

Review Article

Managing Asthma : Must Know Areas for General Physicians

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Asthma is fast emerging as a major public health problem of India. The incidence of Asthma is increasing, so is our knowledge. Out of various guidelines available to manage asthma, that of Global Initiative for Asthma (GINA) is most commonly followed and recommended by practicing physicians. It is updated regularly. But still asthma is sub optimally treated. Most of the death of asthma can be prevented if asthma is treated as per guidelines. Knowledge of the pathogenesis, drugs and proper use of them can help in the long term goals of asthma management of risk reduction and symptom control. Inhalation therapy is the cornerstone of management of asthma. Drugs are available to manage different stages of the disease. Proper use of inhalers makes huge difference in the control of symptoms. Most cases of probable asthma come first to the general physicians or family physicians. These doctors should have basic understanding of pathophysiology and diagnostic criteria of asthma. They should familiarise themselves with latest guidelines and should have knowledge of giving right therapy at the particular stage of asthma. Right drugs at the right time to right patient is the only right way to manage asthma rightly. In this article we have highlighted the pharmacotherapy and step wise management of asthma that a general physician should know.

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Definition of asthma as per the Global Initiative for Asthma (GINA) guidelines involves two components: history of any of the characteristic symptoms – wheeze, shortness of breath (breathlessness), chest tightness or cough, and evidence of variable airflow limitation – based on bronchodilator reversibility testing using spirometry or peak flow meter or other tests. Hence, use of spirometry or peak flow meter is essential to make a reliable diagnosis of asthma¹. Like most chronic diseases, asthma is not curable and so it is justified to have the goals of asthma management. The long-term goals of asthma management are risk reduction and symptom control.

There are around 300 million patients of Asthma worldwide. This number is estimated to increase by another 100 million by 2025. It is estimated that asthma accounts for about 1 death in every 250 deaths across the world. Most of these deaths are preventable, being due to suboptimal long-term medical care and delay in obtaining help during the final attack. Clinical asthma prevalence is 4.5% of total world's population. However,

Editor's Comment :

- Asthma Management is not only about writing a prescription and giving to the patient.
- It is a process more of developing a patient- doctor partnership.
- Inflammation in the airway mucosa is the main cause of symptoms and with regular medication with inhaled corticosteroids hyperreactivity of the airways decreases and subsides.
- Step care management of Asthma as per guidelines achieves the long-term goals of asthma management which are risk reduction and symptom control.
- In addition to selection of medication as per guidelines care should be taken for adherence to the therapy, technique of using the inhaler and the device, avoidance of environmental trigger factors, and identification and treatment of any co-morbidities.

8.6% patients suffer from asthma across the world based on self-reported prevalence. This means around 623 million people around the world are currently living with some level of Asthma symptom².

Symptom Control and Good Quality of Life :

Patients should have a good control of symptoms and should not get recurrent episodes of cough or breathlessness. Ideally, the patient should have:

1. No asthma exacerbations
2. Good symptom control (minimal episodes of cough, breathlessness and wheeze)
3. No dietary restrictions
4. No activity restriction
5. No loss of work or school
6. No night-time awakenings: Asthma symptoms

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are more during the night-time and cause sleepless nights, sometimes for the entire family. This can easily be stopped with proper control.

Minimizing Risks due to Disease and Management :

Asthma can exacerbate in anybody. Asthma exacerbation can cause suffering to individuals and progressive damage to the airways. It also imposes a huge psycho-socio-economic burden on the family. Long standing uncontrolled Asthma can lead to airways remodelling and permanent changes in the airways. This may lead to the patient developing fixed airways obstruction and Chronic Obstructive Pulmonary Disease (COPD) phenotype in future. These can be prevented with regular controller therapy to control the inflammation. A lot of medications both oral and inhalation are used to manage asthma. These all have some side effects. Adverse reactions are less with inhaled medications. Side effects of oral steroids can and must be avoided by using inhaled corticosteroids. Unfortunately, patients of asthma are happy with the little control they get from the medicines, objectively they are either uncontrolled or poorly controlled.

Pharmacotherapy of Asthma :

Medications required for management of asthma are classified into three groups:

1. **Controllers** : Include Inhaled corticosteroids, Long Acting Beta 2 Agonists (LABA), Anti leukotrienes
2. **Relievers** : Short acting Beta 2 Agonists (SABA, Salbutamol) as well as short acting Anti Muscarinics (Ipratropium)
3. **Add on therapy** : These are drugs required only in severe cases where standard therapy does not work.

Inhaled Corticosteroids :

Corticosteroids have a broad-spectrum anti-inflammatory effect in asthma³. Corticosteroids primarily act on the structural cells of the airways, mainly the epithelial cells. It also acts on the smooth muscle cells, the vascular endothelium and the fibroblasts. In these cells, corticosteroids act by suppressing the activation of the inflammatory gene transcription which is responsible for increased expression of multiple inflammatory proteins including cytokines, chemokines, adhesion molecules, inflammatory enzymes and receptors. Thus, at a cellular level, they reduce the number of inflammatory cells in the airways including eosinophils, Tlymphocytes, mast cells and dendritic cells. They also inhibit the survival of these cells in the airways. Corticosteroids also increases the expression of beta -2 adrenergic receptors in the lung and prevent their

down regulation and uncoupling in response to beta -2 agonists. Table 1 shows the recommended dosage of common inhaled corticosteroids used in the management of asthma.

Short Acting and Long Acting Beta 2 Agonists :

β 2 agonists have a major role in asthma and have been the cornerstone for asthma management for several years till the role of steroids was identified. Beta 2 agonists especially short acting beta 2 agonists like Salbutamol have been used for the bronchodilator effects in the airways for a long period of time. However, monotherapy with β 2 agonists leads to desensitization and down regulation of β 2 receptors in the airways. Airways become refractory to their bronchodilator effect. Hence Beta 2 agonists have no role as monotherapy in management of chronic stable Asthma other than to obtain quick onset broncho-dilatation in an acute exacerbation^{4,5}. It this acts as reliever therapy.

Beta 2 Agonists in Combination with Inhaled Corticosteroids :

When combined with Inhaled Corticosteroids, β 2-agonists also exert an anti-inflammatory effect. These effects include inhibition of release of oxidative bursts, thromboxane A2 and Leukotriene C4 from Eosinophils. There is also inhibition of release of mediators from neutrophils, and inhibition of the release of Th2 type cytokines such as IL-5 from peripheral blood lymphocytes. They have also been shown to inhibit release of granulocyte-macrophage colony-stimulating factor (GM-CSF) from cultured human lung fibroblasts. They also exert some amount of mast cell stabilizer activity. Despite this anti-inflammatory activity of the Beta2 Agonists, when used as monotherapy in vivo, (without the ICS), Beta2 Agonists both long acting and short acting, do not show any anti-inflammatory properties and hence cannot be used as monotherapy for management of Asthma. There is substantial down regulation of the Beta2 Receptors on prolonged use of SABAs alone. LABAs too have similar effects. Contrary to their in vitro anti-inflammatory effects, none

Table 1 — Common inhaled corticosteroids and their dosage

Inhaled corticosteroid	Total daily dose (mcg)		
	Low	Medium	High
Budesonide (DPI)	200–400	> 400–800	>800
Fluticasone propionate	100–250	>250–500	>500
Beclometasone dipropionate (CFC)	100–200	>200–400	>400
Ciclesonide (HFA)	80–160	>160–320	>320
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

of the LABAs show an anti-inflammatory effect in vivo when used as monotherapy. Monotherapy with β_2 -agonists may even enhance the asthmatic-inflammatory process leading to a worsening of asthma control⁶.

Antileukotrienes :

Activated Eosinophils, T Lymphocytes, Mast Cells and Basophils release Cysteiny Leukotrienes which are formed by arachidonic acid metabolism. Leukotriene (LT)₃ C₄, LTD₄, and LTE₄, collectively termed the cysteinyl LTs (cys-LTs), are peptide-conjugated lipids that are prominent products of activated eosinophils, basophils, mast cells (MCs), and macrophages⁷. The cysteinyl leukotrienes (Cys LTs) are potent lipid mediators implicated in the pathophysiology of asthma and allergic rhinitis (AR) whose effects include increased airway smooth muscle activity, microvascular permeability and airway mucus secretion⁸. Anti-Leukotrienes block the leukotriene receptors on the target organs thus reducing the inflammation as well as the bronchoconstriction.

Anti-Muscarinic Agents :

Bronchial smooth muscle contraction is the primary cause of reversible airway narrowing in asthma, and the baseline level of contraction is predominantly set by the level of cholinergic tone. Patients with asthma have increased bronchial smooth muscle tone and mucus hyper-secretion, possibly as a result of elevated cholinergic activity. Acetylcholine also exerts an inflammatory effect by inducing attraction and survival of inflammatory cells, with subsequent cytokine release. Hence long acting Tiotropium is now being identified as a potent bronchodilator in cases of severe asthma not responding to conventional optimal anti-inflammatory therapy.

Role of theophylline in Asthma :

Theophylline for several years have been used for their bronchodilator properties in asthma but there is evidence that suggests that Theophylline in a low dose act more as anti-inflammatory agents. At low doses, Theophylline acts by inhibiting Histone De acetylase enzyme (HDAC). This reduces recruitment of eosinophils in the airways. Thus, low dose theophylline act synergistically with the inhaled corticosteroids and can be used in patients who do not respond to regular ICS therapy. However, independently, theophylline are not effective in controlling the airway inflammation.

Anti IgE Antibodies :

Omalizumab is a monoclonal Anti IgE Antibody. It binds to the circulating IgE secreted by activated

plasma cells. It also reduces the expression of high affinity receptors on inflammatory cells like the Basophils, Mast Cells and Eosinophils. Thus, by reducing inflammation, it reduces asthma symptoms and prevents exacerbations⁹. Use of Omalizumab is limited to cases of very severe Asthma or uncontrolled asthma which does not get controlled even with high doses of ICS with optimal add on therapy despite good adherence to therapy and good technique of inhalation. Dose is dependent upon the level of serum IgE and body weight

Anti-IL - 5 Therapy :

Mepolizumab, Reslizumab, Benralizumab are monoclonal Antibodies that inhibits Interleukin 5 which is a key mediator in initiation and sustaining the Eosinophilic Inflammation. These drugs are effective only in those patients who have a predominantly Eosinophilic inflammation in blood and sputum and are steroid responsive. Careful selection of patients is recommended¹⁰.

Oral Steroids :

These are indicated only in those cases of asthma who are experiencing an acute exacerbation. Short burst of oral steroids in such cases for 8 to 10 days are effective and safe and can be stopped abruptly without the need for tapering them. Severe cases of Asthma not responding to conventional therapy may also require oral steroids for long durations. Such cases are rare. In such cases we must keep the patient maintained on a minimal possible dose and monitor for side effects of systemic steroids.

Assessing a Patient and Initiation of Therapy :

Asthma Management is not only about writing a prescription and giving to the patient. It is a process more of developing a patient- doctor partnership which is important for any chronic disease management. There are several other aspects to Asthma Management and a successful Asthma management protocol would include all these activities enlisted below preferably in the order given:

1. Developing a patient doctor Partnership
2. Identification and avoidance of triggers
3. Assessing the severity/level of control
4. Prescribing the medicines
5. Prescribing appropriate devices
6. Regular monitoring to check adherence and level of control
7. Correct technique of usage of device
8. Step up and Step Down
9. Asthma Action Plan

10. Addressing co-morbid conditions

Developing a Patients Doctor Partnership :

All chronic diseases bring with them several challenges in management but the most challenging is to have the patients' concordance in their treatment. This can only be achieved through a well strategized patient counselling session where physician explain the common issues that the patients have while accepting their disease, accepting the preferred modality of treatment, accepting that the treatment will be required for long durations and several other aspects of the disease that intimidate or perturb the patient.

Identification and Avoidance of Triggers :

During the initial visit, it is useful to identify what are the factors that trigger off the patient's asthma. This also helps us explain to the patients why they are getting recurrent symptoms and how can they avoid them. Common triggers are mentioned below:

- Indoor and outdoor air pollution
- Long standing dust inside the house/workplace
- Smoking and environmental tobacco smoke
- Occupational exposures/ Chemicals
- Damp mouldy walls
- Animal dander
- Cockroaches
- Drugs like beta blockers or NSAIDS
- Psychological stress
- Perfumes/ strong odours
- Food and drinks/ cold food

Assessing the Severity/level of Control :

In the first visit it is to be seen if the patient in exacerbation. If the patient is in exacerbation the patient is to be treated as an exacerbation, if not then the patient is to be assessed by level of control, risk factors of exacerbations and spirometry. Nowadays, asthma treatment is guided by the step wise approach and severity of asthma is decided retrospectively depending upon what level of treatment the patient got controlled. Asthma control has two domains, one is the current level of control and the second is the future risk of asthma exacerbation.

Asthma Control :

With regular medications, the inflammation in the airway mucosa subsides and the hyperreactivity of the airways decreases. Thus, patients remain asymptomatic when the disease is well controlled. Symptoms are assessed on 4 parameters, presence of daytime symptoms, use of reliever medication, nighttime symptoms and activity limitation. Presence of one or more of these indicates either partial control or

poor control. Level of control helps us what treatment to initiate and decide whether we need to step up therapy, step down therapy or continue with the current therapy.

Future Risk of Asthma Exacerbation :

Certain patients are predisposed to high chances of getting an asthma exacerbation. Patient with uncontrolled asthma symptoms, high SABA usage, no/inadequate ICS, poor adherence, incorrect inhaler technique, low FEV1 (<60% of predicted), major psychological/ socioeconomic issues and persistent exposure to triggers is at a high risk of exacerbation.

Stepwise Treatment of Asthma

Asthma treatment needs to be individualized as per the patient's severity of symptoms, frequency of symptoms, socio- economic conditions and beliefs and practices. However, while deciding the drugs and dosages, we need to consider the patients severity and frequency of symptoms. The dose needs to be constantly relooked into and titrated as per level of control. The patients need to be regularly monitored and dosages should be titrated as per level of control.

Step Up of Therapy :

Consider stepping up therapy to the next level if the patient does not remain well-controlled on the current step. However, we need to check and recheck the following before deciding step up:

- Adherence to the therapy
- Technique of using the device
- Environmental trigger factors
- Presence of any co-morbidities

Only when one is sure that none of the above factors are responsible for the poor control should one consider stepping up of therapy.

Step Down of Therapy :

Step down is an important aspect of asthma management. We should aim to maintain the patient well-controlled on medications but at the same time avoid any long-term complications of prolonged use of steroids. Hence, we need to identify the minimal possible dose on which the patient remains well controlled and continue the same. In due course we can also stop the therapy and see. If the patient remains well controlled, it is very good. However, if the symptoms recur, we need to restart the minimal dose on which the patient had remained well controlled. Key points to consider during step down:

- The patient should have remained well controlled for the past 3 months before we decide a step down.
- We aim at reducing the ICS by 25 to 50% depending upon the patient's condition.

■ It is essential to convey to the patient that continuous monitoring would be required.

■ The 'Peak Flow Meter' is an excellent tool for monitoring.

■ Stopping the medication does not mean that he/she will never get symptoms. Asthmatic airways are hyper-responsive, and they will remain so.

Treatment of Co-morbidities :

Allergic Rhinitis and Gastro Oesophageal Reflux Disease are important co-morbidities associated with asthma. Identifying and treating these is very important as asthma may not get controlled despite optimal therapy if co-morbidities exist.

Follow-up and Monitoring :

Monitoring the patient for current level of control, any risk factors for exacerbation, adherence and good technique of using the inhaler device are important aspects of asthma management. Early first follow up is useful as one can address issues regarding acceptance of the disease and therapy, check technique of inhalation therapy and if required re-train in the technique. After the first follow up, the follow ups should be once every month. The physician should assess the following during follow ups:

■ Assess symptom control/ Administer Asthma Control Test

■ Check PEFr/ PEFr record if being recorded

■ Check Inhaler technique

■ Administer Asthma Control Test

■ Consider step up/step down depending upon control

■ Gradually introduce:

- PEFr Home Monitoring
- Asthma Diary
- Asthma Action Plan

Conclusion :

Asthma is an important public health problem of our country. It is a chronic disease and thus difficult to manage. The general physician should regularly update himself with the guidelines which are regularly updated for management of asthma. General physicians are

the first point of contact of a patient of asthma. Diagnosing and initiating the the treatment is thus made by them. Correct diagnosis and correct first line of management will go a long way in improving the quality of life of the persons suffering from asthma.

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“Man needs his difficulties because they are necessary to enjoy success.”

— A. P. J. Abdul Kalam