

Asthma: From Disease to Treatment - An OverviewGursharan Kaur¹, Amandeep Singh^{1,2}, Raj Kumar Narang¹, Gurmeet Singh^{1*}¹Department of Pharmaceutics, I.S.F. College of Pharmacy, Moga-142001, Punjab, India.²Department of Pharmaceutical Sciences and Technology, Maharaja Ranjit Singh Punjab Technical University, Bathinda- 151001, Punjab, India.

Abstract: Asthma is the popular respiratory problems in the modern industrialized countries, affecting over 300 million people. It affects all age group from infant to senior citizens, and mortality rate from asthma appear to be increased during the past few years in the United States as well as in the other industrialized area. Asthma tends to occur in the family, associated with other allergic diseases, and may be induced by a variety of environmental allergens, most commonly inhaled allergens such as pollen and dust having numerous types. Bronchial scorns the allergens result in former bronchospastic response for a brief duration and some of the patients there is a late response with onset after 3 to 4 hours, lasting hours to days. This late reaction is related to the bronchial extreme touchiness response. This is a self-evident by vague test testing in the research facility. During the time of bronchial hyperresponsiveness understanding is inclined to create assaults following introduction to a wide assortment of triggers, including cold air, exhaust. The present methodology of the board of patient with it accentuate the anticipation, with shirking of explicit allergens whenever the situation allows and ceaseless utilization of mitigating operators including corticosteroids and cromolyn sodium. The goal is to decrease bronchial hyperresponsiveness. The organization of acute asthma attack consists of bronchodilator therapy, initially with inhaled beta sympathomimetics and administration of oral or systemic corticosteroid, also the role of government in improving it, by introducing the number of programs.

Keywords: Lungs; Asthma; Respiratory infection, Causes

Introduction

Asthma is a customary lung disorder of repetitive symptoms, airflow hindrance, bronchial hyperresponsiveness, coughing, wheezing, rudimentary inflammation, and other breathing problems. Asthma patient can denote with cough notably at night, over wheeze (high pitched whistling sound usually on exhalation), soon chest tightness and tough to breathe which make you feel out of breathing. It can be inherited and caused by the environment. It often occurs in children but can also create problems in the adults [1] [3].

It affects the respiratory system especially the small airway such as bronchi and bronchiole. They have the inner lining named as mucosa which is surrounded by smooth muscle, in people with asthma airways are chronically inflamed and make cells more sensitive to certain triggers which makes the smooth muscles to constrict as time passes they become continuously narrowing, swollen and sticky mucous is produced which reduce airflow based on the seriousness the symptoms might occur daily or occasionally and can be fatal if not treated, leads to death [4], also, it makes

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harden to exhale then inhale leads to an excess of air in lungs the phenomenon called hyperinflation. The accumulation of air in the lungs leads the body to work harder to exhale and inhale over time this leads to a decrease in oxygen delivery to tissues and causes death [10]. It is mostly found in children but can also occur at adults and old age due to several reasons. It is a big misfortune for millions of children especially in underdeveloped countries. Even if it is a manageable disease but cannot be fully cured, its symptoms can be suppressed with medication as well as with some precautions [2]. Almost 300 million people are currently suffering from this [7]. An asthma action plan was introduced by the government. Also, an MCAN was established in 2005 under the sponsor of Merck Company. This company put its huge contribution to elevate the detection, cure, and prevention unit for asthma [2]. As per the site of the problem, there are three types of treatment:

- Preventing the release of histamine using sodium chromoglycate.
- Analogs of beta-agonist.
- Antimuscarinic agents [6, 3].

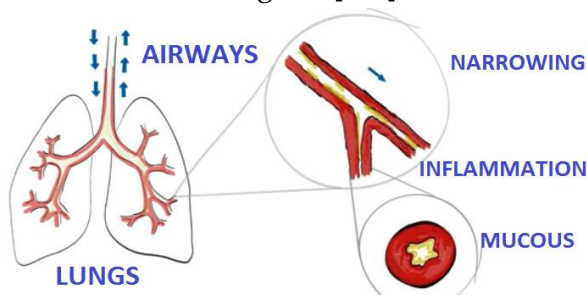


Figure 1: Inflammation in the lungs

Risk Factors

There are many risk factors causing asthma some of them are family history or hereditary, atopic history, allergy caused by allergens, obesity, air pollution, upper respiratory tract infections, drug overdose, occupational exposure, environmental factors, psychological factors, etc. [5].

Sign Symptoms

Some specific symptoms are showing the presence of asthma painful cough, wheezing, chest tightness, breathlessness, shaking chills, fever, tachycardia, tachypnea, respiratory distress, fatigue, orthopnea, poor appetite [5].

Triggers

Asthma symptoms can appear more worst when a person comes in contact with certain triggers (these are the agent which can cause asthma or act as a trigger for asthma, such as cold weather, chemicals and fumes, pollution, strenuous exercise, animal fur, pollen, dust, mold, stress anxiety, cigarette and smoke, perfumes and scents, metals (platinum, chrome, nickel), vegetables (grain, bean, gum, latex), drugs (aspirin, NSAID, beta-adrenergic, antagonists, cholinergic agents, etc [5].

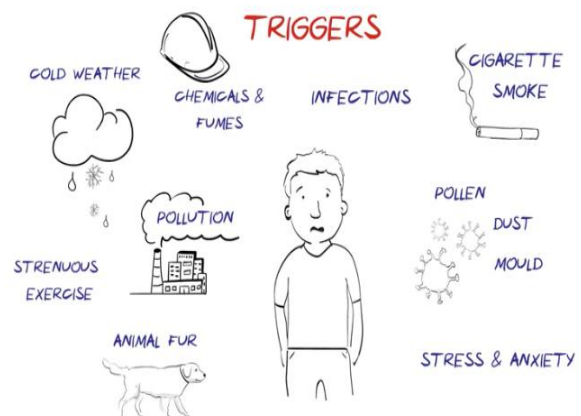


Figure 2: Triggers for Asthma

History

Asthma was first recognized in ancient Egypt. It is derived from the Greek word aazein meaning "sharp breath". In 450 BC Hippocrates reasons that it more probable happen in tailors, fishermen, and metal specialists. Later in the 6th century Galan set forward that it brought about by incomplete or complete bronchial check. At that point in 1190 AD Moses Maimonides composed a treatise on asthma, depicting its avoidance, analysis, and treatment. After that in the seventeenth century, Bernardino ramazzini set forward the association between asthma and natural residue.

After that to treat it utilization of bronchodilators began in 1901 and fiery parts of asthma were perceived and hostile to-provocative meds were added to the regimens [12]. Firstly, Hippocrates link asthma symptoms to environmental triggers and specific trades and professions [12].

Types of Asthma

Asthma can be of many types as considering the concept about types can help to treat it well according to the particular trigger causing it is. It is as follows,

- Allergic asthma (Extrinsic)
- Nonallergic asthma (Intrinsic)
- Cough variant asthma- very common in children
- Occupational asthma
- Exercise-induced asthma
- Medication-induced asthma - Aspirin-induced NSAIDs induced [11]
- Nocturnal (Nighttime) asthma
- Health condition that may mimic asthma

Detail about above mentioned:

Allergic Asthma (Extrinsic)

It frequently goes in hand to hand. Allergic rhinitis caused by asthma also called the hay fever is inflammation of the innermost lining of the nostril. It's the usually occurring chronic allergic disease. In those with victims of this disease, contact with an allergen causes their immune system to release histamine from mast cells as a part of the defense mechanism. Other most common allergens that can trigger it are Tobacco smoke, Animal dander, Dust mites, Cockroaches, Molds, Pollens, and the symptoms involve inpatient suffering from this are: Patient may feel constant running nose, ongoing sneezing, excess production of mucous, watery eyes, inflamed nasal passage scratchy throat and cough may result from the constant postnasal drip. Symptoms can be subsiding by having medicines prescribed by your doctor. The age onset over is 40 years old for this particular disease [11].

Non-Allergic Asthma (Intrinsic)

Intrinsic asthma tends to start later in life, is more common in females, and is more fatal. Intrinsic asthma includes triggers as weather conditions, exercise, infection, and stress. It does not involve the immune system response [13].

Cough Variant Asthma

In this type, hard coughing is a top - tier symptom along with highly sensitive cough reflex. Also, there may be other reasons for cough like postnasal drip, chronic rhinitis, sinusitis, or gastroesophageal reflux disease (GERD or heartburn). Now a day's asthma is a common cause for cough. Cough variant asthma can't diagnose and treat completely. Triggers for this asthma are usually respiratory infections and exercise. Consulting to doctor is necessary in any persistent case. Your doctor can be asked you for a specific diagnostic test are lung function tests. You might need the reference of specialist also [11].

Occupational Asthma

A common respiratory condition that results from exposures in the workplace. With this asthma, the patient might feel difficulty in breathing and other specific symptoms given below as after joining at that workplace:

- ❖ Airways irritation, obstruction, and inflammation.
- ❖ SOB, chest tightness and cough
- ❖ Symptoms may happen not long after a concise scene of activity or 10 to 15 minutes into a more drawn out time of activity [11].

Exercise-Induced Asthma

It is asthma that occurs while performing an exercise or physical workout, although some people feel the same but it doesn't mean that they are suffering from this asthma.

Victims can feel toughness in breathing after 5 to 20 minutes of the beginning of exercise, making the patient difficult to catch breathe. Along with-it the patient may feel wheezing and coughing [11].

Medication Induced Asthma

The given mechanism of asthma induced by non-steroidal anti-inflammatory drugs include distorted sensitivity to leukotrienes and abnormal release of cytotoxic compounds from platelets other agents that infrequently cause asthma include anesthetic agent and muscle relaxant.

Nocturnal Asthma

Nocturnal asthma can also term as night induced asthma. Symptoms of this asthma appear during sleeping as this asthma is prejudiced by the sleep-wake cycle (circadian rhythm). Common symptoms involve coughing, wheezing, and tough to breathe.

Studies show that the majority of the deaths associated with asthma happen during night time. It's the consideration that this may because of elevation in contact with allergens, cool air, reclining pose, and hormone secretion follows a circadian pattern, also heartburn during the night can cause it. often this asthma occur at night, especially with postnasal drip triggering symptom such as coughing. Even sleeping causes changes in airways function. After monitoring the symptoms worsening at night, you can confer with the asthma doctor [11].

Health Condition that can mimic Asthma

A variety of asthma can imitate the similar symptoms of asthma as cardiac asthma is a form of cardiac failure that shows the same symptoms of regular asthma. Vocal cord dysfunction can also mimic the same, many recent reports drawn the attention toward it, so that chances of misdiagnosis of asthma can reduced [11].

Path Physiology of Asthma

Asthma is a chronic inflammation disorder of airway, as it can be divided either in atopic and non-atopic asthma. Atopic asthma is extrinsic asthma meaning is triggered by the environment. It is the most commonly occurring

one. It involves the inflammation mediated by systemic IgE production. Where nonatopic asthma is intrinsic asthma which is not common. Therefore, it refers to inflammation and constriction of the airway that is not caused by the exposure to allergen the inflammation is mediated by local IgE production.

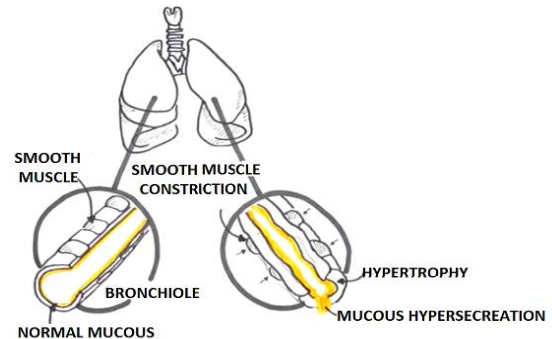


Figure 3: Representation of Hypertrophy

Let us look at the cross-section of a normal lung, the bronchiole of lungs. So here we have a mucous layer and a pseudostratified endothelial cell, the lamina propria, and a smooth muscle surrounding all this and that was normal. If we look at the asthmatic bronchiole the lumen layer inside is much narrow but before we focus on the asthmatic bronchiole let look at a normal histological layer of bronchioles. So here we have the mucous and, on this layer, pseudostratified epithelial cell below this we have the basal membrane with thingy epithelial layer, we can also confine. We have lamina propria which contain many cells including macrophages and mast cells, mast cells are responsible of secreting histamine below the lamia propria or surrounding the lamina propria, we have the smooth muscles, now if we compare the normal bronchial layer to asthmatic we can see many differences, firstly there is an increase in mucous production, so increase in goblet cell. Also increase in other cell types including neutrophils during inflammation as well as t helper cell, we can also find the smooth muscle hypertrophy, because of these changes like Airflow obstruction, Bronchiole hyper-responsiveness because of histamine release and Inflammation.

The main one IgE antibody is important because they can bind to receptor and mast cell forming mast cell-IgE complex. The mast cell-IgE complex will recognize allergens and essentially begin the release of histamine. Now two types of T-helper cell is T- helper -1 and T-helper -2. The T- helper-1 is normally found in lungs however there is an imbalance in asthma because in asthma T- helper- 2 cells that are not normally found in lungs are unregulated in asthma so we have more T-helper -2 cell in asthmatic lungs. T-helper -1 normally promotes an inflammation by increasing cell-mediated immunity. However, T- helper- 2 cells normally promote it by humoral immunity so promoting antibody production.

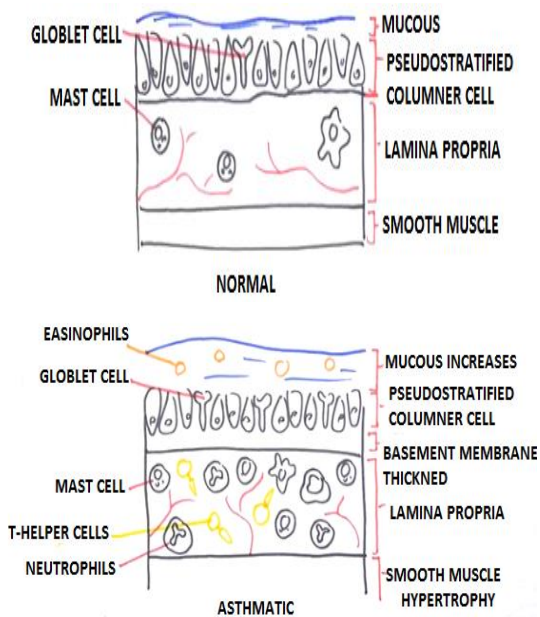


Figure 4: Representation of normal and asthmatic condition

Let put all these cells together and create a diagram looking at the path of asthma and specifically focus on atopic asthma so here we have the pseudostratified columnar epithelial cell with the goblet cell secreting a mucous on top and here we have a lumen below the pseudostratified columnar epithelial and a lamina propria having a mast cell, dendritic cell, and macrophages.

Let allergens enter and they will trigger a reaction so few things can happen, the first

thing is the allergen will engulf by dendritic cell and active this dendritic cell, also the columnar epithelial cell recognize it and secrete a substance called a thymic stromal lymphocyte. It will condition activated dendritic cells to produce a chemokine to attract specifically t helper 2 cells. The activated dendritic cell itself will active the t helper cell to differential t helper 2 cell and also secrete a chemokine to attract the T-helper-2 to the area, to the bronchiole, or the lungs so the activated t helper 2 cell. The first thing the t helper role is to promote a humoral immunity so it will stimulate plasma cell through IL-13 and IL-4 and this will promote IgE production by plasma cell.

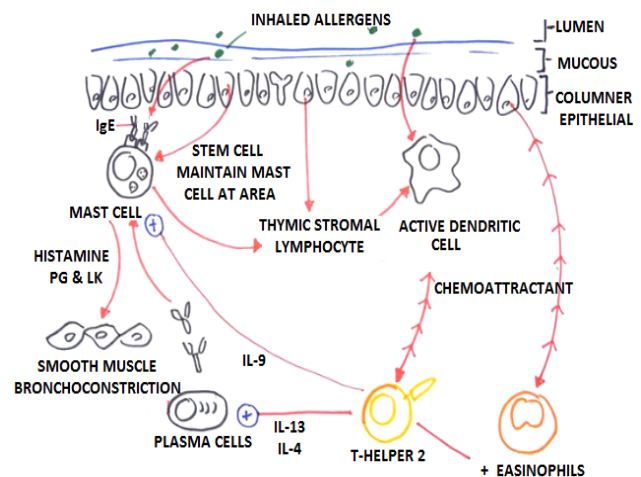


Figure 5: Pathogenesis of asthma

IgE will help to bind a mast cell to make mast cell IgE complex. T-helper-2 itself through IL-9 will stimulate and promote mast cell actively. another important function of t helper cell is to stimulate eosinophil produced from a bone marrow through IL-5. so that more eosinophil, there is a chemotactic thing occurring that attract the eosinophil to the lungs so we have increased in eosinophil amount in lungs so the allergens will bind to IgE mast cell complex, cause the mast cell to release a few things mainly histamine, prostaglandins, all these specifically histamine will stimulate a smooth muscle in the airway to cause a constriction of bronchiole also the endothelial cell released a stem cell that will essentially maintain a mast

cell to the area so that you can imagine If IgE is being produced essentially a memory being produced whenever a same type of allergen is inhaled it will trigger this whole process you get [13].

Diagnosis of Asthma

Diagnosing asthma mild, moderate and severe to learn if you are suffering from asthma see a doctor to be a diagnosis and doctor question you, examine and do lung test and other days you might need some these test on a different day or after taking a certain medicine of asthma can run in family so your doctor will probably ask you if anyone else in your family has asthma allergy or even cold that last the long time your environment meaning your home, inside your home, the place you work and other places where you spend time can cause asthma or make it worse your doctor question you about your environment this include if you have pets, living area with a lot of grass, traffic and spend time around a people who smoke. An important test for it called spirometry.

Spirometry check in what manner will your lungs working you will be approached to blow into a machine as a hard, quick and long as you can if you don't blow air is a lot or quick as a sound people you could have asthma you may step through the examination again after utilizing a medication that opens up the aviation route if your outcome improved this is another indication of asthma. FEV₁ (Forced Expiratory Volume) implies FEV in 1 second for every constrained indispensable limit is under 70% considered as constructive test [8].

There is another test named peak expiratory flow variability test in this your doctor monitor the peak flow variability for around 2 to 4 weeks in the age group of 17 and over. If the value is more than 20% variable then the test is considered to be positive. This test is similar to children and young ones below 16 [8].

Your doctor might order an x-ray and other scans to look out your lungs. you might also have a blood test, one blood test checks the number of WBC called an eosinophil, some people with asthma have high level of eosinophil. Another blood test will check the level of anti-body named IgE. Elevated IgE can be a sign of allergies. The skin test may also be conducted to check the elevation of IgE. A test called a bronchoscopy to use a tiny tube that goes inside your lungs through the tube your doctor can take the sample of mucous or fluid. The sample tells your doctor even more about your condition. Your doctor also should assess the severity of asthma. Therefore, the main level or grade of asthma is intermittent, mild, moderate, and severe.

Intermittent asthma causes symptoms occasionally for example you probably have a cough two days a week or less. Your asthma does not affect a daily activity. In this spirometry results are normal or almost normal. In mild asthma symptoms are more than twice a week but not every day your daily activity is slightly affected. You probably use quick-relief medicine such as inhaler more than twice a week or take asthma controller medicine.

In case of moderate asthma your symptoms will be on every day you use a quick-relief medicine daily and having asthma impacts your daily activity you take one or two daily controller medicine beside your quick-relief medicine.

In case of severe asthma your symptoms bother you each day and wake you upon much night. You use your quick reliever inhaler many times a day you take more than two asthma controller medicine. With still have symptoms you might feel like asthma controls your life. Knowing the causes of severe asthma can help control it. severe asthma can be related to allergens your body produces a certain type of WBC called eosinophils or neutrophils or overdeveloped airways muscle an asthma specialist can prescribe specific treatment that can help to

treat other health problem are important to treat asthma. Triggers term for things that make your asthma worse it important to learn about your asthma trigger around avoid them. In this case you need to see the doctor regularly to control it [8, 9].

Classification of Drugs

Bronchodilators

Bronchodilators are made with the goal that it widens the bronchi and bronchioles, diminishing the obstruction in the respiratory aviation route and expanding the wind stream to the lungs. Bronchodilators might be endogenous bronchodilators that are short-acting or long-acting. For example, Salbutamol, terbutaline, bambuterol, salmeterol, formoterol, ephedrine, Methylxanthines are Theophylline (anhydrous), aminophylline, choline theophylline, hydroxyethyl theophylline.

Mechanism of action: It increases the level of energy-producing cAMP. The enzyme named phosphodiesterase (PDE) inhibits it, this causes the breakdown of cAMP. It causes a decrease in cAMP level, smooth muscle relaxation, bronchodilation, and increased airflow.

Therapeutic uses: dilation of the airway in asthma, chronic bronchitis, and emphysema, treat mild to moderate cases of asthma, also act as adjacent therapy for the relief of pulmonary edema.

Side effects: Nausea, vomiting, anorexia, gastroesophageal reflux during sleep, palpitations, transient increased urination

Leukotriene antagonist

A leukotriene opponent is a medication that works as a leukotrienes related compound inhibitor (arachidonate 5 - lipoxygenase) or leukotrienes receptors rival and therefore contradicts the capacity of these provocative middle people; leukotrienes are created by the resistant framework. Leukotrienes receptor enemies, for example, montelukast, zafirlukast can be utilized to treat these infections. They are

less powerful then corticosteroids for treating asthma, yet progressively compelling for treating certain pole cell issue. For instance Montelukast, zafirlukast.

Mechanism of action: Montelukast, zafirlukast is competitively preventing the broncho-constrictor effects of leukotrienes by blocking their receptor; prevent leukotrienes from attaching to a receptor on cells in the lungs and circulation and blocking the inflammation in lungs.

Uses: Prophylaxis and chronic treatment of asthma.

Side effects: Headache, stomach pain, heartburn, upset stomach, nausea, diarrhea, tooth pain, tired feeling, fever, stuffy nose.

Mast cell stabilizers

Administered by inhalation, they can't act as a bronchodilator and not effective in the attack of asthma, and better in children than adults. For example, Sodium chromoglycate.

Mechanism of action: It blocks the histamine from mast cells also blocks the eosinophils, neutrophils, macrophages, and mast cells.

Side-effects: Bitter taste, minor upper respiratory tracks.

Uses: Prophylactic therapy in asthma especially in children, allergic rhinitis, conjunctivitis.

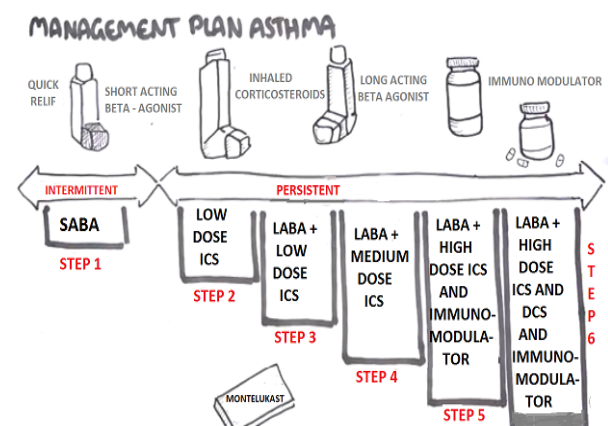


Figure 6: Management of asthma

Corticosteroids

Actually, they are not bronchodilators but given as prophylactic medication and can be used alone or in combination with beta-agonists. For

example hydrocortisone, prednisolone, beclomethasone, fluticasone propionate, flunisolide, ciclesonide.

Mechanism of action: It inhibits the phospholipase A2 and leads to a decrease of prostaglandins and leukotrienes. It also stabilizes the mast cell and decreases the production of histamine release and acts by upregulation of beta 2 receptor.

Side effects: Adrenal suppression, growth retardation in children, glaucoma, osteoporosis.

Anti- IgE antibody

A monoclonal antibody directed against human IgE. It binds to the IgE sensitized mast cell and prevents activation by asthma triggers the subsequent release of inflammation mediators. For example, omalizumab. It is expensive, not a first-line treatment [17].

Government role in eradicating asthma

The higher authorities from every corner of the globe play a vital role to cope up with this chronic disease Asthma. They have started enormous programs to reduce the various effects of asthma on people who are suffering from this disease. The following are some of the major programs which have been embarked on to get up from asthma.

HARP (Home asthma response program)

This program is based on evidence designed to reduce preventable asthma emergency department visits & hospitalizations in high-risk asthma patients, it has been intensively divided into three sessions.

1. Asthma patients, knowledge-based.
2. Self-management education.
3. Cost-effective management.

Its main aim is the reduction in the cost of asthma. HARP is still a cost-effective (investment=saving) and the overall rate of return on investment is positive that is 65% [14].

Implementing an asthma home visit program

US has launched a nationwide asthma public education and prevention program. The aim is to spread awareness among the public and medical community about environmental asthma triggers and simple ways to reduce asthma, especially at home.

Proper medical treatment and effective management of environmental triggers in surroundings can lessen the number and severity of an individual asthma episode. Seven health care's organizations help in guiding with input that offer asthma home visit [2, 15].

An investment in American health

The centers for disease control and prevention (CDC) and national asthma control program (NACCP) helps millions of Americans to understand, manage, and gain control over their asthma. CDC launched the NACCP in 1999 to address the rising public health impact of asthma. An educated family, providers and school systems also help in preventing asthma attacks. Asthma programs can be controlled when people put their all efforts and have appropriate care, education, and guidance [16].

MCAN (Merck childhood asthma network)

It funded the implementation of projects in a varied set to improve high-quality asthma care for children. During its occupancy, MCAN approved more than \$20 million to programs set in some of the nation's most impoverished, at-risk communities to study the impact of evidence-based interventions on symptoms and urgent care use of children living with asthma MCAN works from 2005 to 2015 as a respected authority [2].

Conclusion

The types of asthma according to various triggers have been given in the research paper. Effectively diagnosing people who are having new symptoms of asthma are preventing by some sections on diagnosing and monitoring asthma. This section has developed a

personalized action plan owing to provide clear evidence for health care professionals and people with asthma. Its main objective is to ensure the possible treatment for their current level of illness. This plan can be supported by the self-management of asthma. This is becoming the pathway for uncontrolled asthma by focusing on the pharmacological management of chronic asthma. All kinds of treatments, risk factors, triggers, and self-management are fully covered.


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