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A Systematic Review on Asthma.

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ABSTRACT

Asthma, a reversible and curable disease. Mostly the prevalence of asthma in the developing countries are very high.eventhough governments and NGO's are spreading awareness among the people through stage shows and in canopy setups, still the awareness level is not up to the mark.this review article ,clearly defines about the asthma and its trigger factors ,types of asthma in a detailed manner. Diagnosis of asthma like physical examinations and lung function tests, route of administration plays a major role in asthma. The beneficial of inhalation is compared with the other routes. Treatment is widely distributed with some class of drug in asthma. Mainly β2 agonists and inhaled corticosteroids are important. Some people practicing herbal medications all these are indicated in detail. GINA guidelines suggested regarding the step up and step down medications to be followed in asthma. In addition to this so many drug makers enrolled their presence in the market but still some companies are playing vital role in this sectors and mentioned in this article also.

Keywords: Types of asthma, ICS, LABA, Controllers, Relievers.

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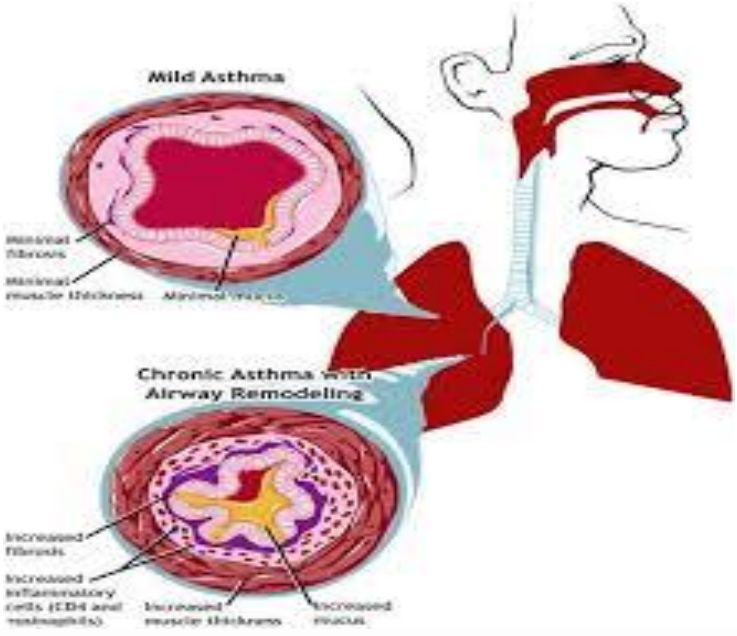
INTRODUCTION

Asthma, a major problem facing in our polluted environment. It is a reversible and curable disease. Like diabetes the prevalence is increasing day by day so the drug makers earning in millions because of asthma. Still in rural areas most of the people thought that asthma is because of god's curse. In olden days it was recognized in Ancient Egypt and was treated by drinking an incense mixture known as kyphi [1].It was officially named as a specific respiratory problem by Hippocrates circa 450 BC, with the Greek word for "panting" forming the basis of our modern name [2].In 200 BC it was believed to be at least partly related to the emotions [3].In recent days, Asthma constitutes a heavy medical, social, and economic burden, and its prevalence is steadily increasing worldwide[4]. Indeed, asthma affects over 300 million people around the world, and some epidemiologic projections estimate that this number will increase further during the next few decades[5].

The prevalence of asthma has increased by more than 75% over the last two decades[6].With rates in children under 5 years increasing by more than 160% [7].Being change in food habits and working culture, most of the people are obese. The prevalence of obesity has increased dramatically over recent decades, and obesity is recognized as an important risk factor for a diagnosis of asthma[8].However, asthma remains poorly controlled in many patients, challenging physicians to reevaluate the current therapy, which should continue to be aimed at improving symptoms and in preventing asthma exacerbations. Approaches to maximizing medication adherence with personalized pharmacotherapy regimens that reduce asthma-related activity impairment and the risk of exacerbation in patients with persistent asthma is a major goal [9, 10]. In addition to the available drugs in the market, Omalizumab is a humanized monoclonal anti-IgE antibody recently approved for the treatment of severe allergic asthma [10].This article will clearly defines about the asthma in all aspects in a simple manner

Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction and bronchospasm [11]. As per the Global Initiative for Asthma (GINA) defined as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with 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 within the lung that is often reversible either spontaneously or with treatment".[12].In short, asthma is a reversible obstructive airway disease along with bronchial hyper responsiveness as a prominent feature.

Pathophysiology [13]



Symptoms of asthma include[14]

- Episodic breathlessness or dyspnoea(especially at night or early morning, or after some exertion)
- Wheezing
- Cough(especially at night or early morning, or after some exertion)
- Chest tightness:

In children, often, the only symptom may be coughing at night or early morning, and after physical activity.

Trigger factors[15]

Triggers may be allergic or non allergic and can be any of the following types:

- Allergens:Inhaled, eg., pollen,house dust mite from carpets, drapes and soft toys, animal dander from pets,fungi,moulds and spores.
- Additives in food: Tartrazine yellow dye used as a coloring agent.
- Metabisulphite preservatives used in beer, wine and preserved foods. Monosodium glutamate (ajinomoto) added to Chinese food, which may precipitate “Chinese restaurant asthma”.
- Occupational: Symptoms usually occur shortly after being exposed to the triggers and often improve or disappear when leave the workplace.
- Inflectional, mainly viral: Most exacerbation of asthma in childhood can be proven to be associated with viral infections. Respiratory viral infections caused by respiratory syncytial viruses (RSVs) are important trigger of asthma attacks.
- Exercise: Exercise can trigger bronchospasm in many asthmatics. Increased breathing rate after exercise leads to cooling and drying of airways, which can trigger asthma.
- Emotions: Although asthma is not caused by psychological factors, emotions like extreme joy or sorrow can provoke bronchospasm in an asthmatic.
- Changes in environmental temperature/humidity, gaes, fumes, smoke:Sudden changes in temperature or seasonal changes may causes bronchospasm. Inhalation of smoke/gases/fumes may irritate the airways, leading to symptoms of asthma.

Types of asthma: Asthma may also be classified as atopic (extrinsic) or non-atopic (intrinsic) [16] where atopy refers to a predisposition toward developing type 1 hypersensitivity reactions [17].

Child-Onset Asthma [18]: Asthma that begins during childhood is called child-onset asthma. This type of asthma happens because a child becomes sensitized to common allergens in the environment - most likely due togenetic reasons. The child is atopic - a genetically determined state of hypersensitivity to environmental allergens.

Allergens are any substances that the body will treat as a foreign body, triggering an immune response. These vary widely between individuals and often include animal proteins, fungi, pollen, house-dust mites and some kind of dust. The airway cells are sensitive to particular materials making an asthmatic response more likely if the child is exposed to a certain amount of an allergen.

Adult-Onset Asthma: This term is used when a person develops asthma after reaching 20 years of age. Adult-onset asthma affects women more than men, and it is also much less common than child-onset asthma.

It can also be triggered by some allergic material or an allergy. It is estimated that up to perhaps 50% of adult-onset asthmas are linked to allergies.[19] However, a substantial proportion of adult-onset asthma does not seem to be triggered by exposure to allergen(s); this is called non-allergic adult-onset asthma. This non-allergic type of adult onset asthma is also known as intrinsic asthma. Exposure to a particle or chemical in certain plastics, metals, medications, or wood dust can also be a cause of adult-onset asthma.

Exercise-Induced Asthma: Exercise can trigger bronchoconstriction in both people with and without asthma.[1] It occurs in most people with asthma and up to 20% of people without asthma[20]. As with other types of

asthma, a person with exercise-induced asthma will experience difficulty in getting air in and out of the lungs because of inflammation of the bronchial tubes (airways) and extra mucus.In athletes is diagnosed more commonly in elite athletes, with rates varying from 3% for bobsled racers to 50% for cycling and 60% for cross-country skiing. With proper asthma management, one can exercise as much as desired. Mark Spitz won nine swimming gold medals during the 1972 Olympics and he suffered from exercise-induced asthma.

Cough-Induced Asthma: Cough-induced asthma is one of the most difficult asthmas to diagnose. The doctor has to eliminate other possibilities, such as chronic bronchitis, post nasal drip due to hay fever, or sinus disease. In this case the coughing can occur alone, without other asthma-type symptoms being present. The coughing can happen at any time of day or night. If it happens at night it can disrupt sleep.

Occupational Asthma: This type of asthma is triggered by something in the patient's place of work. Factors such as chemicals, vapors, gases, smoke, dust, fumes, or other particles can trigger asthma. It can also be caused by a virus (flu), molds, animal products, pollen, humidity and temperature. Another trigger may be stress. Occupational asthma tends to occur soon after the patients starts a new joband disappears not long after leaving that job. It is estimated that 5–25% of asthma cases in adults are work–related. The employment associated with the highest risk of problems include: those who spray paint, bakers and those who process food, nurses, chemical workers, those who work with animals, welders, hairdressers and timber workers[21].

Nocturnal Asthma: Nocturnal asthma occurs between midnight and 8 AM. It is triggered by allergens in the home such as dust and pet dander or is caused by sinus conditions. Nocturnal or nighttime asthma may occur without any daytime symptoms recognized by the patient. The patient may have wheezing or short breath when lying down and may not notice these symptoms until awoken by them in the middle of the night - usually between 2 and 4 AM.

Nocturnal asthma may occur only once in a while or frequently during the week. Nighttime symptoms may also be a common problem in those with daytime asthma as well. However, when there are no daytime symptoms to suggest asthma is an underlying cause of the nighttime cough, this type of asthma will be more difficult to recognize - usually delaying proper therapy. The causes of this phenomenon are unknown, although many possibilities are under investigation.

Steroid-Resistant Asthma (Severe Asthma): While the majority of patients respond to regular inhaled glucocorticoid (steroid) therapy, some are steroid resistant. Airway inflammation and immune activation play an important role in chronic asthma. Current guidelines of asthma therapy have therefore focused on the use of anti-inflammatory therapy, particularly inhaled glucocorticoids (GCs). By reducing airway inflammation and immune activation, glucocorticoids are used to treat asthma. However, patients with steroid resistant asthma have higher levels of immune activation in their airways than do patients with steroidsensitive (SS) asthma. Furthermore, glucocorticoids do not reduce the eosinophilia (high concentration of eosinophil granulocytes in the blood) or T cell activation found in steroid resistant asthmatics. This persistent immune activation is associated with high levels of the immune system molecules IL-2 (interleukin 2), IL-4 and IL-5 in the airways of these patients.

Acute severe asthma: It is previously known as status asthmatics, is an acute exacerbation of asthma that does not respond to standard treatments of bronchodilators and corticosteroids. Half of cases are due to infections with others caused by allergen, air pollution, or insufficient or inappropriate medication use[22].

Brittle asthma: It is a kind of asthma distinguishable by recurrent, severe attacks. Type 1 brittle asthma is a disease with wide peak flow variability, despite intense medication. Type 2 brittle asthma is background well-controlled asthma with sudden severe exacerbations[23].

Diagnosis

Making a correct diagnosis is extremely important. If asthma is correctly diagnosed it can be treated appropriately. The diagnosis of asthma involves all of the following:

Medical history[24]

History of recurrent and persistent cough following a cold, frequent colds, seasonal changes, exercise limited by breathing problems, waking at night with symptoms, school absentism,emergency room visits, family history of asthma,allergies,allergic rhinitis.

- Physical examinations:

  It includes listening to the lung with a stethoscope, examination of nasal passage etc.,

- Lung function tests:
  It is carried out by using:

Peak flow meter: It is like a thermometer for asthma which measures the peak expiratory flow rate(PEFR)in 2/min. and also used for diagnosis and monitoring.

Spiro meter: It is a sophisticated instrument which measures the lung function in term of forced expiratory volume in one second (FEV1) and force vital capacity (FVC)[25].Spirometry is then used to confirm the diagnosis [26].Spirometry is recommended to aid in diagnosis and management[27]. It is the single best test for asthma. If the FEV1measured by this technique improves more than 12% following administration of a bronchodilator such as salbutamol, this is supportive of the diagnosis [28].

Route of administration: A route of administration in pharmacology and toxicology is the path by which a drug, fluid, poison, or other substance is taken into the body[29].[29]. Medicines can be taken in three routes oral, parentral and inhalation. In asthma therapy most preferred route is inhalation because the drug acts in the site of action. This table shows the comparisons of the different route of administration [30].

Sl.no	Parameters	Inhalation	Parental	Oral
1	Dose	Low(mcg)	High(mg)	High(mg)
2	Onset of action	Rapid(bronchodilator)	Rapid(bronchodilator)	Slow
3	Site of action	Direct	Indirect	Indirect
4	Systemic side effects	Few	Many	Many

Treatment:

Most of the asthma medications are in inhalation routes. The class of drugs used are β2 agonists, inhaled corticosteroids, anti cholinergic and leukotriene antagonists.

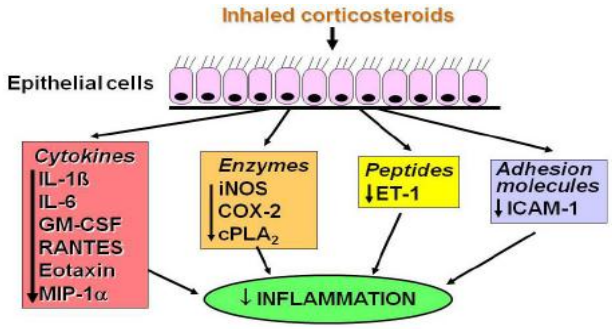
β2agonists [31]:They work by relaxing the muscles around the airways during an asthma attack.β2 agonists bind to β2 receptors in the lungs.β2 agonists do not reduce inflammation or airway responsiveness but serve as bronchodilators, relaxing and opening constricted airways.

Mode of action [32]: B2 agonist bind to the β2 receptors present on the smooth muscle cells in the lungs and brings about reduction in intracellular calcium levels. This brings about smooth muscle cell relaxation and bronchodilation.There are two types short acting(e.g., salbutamol and levosalbutamol) and long acting(salmeterol and formoterol)

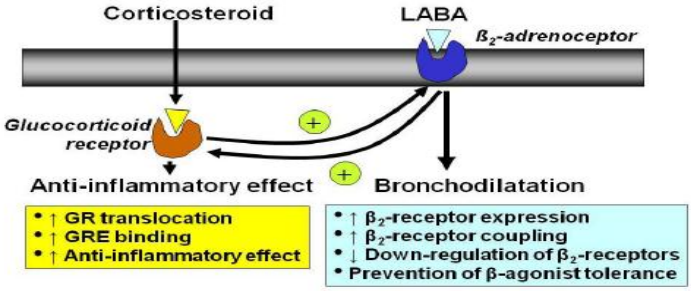
Inhaled corticosteroids [33]**:** These are not bronchodilators and have little effect if used only for acute asthma attacks. These work over time by reducing inflammation and allowing lungs [to] function properly and may even prevent long term complications.

Mode of action [34]**:** Corticosteroid mechanisms of action on the inflammatory process are complex. On the one hand there is a classical anti inflammatory action, in which corticosteroid molecules are diffused across the target cell membrane and bind with corticosteroid receptors in the cytoplasm. The corticosteroid – receptor complex is then rapidly transported to the cell nucleus, where it binds to specific DNA sequences and changes the gene transcription mechanism so that messenger RNA molecule synthesis is activated, leading to the production of new proteins.corticosteriods reduce inflammation, therefore by increasing the synthesis of

anti inflammatory proteins..eg., beclomethasone,budesonide,fluticasone,momentasone etc.,this figure clearly gives the idea about the mode of action of inhaled corticosteroids.



Methylxanthines: It was once widely used, but do not add significantly to the effects of inhaled beta-agonists [35]. Their use in acute exacerbations is controversial [36].



Leukotriene antagonists: It may be used in addition to inhaled corticosteroids, typically also in conjunction with LABA [37]. Evidence is insufficient to support use in acute exacerbations [38]. In children they appear to be of little benefit when added to inhaled steroids. In those under five years of age, they were the preferred add-on therapy after inhaled corticosteroids by the British Thoracic Society in 2009[39].e.g., montelukast and zafirlukast.

Herbal drugs: A list of 54 plant species belonging to50 genera and 39 families were used as folk medicine for asthma. Of these 54 species, 50 are dicots, 4 (Cynodon dactylon, Curculigo orchioides, Zingiber capitatum and Zingiber officinale) are monocots respectively [40].

Relievers

These are basically bronchodilators-they dilate the bronchus. It meant to be used for immediate relief of symptoms. It has a short duration of action. It can be used up to 3-4 times per day. Frequent use of relievers indicates poor control of asthma and probable under use of preventors.relievers are also used as rescue medicines or SOS treatment in acute cases. These include the class of drugs known a short acting β2 agonists (salbutamol and levosalbutamol)[41].

Controllers [42]

It take time to act and control airway inflammation,i.e.,the root pathology of asthma .most preventers need to be administered only once or twice daily, since they have a prolonged effect. in controlling asthma inflammation on an ongoing basis, the anti-inflammatory corticosteroids are used to reduce inflammation in moderate to severe asthma.Interaction between corticosteroids and long-acting β2-agonists (LABA).Corticosteroids have anti-inflammatory effects but also increase the numbers of β2-Receptors, whereas β2-agonists, as well as inducing direct bronchodilation, act on Glucocorticoid receptors to increase the anti-inflammatory effects of corticosteroids[43].

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MANAGEMENT OF ASTHMA

Although there is no permanent cure for Asthma, the disorder can be adequately controlled with drugs. Under diagnosis 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[44]. As per:the GINA guidelines [45]some of the choices of medications are

	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred controller choice		Low dose ICS/LABA	Low dose ICS/LABA	Med/high dose ICS/LABA	Refer for add-on treatment eg.anti IgE
Other controller options	Consider low dose ICS	Leukotrine receptor antagonist(LTRA)	Med/high dose ICS /low dose ICS+LTRA(or Theophylline)	High dose ICS+LTRA (or Theophylline)	Add low dose of oral corticosteroids

Prevalence of asthma

An estimated 300 million people worldwide suffer from asthma, with 250,000 annual deaths attributed to the disease. It is estimated that the number of people with asthma will grow by more than 100 million by 2025. Workplace conditions, such as exposure to fumes, gases or dust, are responsible for 11% of asthma cases worldwide. About 70% of asthmatics also have allergies. Approximately 250,000 people die prematurely each year from asthma. Almost all of these deaths are avoidable. Occupational asthma contributes significantly to the global burden of asthma, since the condition accounts for approximately 15% of asthma amongst adults [46].

The prevalence of asthma in different countries varies widely, but the disparity is narrowing due to rising prevalence in low and middle income countries and plateauing in high income countries[47]. There is limited data on Asthma epidemiology from the developing world, including India . Although some attempts have been made, studies suffer from several scientific drawbacks including lack of uniformity of methodology and analysis of data[48]. Asthma rates are officially low in India, although there is some recent evidence that the true prevalence is higher than previously thought. To date, the total estimated burden of Asthma is an overall prevalence of 3% and among adults over the age of 15, a median prevalence of 2.4% [49]. As per the Asthma statistics in India by WHO about 5.1 estimated deaths per 100000 population,277 DALYs (disability adjusted life-year) per 100,000 ,6.5 age-standardized deaths per 100,000 and268 age-standardised DALYs per 100,000[50]. It constitutes 0.2% of all deaths and 0.5% of National Burden of Diseases[51].

List of some drugs available in Indian market:

Most of the drug makers in India entered in the asthma market. Some of the important drug makers and brand names are given in below table:

s.no	Brand name	Combination	Company
1	Asthalin	Salbutamol	Cipla
2	Ventrolin	Salbutamol	GSK
3	Rheolin	Salbutamol	ranbaxy
4	Levolin	Levosalbutamol	Cipla
5	Duolin	Levosalbutamol+Ipratropium	Cipla
6	Budecort	Budesonide	Cipla
7	Foracort	Formoterol+Budesonide	Cipla
8	Budamate	Formoterol+Budesonide	Lupin
9	Seroflo	Salmetrol+Fluticasone	Cipla
10	Esiflo	Salmetrol+Fluticasone	Lupin
11	Fullform	Formoterol+Beclomethasone	Cipla
12	Evacort	Formoterol+Momentasone	Cipla
13	Seratide	Salmetrol+Fluticasone	GSK
14	Aerocort	Levosalbutamol;+Beclomethasone	Cipla
15	Maxiflo	Formoterol+Fluticasone	Cipla
16	Avessa	Formoterol+_Fluticasone	Ranbaxy
17	Ipravent	Ipratropium bromide	Cipla

CONCLUSION

In developing countries the prevalence of asthma is quiet high compare to the developed nation due to urbanization and industries.eventhough physicians prescribing inhaler medications, the people should follow the proper inhaler technique, so the physician should take care of their technique or examine them on each visit to the hospitals. Because inhalers play a major role in the asthma treatment, and directly proportional to the cure rate of asthma. Majority of the drug makers, conducting asthma identification free camps, issuing pamphlets regarding awareness of asthma, in urban and rural too. But still most of the people are unidentified. So people are advised to take part in the identification camps for a better life without asthma

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