the reliability of results from skin tests and is more expensive. Skin tests with allergens represent the primary diagnostic tool in determining allergic status. They are simple and rapid to perform, have a low cost and high sensitivity [27].

1.5.5 Measurement of airway responsiveness

For patients with normal spirometry but consistent asthma symptoms, measurements of airway responsiveness to methacholine, histamine, mannitol or exercise challenge may help establish a diagnosis of asthma [28, 29].

1.5.6 Coding

It is recommended that every patient is coded for asthma once a diagnosis has been confirmed. Asthma patients are coded under ICD-10 as J45 and ICPC as R96 [27].
1.6 MANAGEMENT OF ASTHMA

The primary goal of asthma treatment specified by the GINA guideline [2] is

- To prevent troublesome symptoms
- To maintain near normal lung function
- To maintain normal activities like exercise and other physical activities
- To prevent recurrent exacerbations of asthma
- To minimize the need for an emergency visit to the hospital
- To provide optimal pharmacotherapy with minimal or no adverse effects
- To provide patient care and satisfy the patient and their family

1.6.1 Pharmacological management

Stepwise approach is designed to individualize the therapy for asthma patients (Figure 1.1). The drugs used for the treatment of bronchial asthma are broadly classified as controllers and relievers [2, 3, 23, 30-34].

1.6.1.1 Controllers

Controllers or Preventers are the medications which are taken on a long term basis to keep the asthma under control. They include corticosteroids (inhaled or systemic), long acting β₂-agonists, leukotriene antagonists, sustained release theophylline, anti IgE, oral anti-allergic compounds, mast cell stabilizers.

a) Corticosteroids

The anti-inflammatory action of corticosteroids (glucocorticosteroids) is mediated through the glucocorticoid receptors. It may act either directly to inhibit cytokine induced production of proinflammatory proteins or indirectly by acting as a transcription factor, binding to specific glucocorticoid response elements, that leads to an increase or decrease in specific messenger ribonucleic acid production. This indirect action results in a wide range of suppressing effect on the inflammatory
system and production of anti-inflammatory mediators and proteins such as lipotrotein-1 and β2 adrenergic receptors.

- **Inhaled corticosteroids (ICS)**

  The use of ICS has revolutionized the management of asthma. It has reduced asthma morbidity and improved the health status. ICS is the most effective anti-inflammatory medications for the treatment of persistent asthma.

  eg. Beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone and riamcinolone.

- **Systemic corticosteroids**

  They are used in case of severe uncontrolled asthma. Its long term use beyond two weeks is limited because of its adverse effects. Oral preparation is preferred over parenteral therapy for long term use.

  eg. Methylprednisolone, triamcinolone, prednisolone and prednisone.

b) **Long acting β2 - agonists (LABA)**

  It includes formoterol and salmeterol. LABA are the preferred and most effective bronchodilators for the treatment of bronchial asthma. It has a rapid onset of action. It directly acts on airway smooth muscle by stimulating β2 receptor which in turn increases cyclic AMP level and produces antagonism to bronchoconstriction. It should never be used as monotherapy and it is most effective when used in combination with ICS. The fixed dose combination has been developed to achieve the clinical control.

  eg. Budesonide plus formoterol and fluticasone plus salmeterol.
c) **Leukotriene antagonists (LTA)**

They are non-steroid class of oral medication. LTA besides being effective in preventing bronchoconstriction due to various triggers, they also affect eosinophil reflux, micro vascular permeability proliferation of airway smooth muscle cells in chronic severe asthma, mucous secretion, mucciliary transport and interaction with nerves. They reduce bronchoconstriction induced by several natural triggers of asthma, including exercise, cold air, allergen and aspirin. It can be used as an add-on therapy with ICS in patients with persistent asthmas. This may reduce the dose of ICS.

eg. Montelukast, pranlukast and zafirlukast.
d) **Sustained release theophylline (SR-T)**

Theophylline is a xanthine derivative drug used in asthma over the past six decades. Because of its narrow therapeutic index, it warrants routine monitoring of its levels in the blood. SR-T can be used as an add-on therapy with ICS. Doxofylline, a new methyl xanthine derivative, is shown to have similar efficacy with significantly less side effects. It works by relaxing the muscle around the airways in the lungs, which allow them to widen and makes breathing easier. It also improves contraction of the diaphragm and decreases the response of the airways to irritants.

e) **Mast cell stabilizers**

Sodium cromoglycate and nedocromil sodium are the best non-steroidal anti-inflammatory drug, available currently for asthma. They control the symptoms and BHR and reduces the number of acute exacerbations with an acceptable safety profile. They prevent the activation of many inflammatory cells, particularly mast cells, eosinophils and epithelial cells, but not lymphocytes. These drugs are particularly effective in children with milder asthma. Their use in adults is limited.

f) **Anti IgE**

IgE plays a central role in the initiation and propagation of the inflammatory cascade and thus the allergic response. Omalizumab is a recombinant humanized monoclonal antibody directed against IgE. The usual dose of omalizumab depends on patient’s serum IgE level. This treatment has been shown to reduce the number of exacerbations in patients with severe asthma and may improve asthma control. However, the treatment is very expensive and is only suitable for highly selected patients who are not controlled on maximal doses of ICS.

g) **Oral anti allergic compounds**

Oral anti allergic compounds include ozagrel (available in India), tazanolast, pemirolast, repirinast, tranilast, celatrodast, amelexanox and ibudilast. Antiasthmatic effects of these drugs appear to be limited.
1.6.1.2 Relievers

Relievers are the medications used on as needed basis, which acts quickly to reverse bronchoconstriction and relieve asthma symptoms. They include short acting β-2 agonists and anticholinergics.

a) Short acting β₂ - agonists (SABA)

They are called reliever or rescue medicines since they stop asthma symptoms very quickly by opening the airways. SABA are the best medicines for treating sudden or new asthma symptoms. They are also the drug of choice for relieving bronchospasm during acute exacerbations of asthma and for the pre-treatment of exercise induced bronchoconstriction. Failure to achieve a quick response to SABA during exacerbation mandates medical attention.

e.g. Salbutamol, terbutaline, fenoterol, reproterol, pirbuterol.

b) Anticholinergic agents

There are two anticholinergic bronchodilators currently available, namely ipratropium bromide and tiotropium bromide. Ipratropium is used 4 times per day, whereas tiotropium is used only once per day as its action lasts for 24 hours. These are not quick relief medications, but can be added to the bronchodilator effect for certain asthmatics with difficult-to-control symptoms. They are routinely used in the treatment of chronic obstructive pulmonary disease (COPD).

1.6.2 Novel mediator antagonists

Blocking the receptors or synthesis of inflammatory mediators is a logical approach to the development of new treatments for asthma and COPD. Since many mediators are involved, blocking a single mediator is unlikely to be very effective, unless it plays a unique and key role in the disease process. Several specific mediator antagonists have been found to be ineffective in asthma, including antagonists or inhibitors of thromboxane, platelet activating factor, bradykinin and tachykinins.
a) **CRT\textsubscript{h}2 antagonists**

Chemo-attractant Receptor-homologous molecule expressed on T\textsubscript{h}2 cells (CRT\textsubscript{h}2) is a G-protein coupled receptor expressed by T\textsubscript{h}2 lymphocytes, eosinophils and basophils. The receptor mediates the activation and chemotaxis of these cell types in response to PGD\textsubscript{2}. PGD\textsubscript{2} is released through mast cell degranulation in the initial phase of IgE-mediated reactions. This process is also thought to occur at the site of inflammation [35]. Several CRT\textsubscript{h}2 antagonists are now in development for asthma with promising initial results.

b) **Endothelin antagonists**

Endothelin - 1 is a potent vasoconstrictor. Its use results in increased pulmonary vascular resistance. It also has proliferative effects on vascular smooth muscle cells. Endothelin antagonists are approved for the treatment of pulmonary hypertension and might be useful in treating the structural changes that occur in asthma and COPD [36], but so far they have not been tested.

c) **Inducible nitric oxide synthase inhibitors**

Nitric oxide (NO) production is increased in asthma and COPD as a result of increased inducible NO synthase expression in the airways. NO and oxidative stress generates proxy nitrite anion, leading to altered cell function. Several selective inducible NO synthase inhibitors are now in development and one of these, L-N6 -(1-Imminoethyl) Lysine (L-NIL), gave a profound and long-lasting reduction in the concentrations of NO in exhaled breath [37]. However, in certain study, inducible NO synthase inhibitor was found to be ineffective in asthma.

d) **Cytokine modifiers**

Cytokines play a critical role in perpetuating and amplifying the inflammation in asthma and COPD, suggesting that anti-cytokines may have therapeutic potential. However, no significant improvement in FEV\textsubscript{1} was observed with antagonisms of IL-4 (Pitrakinra), IL-5 (Reslizumab) and IL-13 (Lebrikizumab) in asthma patients [38,
TNF-α plays a key role in amplifying airway inflammation, through the activation of NF-κB and other transcription factors. In COPD and severe asthma patients, anti-TNF-α blocking antibodies have been ineffective, at the expense of increasing infections and malignancies [40].

e) **Chemokine receptor antagonists**

Chemokines play a major role in the recruitment of inflammatory cells, such as eosinophils, neutrophils, macrophages and lymphocytes into the lungs. An oral CCR1/CCR2 antagonist (navarixin) is currently in clinical trials in patients with severe asthma [41, 42]. CCR4 antagonist (mogamulizumab) results in prolonged cytotoxic effects on Th2 cells and reduced lung inflammation in animal models. This antibody is now in early clinical trials for asthma. Antagonism of CCR3 and CCR8 are ineffective in a primate model of asthma [43].

1.6.3 **Newer anti-inflammatory drugs**

a) **Phosphodiesterase inhibitors**

*Phosphodiesterase* (PDE) inhibitors are a drug that blocks one or more of the five sub-types of the enzyme PDE, thereby preventing the inactivation of cAMP in inflammatory cells and reduces cell activation and release of inflammatory mediators. PDE4 is the major enzyme found in inflammatory and immune cells. PDE4 inhibitors like roflumilast have proven its potential as anti-inflammatory drugs, especially in asthma, COPD and rhinitis [44].

b) **Mitogen activated protein kinase inhibitors**

There are three major *mitogen activated protein kinase* (MAPK) pathways and these pathways are involved in chronic inflammation. The p38 *MAP kinase* inhibitors such as SB203580 and RWJ67657 inhibit the synthesis of many inflammatory cytokines and chemokines and therefore, they are in the process of development for the treatment of asthma and COPD [45].
1.6.4 **Novel classes of bronchodilators**

Several once daily β₂-agonists (ultra LABAs) are in clinical trial, that include indacaterol, carmoterol, vilanterol and olodaterol. For asthma patients, these ultra LABAs should be available only with a corticosteroid in a fixed dose combination. Currently, fluticasone furoate plus vilanterol and mometasone plus indacaterol are in clinical trial for the management of asthma as once-daily combination inhalers [46].

1.6.5 **Mast cell inhibitors**

Stem cell factor is a key regulator of mast cell survival in the airways and acts through the receptor c-Kit on mast cells. Plasma concentrations of stem cell factor are increased in patients with severe asthma. Blockade of stem cell factor or c-Kit is effective in animal models of asthma, suggesting that this pathway might be a good target for new asthma therapies [47]. Masitinib is a potent tyrosine kinase inhibitor that blocks c-Kit (as well as platelet-derived growth factor receptors) and provides some symptomatic benefit in patients with severe asthma. More selective c-Kit inhibitors are in development [48].

1.6.6 **Non-pharmacological management**

Non Pharmacological methods are not substitutes for recommended pharmacological therapy. The effect of non-pharmacological management of asthma is not well established and it requires more number of evidence based well controlled intervention studies [28].

a) **Allergen avoidance**: Avoidance of known allergic triggers can improve symptoms, reduce medication use and decrease bronchial hyper responsiveness [29, 30]. However, studies pertaining to allergen avoidance have failed to demonstrate beneficial effects.

b) **Dietary manipulation**: Low magnesium intake has been associated with high prevalence of asthma. Supplementation of diet with the omega 3 fatty acids might reduce the inflammation associated with asthma [31].
c) Environmental factors: Series of the study states that, air pollution and tobacco smoke may provoke acute asthma attacks or aggravate existing chronic asthma.

d) Patients with acute severe asthma should receive supplemental oxygen therapy by mask or nasal cannulae titrated to maintain SaO2 normal.

1.6.7 Immunotherapy in asthma

Use of specific immunotherapy in the treatment of asthma is still controversial. Immunotherapy should not be regarded as an alternative to established forms of preventive therapy. Numerous studies have been conducted to explore the role of immunotherapy in asthma [49]. The comparison was difficult because of the inherent problems of trials involving asthma, different allergen extract and dosage regimens. However, meta-analysis concluded that immunotherapy is a treatment of option in highly selected patients with allergic asthma [50].

1.6.8 Alternative and complementary therapies

It is common to find patients with asthma, seeking medications from alternative systems of medicine. Qualitative studies indicate that patients use such therapies because of dissatisfaction with conventional medicine, perceived harmful effects of conventional treatments, desire for a more holistic approach and greater philosophical congruence with complementary therapies. Prevalence of use of complementary therapy for asthma varies widely from 6 to 70% [51]. Such treatments include acupuncture, homeopathy, fish therapy, other herbal therapy, including ayurvedic drugs, ionizers and spiritual healing which are tried by many but have not stood the test of controlled clinical trials.