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An Overview and Update on Asthma and its Management

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Asthma has been declared as a disease of major public health importance by the World Health Organization (WHO). An optimal strategy for asthma management and prevention was implemented in 1992 by the Global Initiative for Asthma (GINA) which was constituted by WHO and the National Heart, Lungs and Blood Institute (NHLBI). Asthma has affected 300 million people worldwide and 255,000 people died of asthma in 2005. Each decade prevalence of asthma increases by 50%. The disease is predicted to affect an additional 100 million population by 2025. The present article deals with the detailed review of pathophysiology, classification, diagnosis and management of asthma.

Key words: Asthma, WHO, NHLBI, GINA

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INTRODUCTION

Global Initiative for Asthma (GINA) program defined asthma as a chronic persistent inflammatory disease of the airways, which is characterized by recurrent attacks of breathlessness and wheezing due to chronic airway inflammation, reversible airway obstruction and hyper responsiveness to a variety of specific and nonspecific stimuli (Fanta, 2009; GINA., 2014). The severity and frequency of asthma are varying from person to person. In an individual, it 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 (Rai *et al*., 2007).

Since, asthma is a complex disease condition, the risk factors are not absolutely understood (Aggarwal *et al*., 2006). However, the risk factors for asthma can be divided as causal factors (Eg. Host factors such as genetic, gender and obesity, which influence the development of the disease) (Ober, 2005; Gilmour *et al*., 2006) 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) (Busse and Lemanske, 2001; Eder *et al*., 2006). The present article deals with the detailed review of pathophysiology, classification, diagnosis and management of asthma.

STATEMENT OF PROBLEM

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 (To *et al*., 2002; Braman, 2006; Smith, 2000; Masoli *et al*., 2004; Jindal, 2007). Worldwide, the economic costs associated with asthma are estimated to exceed as that of tuberculosis, HIV and AIDS. 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 (Bousquet *et al*., 2005). These deaths are due to poor medical care for prolonged periods and delay in obtaining help during the final attack.

PATHOPHYSIOLOGY

Being an inflammatory disorder of the airways, asthma involves several inflammatory cells and multiple mediators that result in characteristic pathophysiological changes. Inflammatory cells like mast cells, eosinophils and T_h2 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. Inflammatory mediators were also produced by structural cells of the airways and they contribute to the perseverance of inflammation in other ways (Rajanandh *et al*., 2015).

As the disease becomes more progressive and persistent, other factors such as edema, mucus hyper-secretion, inflammation, mucus plugs and structural changes such as hypertrophy and hyperplasia of the airway smooth muscle further limit the bronchial air flow (Hirst *et al*., 2004). Due to augmentation of goblet cells in the airway epithelium, it leads to mucus hyper-secretion and increased size of sub-mucosal glands. These latter changes are usually not responded with usual treatment (Cohn *et al*., 2004).

Bronchial Hyper Responsiveness (BHR) is an exaggerated broncho-constriction response to a wide variety of stimuli. It is a major feature of asthma. The mechanisms influencing BHR are dysfunctional neuro-regulation, structural changes and inflammation. Among these factors, inflammation appears to be a major one in determining the degree of BHR. Treatment directed towards reducing the inflammation can reduce BHR and improve asthma control (Akbari *et al*., 2006). 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, airway smooth muscle hyperplasia and hypertrophy, sub-epithelial fibrosis, mucous gland hyperplasia and hyper-secretion (Kuipers and Lambrecht, 2004; Peters-Golden, 2004).

CLASSIFICATION

Asthma is classified into intermittent and persistent type. Under persistent, further it is divided into mild persistent, moderate persistent and severe persistent by the National Asthma Education and Prevention Program (NAEPP) (Rajanandh *et al*., 2014a). This classification is determined by symptoms and lung function i.e., based on severity. However, this is useful at initial visit before prescribing controller therapy.

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 and 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 (GINA., 2014). However, classification of asthma by severity is used for research purposes and for initial assessment of a patient.

Table 1: Classification of asthma based on severity

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

Table 2: Classification of asthma based on level of control

Characteristics	Controlled (All of the following)	Partly controlled (Any measure present in a week)	Uncontrolled
Day-time symptoms	Twice or less per week	More than twice per week	Three or more features of partly controlled asthma in a week
Nocturnal symptoms	None	Any	
Lung function	Normal	<80 % predicted	
Normal activities	None	Any	
Exacerbations	None	One or more per year	Once in a week

DIAGNOSIS

As early diagnosis and management of asthma may improve the long term prognosis of the disease, special attention is required in under diagnosis, delayed diagnosis and misdiagnosis of asthma (Rajanandh *et al*., 2014b).

Symptoms: Wheezing, cough, breathlessness and chest tightness are the prime symptoms of asthma. Episodic symptoms after an incidental exposure of allergen, positive family history and seasonal variability of symptoms are also the useful marker in the diagnosis of asthma (Kim and Rhee, 2010).

Physical examination: The most typical abnormal physical finding in asthma is wheezing on auscultation, which confirms the presence of airway limitation. Seldom, in severe asthma exacerbations, wheezing may not be present due to severe obstruction in airflow and ventilation (Shaw *et al*., 2005). However, other physical findings such as drowsiness, cyanosis, tachycardia, difficulty in speaking, hyper inflated chest, intercostal recession and use of accessory muscles reflect the severity of exacerbation (Holgate and Polosa, 2006).

Measurements of lung function: Asthma patients in general have poor recognition of their symptoms and perception of symptom severity. Pulmonary function assessment measures the severity of airflow limitation, its reversibility and variability and thereby confirms the diagnosis of asthma (Rajanandh *et al*., 2014c).

Spirometry is the most recommended tool to measure the airflow limitation and reversibility. It measures the % predicted Forced Expiratory Volume in 1 sec (FEV_1). The ≥12% (or ≥200 mL) improvement in the reversibility of % predicted FEV_1 conforms the presence of asthma (Ilango *et al*., 2013).

Measurement of allergic status: Allergic status in asthma can be identified by measuring IgE and skin allergy tests. However, measurement of specific IgE in serum is more expensive, whereas skin allergy test is simple, rapid to perform, low cost and high sensitivity. Skin tests with allergens represent the primary diagnostic tool in determining allergic status (Kaplan *et al*., 2009).

Measurement of airway responsiveness: Measurement of airway responsiveness is useful for patients with normal spirometer value, but consistent asthma symptoms. Measurements of airway responsiveness to histamine, methacholine, mannitol or exercise challenge may help in diagnosing of asthma (Dipiro, 2005; Arshad *et al*., 2003).

Coding: Once diagnosis is confirmed, every patient should be coded for asthma. Asthma patients are coded under ICPC as R96 and ICD-10 as J45 (Nageswari *et al*., 2014).

MANAGEMENT

Pharmacological management: Stepwise approach is designed to individualize the therapy for asthma patients (Fig. 1). The drugs used for the treatment of bronchial asthma are broadly classified as controllers and relievers (Suda *et al*., 2009; Chapman, 2003; Barnes, 2003).

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 β_2-agonists, leukotriene antagonists, sustained release theophylline, anti IgE, oral anti-allergic compounds and mast cell stabilizers.

Corticosteroids: The anti-inflammatory action of corticosteroids is mediated through the glucocorticoid receptors. It may act by directly inhibiting the production of proinflammatory cytokines and thereby suppress the production of anti-inflammatory mediators and proteins such as lipoprotein-1 and β_2 adrenergic receptors.

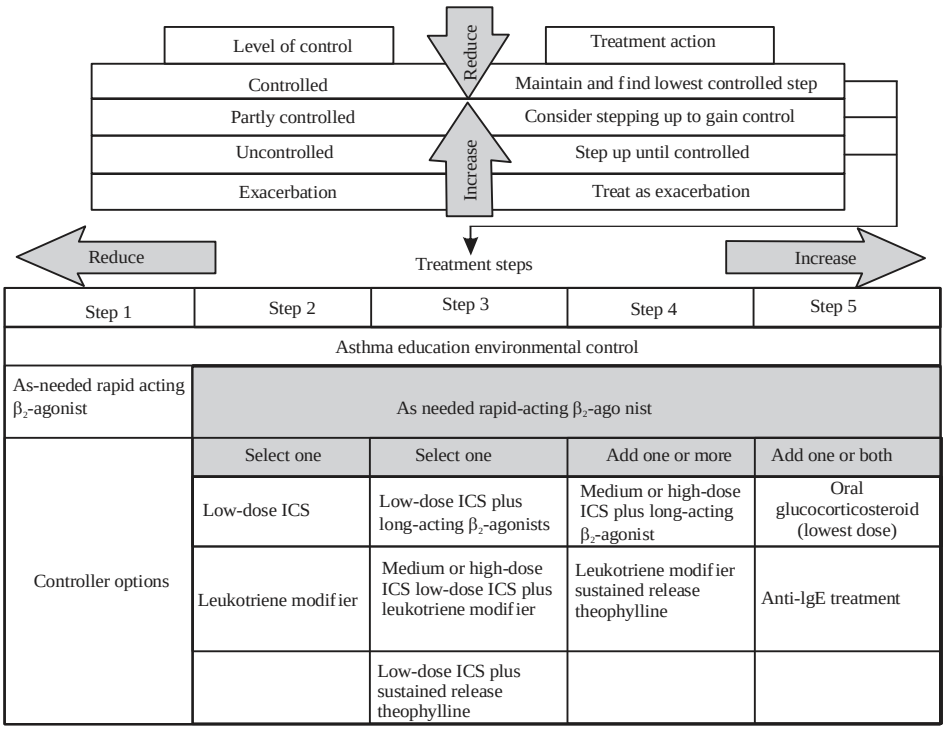

Fig. 1: Stepwise asthma management for adults-GINA guideline reproduced with permission of the GINA

Inhaled corticosteroids (ICS): The use of ICS has revolutionized the management of asthma. It has reduced asthma morbidity and improved the health status of patients. ICS is the most effective anti-inflammatory drugs for the management of persistent asthma. e.g. 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 parental therapy for long term use. eg. Methylprednisolone, triamcinolone, prednisolone and prednisone.

Long acting β_2-agonists (LABA): It includes formoterol and salmeterol. The 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 β_2 receptor which in turn increases cyclic AMP level and produces antagonism to broncho-constriction. 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.

Leukotriene antagonists (LTA): They are non-steroid class of oral medication. The 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, mucociliary transport and interaction with nerves. They reduce broncho-constriction 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 asthma. This may reduce the dose of ICS. eg. Montelukast, pranlukast and zafirlukast.

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. The 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.

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.

Anti IgE: The IgE plays a vital role in the initiation and propagation of the inflammatory cascade. Omalizumab is a recombinant humanized monoclonal antibody directed against IgE. The usual dose of omalizumab depends on patient's serum IgE level. Treatment with antiIgE reduces the exacerbation rate in severe persistent asthma and may improve asthma control. However, the treatment is costly and is suitable for highly selected patients who are not controlled on maximal doses of ICS.

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

Relievers: Relievers are the medications which are used on as needed basis. They give quick action in reversing the bronchoconstriction and relieve asthma related symptoms. They include short acting β-2 agonists and anticholinergics.

Short acting β_2-agonists (SABA): They are generally known as "rescue medications" since they stop asthma symptoms very quickly by opening the bronchial airways. The 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.

Anticholinergic agents: There are two anticholinergic broncho-dilators 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 h. 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).

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.

CRT_h2 antagonists: Chemo-attractant Receptor-homologous molecule expressed on T_h2 cells (CRT_h2) is a G-protein coupled receptor expressed by T_h2 lymphocytes, eosinophils and basophils. The receptor mediates the activation and chemotaxis of these cell types in response to PGD_2. The PGD_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 (Pettipher *et al*., 2007). Several CRT_h2 antagonists are now in development for asthma with promising initial results.

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 (Undem, 2001), but so far they have not been tested.

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 (Singh *et al*., 2007). However, in certain study, inducible NO synthase inhibitor was found to be ineffective in asthma.

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_1 was observed with antagonisms of IL-4 (Pitrakinra), IL-5 (Reslizumab) and IL-13 (Lebrikizumab) in asthma patients (Wenzel *et al*., 2007; Corren *et al*., 2011). The TNF-α plays a key role in amplifying airway inflammation, through the activation of NF-B 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 (Rennard *et al*., 2007).

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 (Viola and Luster, 2008; Holz *et al*., 2010). The CCR4 antagonist (mogamulizumab) results in prolonged cytotoxic effects on T_h2 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 (Wang *et al*., 2013).

Newer anti-inflammatory drugs

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. The PDE4 is the major enzyme found in inflammatory and immune cells. The PDE4 inhibitors like roflumilast have proven its potential as anti-inflammatory drugs, especially in asthma, COPD and rhinitis (Houslay *et al*., 2005).

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 (Rajanandh *et al*., 2015).

Novel classes of bronchodilators: Ultra LABAs (once daily β_2-agonists) are in clinical trials which include indacaterol, olodaterol, carmoterol and vilanterol etc. These ultra LABAs should be in a fixed dose combination with corticosteroids. Indacaterol plus mometasone and Fluticasone furoate plus vilanterol are currently in clinical trial for the management of asthma (Cazzola *et al*., 2011).

Mast cell inhibitors: Mast cells are the main culprit in the progression of asthma. The survival of mast cells in the airways depends on the stem cell factor. A persistent elevation of stem cell factor in plasma concentration is observed in asthmatics. Inhibition of stem cell factor is an effective treatment modality in controlling asthma, which is proved in animal models (Makowska *et al*., 2009). Masitinib is a potent blocker of c-Kit and provides some symptomatic benefit in patients with severe asthma. More selective c-Kit inhibitors are in development (Humbert *et al*., 2009).

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 (Dipiro, 2005).

Allergen avoidance: Avoidance of known allergic triggers can improve symptoms, reduce medication use and decrease bronchial hyper responsiveness (Arshad *et al*., 2003; Nageswari *et al*., 2014). However, studies pertaining to allergen avoidance have failed to demonstrate beneficial effects.

Dietary manipulation: Low levels of magnesium intake have been associated with high prevalence of asthma. Supplementation of diet rich in omega 3 fatty acids might reduce the inflammation associated with asthma (Thien *et al*., 2001).

Environmental factors: Series of the study states that, air pollution and tobacco smoke may provoke acute asthma attacks or aggravate existing condition.

Patients with acute severe asthma are advised to receive supplemental oxygen therapy by mask or nasal cannulae titrated to maintain the normal level of SaO_2.

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 (Abramson *et al*., 2010). 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 (Rajanandh *et al*., 2014d).

Alternative and complementary therapies: It is common to find patients with asthma, seeking medications from alternative systems of medicine. Studies have shown that patients use either complementary or alternative medicine only if they are not satisfied with conventional medicine. Adverse effects of conventional medicines, holistic approach in the disease management are also the reason for choosing complementary and alternative medicine. A wide range of 6-70% prevalence of use of complementary therapy for asthma is reported (Partridge *et al*., 2003). 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.

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