International Journal of Rural Development, Environment and Health Research
[Vol-8, Issue-2, Apr-Jun, 2024]
Issue DOI: https://dx.doi.org/10.22161/ijreh.8.2
ISSN: 2456-8678 ©2023 IJREH Journal

Diagnosis and Management of Asthma: A Review

Racheal Gill *, Rajesh Kumar, Ajeet Pal Singh, Amar Pal Singh, Prachi sharma

Department of pharmacy, St. Soldier Institute of Pharmacy, Lidhran campus, Behind Nit(R.E.C), Jalandhar-Amritsar By Pass, Nh-1, Jalandhar-144011, Punjab, India
*Address of correspondence: Department of pharmacy, St. Soldier Institute of Pharmacy, Lidhran campus, Behind Nit(R.E.C), Jalandhar-Amritsar By Pass, Nh-1, Jalandhar-144011, Punjab, India
Email-rachealgill67@gmail.com

Received: 30 Jan 2024; Received in revised form: 12 Mar 2024; Accepted: 22 Mar 2024; Available online: 03 Apr 2024

Abstract—*Asthma is a common chronic disease characterized by respiratory symptoms such as wheezing, coughing, chest tightness, and shortness of breath. These symptoms are usually associated with airflow limitation due to inflammation and airway constriction. Asthma is a significant global health issue, impacting millions of people and causing considerable morbidity.It is known for its heterogeneity and its pathophysiology involves a complex interplay of genetic, environmental factors, leading to inflammation, airway hyperresponsiveness and airway remodeling. Grasping the severity of asthma is crucial for tailoring treatment strategies effectively. Treatment of asthma aims to achieve symptom control , improve ling function and prevent its worsening. The pharmacologic treatment of asthma typically involves a stepwise approach based on severity and frequency of symptoms. For intermittent asthma , short -acting beta agonists (SABAs) are commonly used for quick relief of symptoms and for persevere asthma , inhaled corticosteroids (ICS) are main stay of treatment to reduce airway inflammation and prevent axacerbations. In more severe cases or when ICS alone are not sufficient ,a combination therapy of ICS with long - acting beta agonists (LABAs) is recommended to provide both anti-inflammatory and broncodilator effects.*

Keywords— Asthma; asthma dignosis; asthma pathophysiology; asthma treatment; biologics.

I. INTRODUCTION

Asthma is indeed a significant global health issue,impacting a large number of individuals worldwide. Estimates suggest that as many as 235 million people suffer from asthma ,making it one of the most common chronic respiratory conditions characterized by inflammation and narrowing of the airways, leading to symptoms like wheezing ,coughing, chest tightness ,and difficulty in breathing.[1].Pathophysiology of asthma is multifaceted and involves a combination of genetic, environmental, and immunological factors .At the genetic level ,there are variations in genes related to immune responses and airway inflammation. Environmental factors such as allergens ,air pollution, respiratory infections, and occupational exposures can trigger or exacerbate asthma symptoms.[2].At organ level, asthma involves inflammation and hyperresponsiveness of the airways, leading to bronchoconstriction and airway obstruction. This inflammatory response is mediated by various immune cells, cytokines and inflammatory mediators.[2] Asthma is indeed a common chronic disease characterized by recurrent episodes or persistent respiratory symptoms such as wheezing, shortness of breath,coughing, and chest tightness. These symptoms are often associated with airflow limitation due to inflammation and constriction of the airways.[3,4].Asthma treatment is vital for managing symptoms, preventing exacerbations, and enhancing quality of life. However, several barriers can hinder effective management, including medication non-adherence, limited access to healthcare, socioeconomic disparties, comorbidities, and environmental triggers.[4].Overcoming these barriers is crucial to

achieving optimal patient outcomes and reducing the risk of morbidity and mortality associated with uncontrolled asthma [4].This review will focus on diagnosis and treatment of asthma.

II. DIAGNOSIS

The following criteria were used to diagnose asthma: (i) reversible obstruction of the airways that varied significantly, both spontaneously and in response to treatment, (ii) sporadic wheezing (usually worsened on expiration and typically relieved by inhaled beta2 agonists),coughing (usually ineffective), shortness of breath (not always associated with wheezing), and chest tightness;(iii) the possibility of being triggered by various factors, emotions, occupational agents, food additives, weather variations, endocrine factors, and upper respiratory tract viral infections; and (iv) a decrease in forced expiratory volume in one second (FEV1; absolute value and/or percentage of predicted value) and/or peak expiratory flow (PEF) during the breathing cycle.[3].Spirometry, which measures lung function while diagnosing asthma, and pulse oximetry which measures the amount of arterial hemoglobin coupled with oxygen and monitors oxygen saturation (SpO_2), are used to diagnose asthma.

CLINICAL DISPLAY OF ASTHMA:- It can be challenging to diagnose Asthma because the symptoms might be vague and variable. Sickness that worsens during the night and early morning is common in patients who also regularly complain of coughing and wheezing [4].Exercise, certain allergens, irritants and other triggers can all contribute to the symptoms which are frequently episodic.Wheezing is the most common and sensitive symptom for the diagnosis of asthma and nocturnal dyspnea and asthma diagnosis has a substantial link (Relative risk: 26% and 29% respectively)[5,6]. Breathing problems that are worse at night or in the morning, that fluctuate in duration and severity and has an increased risk of receiving an asthma diagnosis is linked to particular triggers [7]. Conversely, persistent sputum production, chest pain and a single cough without any other respiratory symptoms reduce the likelihood of asthma. In order to diagnose asthma and confirm the existence of variable airflow limitation, a thorough history- taking is crucial. Confirmation of the disease‘s existence by a doctor is necessary [7].

DIGNOSTIC DIFFENTIATION :- Considering different differential diagnosis is crucial .Since, asthma can mimic other illness .Diagnosis make on other patients who exihibit symptoms similar to asthma. Other conditions that might be differentiated from asthma include illnesses of upper and lower respiratory tracts, disorders of the mental disorders as well as digestive and cardiovascular system [8]. For instance, wheezing and pulmonary vascular congestion and edema [9]. Treatment for the underlying heart failure frequently results in symptom alleviation for this illness which has been dubbed as ‘Cardiac Asthma‘‘[10].Another typical differential diagnosis for asthma is vocal cord dysfunction(VCD). These individuals frequently have recurring episodes of asthma that do not respond to corticosteroids orbronchodilator therapy. The cause of VCD is paradoxical vocal cord motion-induced episodic extrinsic airway obstruction, which is intimately linked to gastro oesophageal reflux disease. Acid reflux,sadness,anxiety and laryngopharyngeal reflux [11].Acknowledging VCD is critical to reducing needless corticosteroids exposure and medical use [11].Occlusive lung illness that progress over time and manifests similarly to asthma is called chronic obstructive pulmonary disease(COPD). Each illness impairs the small airways and cause airflow obstruction as detected by spirometers; however, patients with COPD often have a substantial smoking history and have limited airway hyper responsiveness(less than 12% improvement in forced expiratory flow in one second [FEV]following bronchodilator inhalation on the pulmonary function test[PET]. There is a range of obstructive disorders that includes asthma and COPD and it can be challenging to differentiate between them. Since, this can make the difference between the two diseases more challenging particularly in individuals with chronic, poorly managed asthma that results in fixed airflow obstruction due to persistent inflammation and airway remodeling[4,12]. Certain patients may develop long-term, ongoing airflow restriction that resembles asthmatic symptoms and satisfy the identification of the asthma-COPD overlap Syndrome[13].Comprehending and identifying these two illness process is crucial.

BOX:1 Differential Asthma Diagnosis

1. **Upper Respiratory tract**
Dysfunction of the vocal cords
Both sinusitis and allergic rhinitis
Phenotypic bronchomalacia
Stenosis of the trachea

2. Lower Respiratory tract
Long term obstructive lung disease
Aspergillosis bronchopulmonary allergic
Blockage of the endobronchi due to a foreign body or mass
Churg-strauss illness
Blepharitis obliterativa
3. Heart Related
Heart failure with congestion
Pulmonary embolism
Heart hypertension
4. Gastrointestinal Disease
Gastro-oesphageal reflux
5. Psychiatric
Nervousness
Panic attacks

SPIROMETRY AND BRONCOPROVOCATION EXAMINATION;- Now, the Global Initiative Spirometers testing is advised for patients suspected of having Asthma by the Global Initiative for Allergy and Allergy prevention (GINA) and other organizations [7,14,15].The Symptoms of Asthma includes variable airway obstruction, hyper responsiveness and airflow obstruction with a FEV/FVC ratio<0.7 or less than the lower limit of normal(LLN). Additionally, airflow reversibility following inhalation of a short-acting beta-2 agonist (SABA) is defined as FEV improvement of at least 12% and 200ml indicates an asthma diagnosis. Nonetheless, Asthma patients may exhibit normal spirometers results due to the fluctuating nature of airway restriction.Met choline or mannitol bronchoprovocation can be helpful in diagnosing asthma in these patients with normal spirometers values. Currently utilized and recommended for diagnosis include a provocation dose(PD20)<400Hg and a decline of >20% in FEV provocation concentration(PC20<16 mg/ml). Met choline is a sensitive diagnostic technique for asthma because it directly stimulates the smooth muscles in the airway by binding to acetylcholine receptors, which causes bronchoconstriction and airflow blockage. Met choline inhalation will cause a heightened reaction in asthmatic patients and this test can help identify asthma particularly in people who are experiencing acute asthma[16].As an indirect inducer of bronchoconstriction mannitol dry powder is more sensitive than specific diagnostic tool. Met choline and mannitol have comparable sensitivities and specificities when it comes to diagnosing asthma, according to several studies particularly when the patients doesn‘t have any current symptoms[17,18]. Therefore, bronchoprovocation testing can be helpful in ruling out asthma, particularly in patients who are not receiving inhaled corticosteriods medication this time.

NITRIC OXIDE FRACTIONAL EXCREATION:-The airway epithelium produces nitric oxide(NO), which is an indirect indicator of the heightened irritation of the airways[19,20].It is simple to measure the amount of NO in exhaled breath and it has been used to identify the airway inflammation in patients both diagnosed with suspected of having asthma.Nevertheless, fractional excretion of NO (FeNO)is less helpful in the diagnosis of the non-eosinophilic asthma since it is more susceptible to eosinophilic airway inflammation. FeNO <25ppb in adults are advised by the American Thoracic Society (ATS) as a sign of the decreased probability of corticosteroid responsiveness and eosinophilia inflammation[20].Data on the use of FeNO in asthma monitoring have proven inconclusive. Research has demonstrated that there is a correlation between closely with the severity of Asthma and that sputum eosinophil count and FeNO monitoring for asthma can help lower the overall amount of inhaled corticosteroid exposure (ICS)[21,22].Nevertheless, a research by show and colleagues [23]. Demonstrated that neither the overall amount of ICS use nor the the number of asthmatic exacerbations in those patients had significantly decreased. Monitored with FeNO as opposed to unmonitored. Furthermore, a research by Szefler etal.[24] revealed that ICS dosages were higher in individuals under FeNO testing monitoring than in those not under FeNO monitoring ,despite no improvement in symptoms. The ATS guidelined still advise using FeNO measurements to track asthma patients disease activity in spite of these findings[20,25].

TRY-OUT CHALLENGE TESTING:-Exercise-induced bronchoconstriction (EIB) patients can be diagnosed with exercise challenge testing.26 Patients quickly increase their exercise intensity on a treadmill or stationary bike every 2-4 minutes throughout this test in order to reach a high level of ventilation that

is at least 17.5–21.0 times their baseline FEV1. The diagnosis of EIB is made when the FEV1 falls by more than 10%; levels of >25% and <50% indicate moderate EIB, while >50% indicates severe EIB.26 Consideration should be given to exercise challenge testing in individuals who have a negativework-up and a suspicion of EIB.

ASTHMA SEVERITY :-For an illness to be managed, it is critical to comprehend its severity. NAEPP guidelines emphasize the need of understanding illness severity in order to commence therapy and achieve disease control[15]. The definition of severity according to the NAEPP is the intrinsic intensity of the disease prior to treatment with long-term control therapy. The severity of asthma can be classified as severe and persistent, mild, moderate, and intermittent. In asthmatics who have not yet started therapy, factors such as the frequency of daily activities, and lung function are taken into consideration when assessing the severity of the disease. Based on the level of active treatment required to attain adequate asthma control, GINA determines the severity of the condition. To determine severity, patients must have been using controller drugs for a few months. The idea is to gradually increase treatment to the lowest level that will still keep the patient under control.[7].Long-acting controller drugs often provide effective symptom control for most patients; nevertheless, in patients who continue to have symptoms, it is important to evaluate the patient's proper diagnosis, compliance, inhaler technique, co-occurring diseases, and continued exposure to sensitizing agents. Symptom control questionnaires have been created and validated as a quantitative assessment of patient symptoms, as asthma is a clinical condition and sometimes a patient's disease severity cannot be accurately determined by Spiro metric measurements. To help a clinician better understand a patient's symptoms, the Asthma Control Test (ACT), the Asthma Quality of Life Questionnaire (AQLQ), and the Asthma Control Questionnaire (ACQ) can be utilized at every appointment.From [27 , 29].Peak expiratory flow rate (PEFR) measurements are another crucial objective tool for tracking a patient's illness course and escalating the controller regimen. Research conducted by Ignacio-Garcia and Gonzalez-Santos [30] and Lahdensuo et al. [31] demonstrated that participants in an asthma self-management program who underwent daily PEFR home monitoring experienced enhanced lung function, decreased usage of extra medication, and better healthcare utilization. But because PEFR readings can vary significantly during the day—up to 20%—GINA now advises against using PEFR monitoring for anyone other than individuals with severe asthma or those who have trouble perceiving a major airflow restriction.[7]

THE PHENOTYPIC MANIFESTATIONS AND ASTHMA PATHOLOGY :-Chronic asthma is a disease of the airways with a variety of pathophysiologies, including pathways involving neutrophils, granulocytes, eosinophils, and paucigranulocytes. When an allergen or pathogenic agent enters the airway, epithelial cells release thymic stromal lymphopoietin, which is part of the traditional pathway of asthma. Th2 cells are then stimulated by this, and they start to release a variety of cytokines, such as IL-4, IL-5, and IL-13. The airway hyperresponsiveness that results from these cytokines is subsequently caused by the production of IgE and the activation of eosinophils (Figure 2).(25)Histamine, prostaglandins, and cysteinyl leukotrienes are released when IgE attaches to high-affinity IgE receptors on mast cells, and these substances also contribute to bronchoconstriction.[32]The non-eosinophilic pathway of asthma is characterized by the activation of macrophages and airway epithelial cells by TLR4 and CD14. This process produces IL-8 and NFκB, which in turn activate neutrophils.[33, 34] Asthma comes in a variety of phenotypes and endotypes, each with a unique mechanism and clinical manifestation. Previous large-scale investigations have classified asthma patients into clusters based on clinical characteristics such as sex, age of onset, allergy status, lung function, and asthma symptoms. Although a wide variety of phenotypes have been identified, the majority can be identified based on factors such as early or late onset, the existence of atopy and notable allergy symptoms, the degree of lung function decrease, and the response to treatment.[32, 35, 36]Individuals with early-onset allergies are individuals who exhibit symptoms that persist into adulthood, beginning in childhood. These patients respond effectively to therapies that focus on the Th2 response and IgE downregulation. They frequently exhibit elevated IgE levels along with related allergy and atopic symptoms. In contrast, patients with the late-onset eosinophilic phenotype exhibit symptoms that are less allergic in nature but more severe and chronic.Cysteinyl leukotriene pathway overexpression is the primary cause of these patients'

disease process, and they frequently do not respond as well to corticosteroids. Patients with a substantial sputum eosinophil count (>2%) and a favorable response to corticosteroids are classified as having an eosinophilia phenotype. The phenotype of exercise-induced asthma is the activation of Th2 and mast cell cytokines, frequently accompanied by moderate, intermittent symptoms that worsen during physical activity.Individuals that have a phenotype linked to obesity do not have Th2 biomarkers and their road to airway hyperresponsiveness is less obvious. Patients who have persistent asthma and are less sensitive to corticosteroids are included in the neutrophilic phenotype. These individuals typically respond well to biologics and other therapies, such as macrolide therapy, and frequently have higher neutrophil counts with exacerbations. Patients with bronchopulmonary mycosis, exercise-induced asthma, and aspirin sensitivity will require extra therapy aimed at addressing each non-allergic cause. Determining one's treatment plan thus requires an understanding of the various phenotypes and endotypes.We can more precisely target medical therapy and create new drugs that target particular pathogenic pathways of asthma as we gain a deeper understanding of the many asthma phenotypes and the biomarkers that distinguish them.

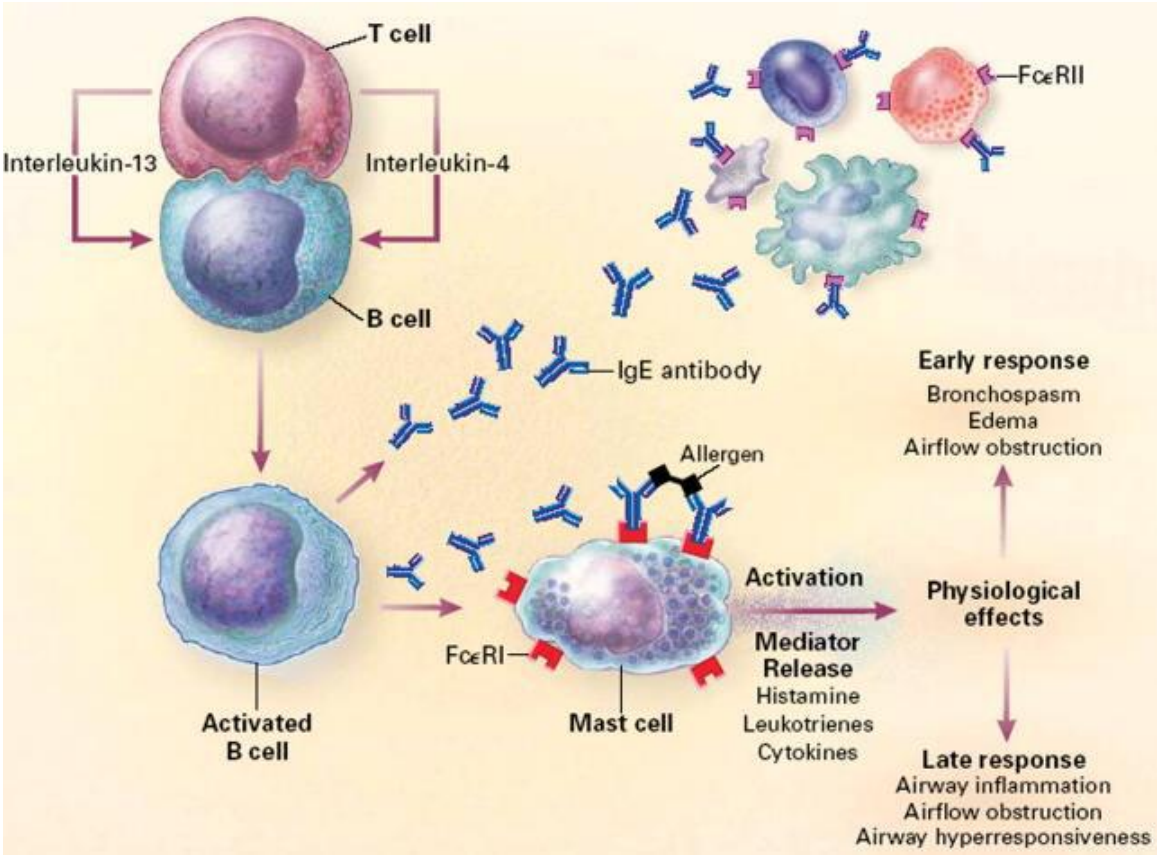

Fig 1:- Asthma Pathology

III. TREATMENT

Controlling symptoms and averting further exacerbations are the main objectives of asthma treatment.(7,8). It entails a personalized treatment plan in addition to knowledge of the diverse pathophysiology and phenotypes of asthma. Increased awareness of deteriorating symptoms, approaching exacerbations, and the necessity of titrating treatment for better symptom management can be achieved by patient education and a documented asthma action plan.(7, 8, 15). It has also been demonstrated that self-management and a shared care strategy enhance asthma results.(37, 38). Furthermore, it is imperative that all asthma patients receive education regarding correct inhaler usage, medication compliance, and allergy and irritant avoidance.It is advised to address pharmaceutical conditions step-by-step. The previously mentioned NAEPP asthma severity classification—intermittent, mild, moderate, and severe persistent—determines the first treatment option.(15)According to GINA standards, a step-up or step-down therapy is advised based on symptom control.(7). As of right now, SABA inhalers are advised for all asthma sufferers as a form of rescue medication. It is advised to add low-dose ICS when titrating dosages for individuals with chronic asthma. Leukotriene inhibitors or long-acting beta-2 agonists (LABA) are frequently added to the lCS regimen for patients with moderate-to-severe chronic asthma. Biologic drugs may be used selectively for people whose asthma is more severe or challenging to manage.

Table: Treatment steps for bronchial asthma

	Treatment step 1	**Treatment step 2**	**Treatment step3**	**Treatment step 4**
Long-term management agents	Inhaled corticosteroid (low dose)	Inhaled corticosteroid (low to medium doses)	Inhaled corticosteroid (medium to high doses)	Inhaled corticosteroid (high doses)
	If the above agent cannot be used, use one of the following agents.LTRA Theophylline sustained release preparation (unnecessary for rare symptoms)	If the above agent is ineffective, concomitantly use one of the following agents,LABA(a compounding agent can be used) LTRA Theophylline sustained release preparation	Concomitantly use one or more of the agents of those below. LABA (a compounding agent can be used) LTRA Theophylline sustained release preparation LAMA	Concomitantly use multiple agents of those below.LABA (a compounding agent can be used) LTRA Theophylline sustained release preparation LAMA Anti-IgE antibody oral corticosteroid
Additional treatment	Anti-allergics other than LTRA	Anti-allergics other than LTRA	Anti-allergics other than LTRA	Anti-allergics other than LTRA
Excerbation treatment	Inhaled SABA	Inhaled SABA	Inhaled SABA	Inhaled SABA

BETA -2 AGONISTS:-When it comes to managing acute exacerbations of asthma and controlling the condition overall, beta-2 agonists are crucial bronchodilators. They cause bronchodilation and smooth muscle relaxation by binding to the beta-2 adrenergic receptors on the smooth muscle cells in the bronchi.[39, 40]ICS can occasionally be added to the treatment of individuals with mild intermittent asthma to limit the use of SABA. SABA are frequently used to treat mild intermittent asthma and acute exacerbations, but they shouldn't be viewed as controller medications; increased use of SABA has been linked to worse asthma control.[41] SABA have a quick beginning of action (one to five minutes), peak effects at two hours, and a median duration of action of three hours. They are particularly useful in treating acute bronchoconstriction.[42–44] Albuterol, levalbuterol, terbutaline, metaproterenol, pirbuterol and other SABA examples.Salmeterol and formoterol are examples of LABA, which can have bronchodilator effects that persist longer than 12 hours.[44] However, patients with

asthma should only be taken LABA in addition to ICS. More than 26,000 asthma patients were examined in a sizable randomized control study (SMART45), which contrasted the effects of adding LABA (salmeterol) and a placebo to standard asthma treatment. Researchers discovered that those treated with LABA experienced more life-threatening events and deaths linked to respiratory and asthma than those getting a placebo. However, numerous studies have demonstrated the safety and advantages of the LABA/ICS combination. Research conducted by Peters et al. [46], O'Byrne et al. [47], and others revealed that using a combination of LABA and ICS was linked to better lung function and a decreased chance of aggravation of asthma when compared to using ICS alone. As a result, using a combined LABA–ICS inhaler is a safe and possible next step for asthmatic patients.

CORTICOSTERIODS: Since many patients with asthma have an inflammatory phenotype, corticosteroids are essential for controlling chronic illness and managing acute asthma exacerbations. ICS have a significant role in the therapy of chronic asthma, particularly in individuals who exhibit an eosinophilic phenotype. By inhibiting eosinophil and mast cell activation, the medications reduce airway hyperresponsiveness and the inflammatory reaction to allergens.[48] Research has demonstrated that when ICS (budesonide) was used, peak flow measurements were higher in asthma patients than in those receiving only beta-agonist therapy.Additionally, it has been demonstrated that ICS enhance lung function and lower exacerbation rates.[51, 52] It has been discovered that adding LABA to ICS helps people with moderate-to-severe chronic asthma. When compared to fluticasone alone, studies by Kavuru et al.[53] and Shapiro et al.[54] shown that salmeterol and fluticasone combination improved PEFR, symptom scores, nocturnal symptoms, and albuterol use. According to a research by O'Byrne et al.[47], adding LABA to ICS further enhanced overall lung function and decreased the likelihood of severe exacerbations and poorly managed symptom days. Beclomethasone, triamcinolone, flunisolide, ciclesonide, budesonide, fluticasone, and mometasone are a few examples of ICS that are now on the market. Particularly crucial for the management of uncontrolled asthma and acute asthma exacerbations are systemic corticosteroids. Reduced systemic inflammation and constriction of the bronchi can be achieved with systemic corticosteroids used for a brief period of time. However, because systemic corticosteroids are linked to a number of long-term side effects, including as weight gain, gastritis, osteoporosis, hypertension, adrenal suppression, and psychosis, their long-term usage is discouraged. When treating an acute asthma exacerbation, there is no set amount or duration of corticosteroids that is advised.[55] Patients should be evaluated for biologic pharmaceutical treatment and for co-occurring diseases before being directed to an asthma specialist if they are unable to wean themselves off of systemic corticosteroids to maintain disease control.

LEUKOTRIENES RECEPTORS AND INHIBITORS OF SYNTHESIS :-Lipid mediators called leukotrienes contribute to airway inflammation and bronchoconstriction. Leukotriene - modifying medications, such as zileuton, montelukast, and zafirlukast, function as competitive antagonists of the leukotriene receptors or by preventing the production of leukotrienes.[45] Mast cells and eosinophils release cycloxyl leukotrienes, which are involved in increased mucus secretion and smooth muscle contraction in the bronchi.[56] These medications reduce airway inflammation by acting as receptor antagonists and blocking the production of leukotrienes; they have also been demonstrated to enhance lung function and asthma symptoms, and they can be used as a supplement to ICS. According to current guidelines, leukotriene receptor antagonists should only be used as an adjuvant therapy for patients undergoing combined LABA/ICS or as an alternative to ICS in cases of moderate persistent asthma in patients who cannot tolerate ICS.

ANTAGONIST OF MUSCARINICS :-Antimuscarinics have been used for hundreds of years to treat dyspnea and bronchoconstriction.[57] Mucus secretion and airway smooth muscle constriction are facilitated by the parasympathetic nervous system, which is regulated by acetylcholine and the activation of muscarinic receptors.[58] In order to prevent this vagally mediated muscarinic receptor activation, which results in bronchodilation, antimuscarinics are utilized. As of right now, ipratropium is a short-acting muscarinic antagonist (SAMA) whereas tiotropium, aclidinium, umeclidinium, and glycopyrronium are long-acting muscarinic antagonists (LAMA) .In order to treat severe, poorly managed asthma exacerbations, SAMA and LAMA might be added to LABA/ICS therapy as a maintenance medication.[59] Peters et al.[60] examined the effectiveness of tiotropium added to beclomethasone vs

increasing the dosage of beclomethasone or adding salmeterol to beclomethasone in 210 asthma patients. Tiotropium was found to have superior improvements in PEFR, asthma control days, FEV1, and daily symptoms when compared to increasing the quantity of ICS or adding salmeterol.[60].Additionally, the efficacy of tiotropium in patients with poorly controlled asthma on high-dose ICS/LABA treatment was examined in two replication trials, PrimoTinA-asthma 1 [61] and PrimoTinA-asthma 2, [62].According to this study, patients who received more tiotropium had better FEV1 and a shorter duration to their first severe exacerbation, as well as a 21% lower chance of exacerbation.[63] LAMA is still an option for treating people with poorly managed asthma.

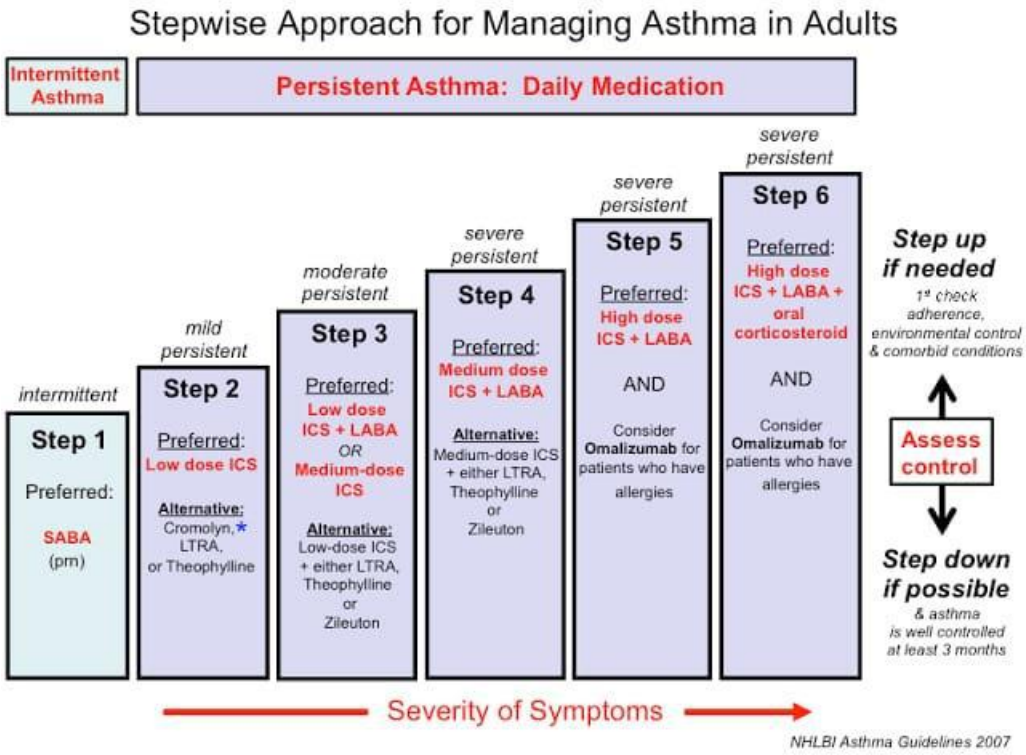

Fig2: Stepwise approach for managing asthma

BIOCHEMICAL INTERVENTIONS:-It is important to use caution while using biological agents in people with severe asthma. These individuals can attain control while reducing their exposure to oral corticosteroids thanks to the targeted use of biologic therapy (Table 1).[64–72]The first biologic for asthma to be approved, omalizumab functions by attaching to IgE and reducing the activation of airway inflammation. Omalizumab has been demonstrated in clinical trials to improve the quality of life for people with uncontrolled moderate-to-severe asthma who have persistent allergy sensitivity, as well as to lower overall asthma exacerbation rates by 25% and severe exacerbations by 50%.[64] There are also more recent biologic medicines that target IL-5 pathways. One important cytokine that contributes significantly to airway inflammation is IL-5, which is also necessary for the development, differentiation, and survival of eosinophils.Mepolizumab inhibits the IL-5 pathway since it is a humanized monoclonal antibody that is antagonistic to IL-5.Research on mepolizumab has demonstrated increases in quality of life scores, a reduction of 50% in the oral corticosteroid dose for individuals on chronic oral corticosteroids, and a reduction of >60% in hospitalization or ER visiting rates, as well as an overall exacerbation rate of >50%.[66, 65] Another monoclonal antibody against IL-5, reslizumab, has been approved for use in patients with IgE levels ≥400 cells/uL and poorly managed asthma. Clinical trials have demonstrated improvements in asthma quality of life, exacerbation rate by more than 50%, and lung function by 90–160 mL above placebo, particularly in patients with higher peripheral eosinophil counts.[67] Another monoclonal antibody that targets the IL-5 receptor and makes the body's natural killer cells target and destroy eosinophils is benralizumab. It has been demonstrated to enhance lung function by 24%, lower

the dosage of long-term oral corticosteroid use by 75%, and reduce exacerbations by more than 50%.[68,69] Dupilumab, a monoclonal antibody that blocks IL-4 and IL-13, is one of the other biologics. Dupilumab has been demonstrated to enhance lung function, lessen the need for long-term oral corticosteroids, and lessen exacerbations based on findings from Phase III trials.[70,71] Patients with peripheral eosinophil counts >300 cells/μL and FeNO levels ≥25 ppb benefit most from it. A monoclonal antibody called tesepelumab inhibits the inflammatory process that causes asthma by blocking the function of the cell signaling molecule thymic stromal lymphopoietin. Although a Phase II research found a significant reduction in asthma exacerbation rates, this medication is currently undergoing Phase III trials.[72]Phenotyping and endotyping of each patient are required asadditional biologics become available in order to offer insights into the most suitable long-term therapy.

Table :- Biologics for Asthma Treatment

Biologics Available for Asthma

	OMALIZUMAB (XOLAIR)	MEPOLIZUMAB (NUCALA)	BENRALIZUMAB (FASENRA)	RESLIZUMAB (CINQAIR)	DUPILUMAB (DUPIXENT)	TEZEPELUMAB-EKKO (TEZSPIRE)
Molecule/ Target	IgE/Anti-IgE monoclonal antibody	IL-5/Anti-IL-5 monoclonal antibody	IL-5 receptor/ Anti-IL-5 receptor monoclonal antibody	IL-5/An-ti-IL-5 monoclonal antibody	IL-4 and IL-13/ Anti-IL-4R alpha monoclonal antibody	TSLP/Anti-TSLP monoclonal antibody
Age Approved for Asthma Indication	6+	6+	12+	18+	6+*	12+
Asthma Indication	Moderate-to-severe persistent asthma and a positive skin test or in vitro reactivity to a perennial aeroallergen (allergic asthma)	Severe eosinophilic asthma	Severe eosinophilic asthma	Severe eosinophilic asthma	Moderate-to-severe eosinophilic asthma and OCS-dependent asthma	Severe asthma
Mode of Administration	Subcutaneous injection (shot)	Subcutaneous injection (shot)	Subcutaneous injection (shot)	Intravenous infusion (IV)	Subcutaneous injection (shot)	Subcutaneous injection (shot)
Setting of Administration	Clinic or home	Clinic or home	Clinic or home	Clinic	Clinic or home	Clinic or home
Dosing Interval	Every two to four weeks	Every four weeks	Every four weeks for the first 3 doses, and then every 8 weeks thereafter	Every four weeks	Every one to four weeks	Every four weeks

Abbreviations used: immunoglobulin-E (IgE), inhaled corticosteroids (ICS), interleukin (IL), oral corticosteroids (OCS)
*DUPIXENT is also approved for moderate-to-severe atopic dermatitis (eczema) for a younger age.
Updated: March 2023 • aafa.org

SURGICAL BRONCHIOPLASTY:- For asthmatics who do not respond to ICS and bronchodilators as a typical course of treatment, bronchial thermoplasty (BT) provides a non-pharmacologic option. In order to reduce bronchoconstriction and airway hyperplasia, BT uses thermal energy to bronchoscopically ablate the smooth muscles of the airways.[73] The AIR trial from 2007 demonstrated the efficacy of this treatment when patients with moderate to severe asthma were randomly assigned to either BT or a control group. Significant gains were seen in the morning PEFR, proportion of days without symptoms, and symptom score reduction in those who got BT.[74] Furthermore, the RISA trial randomized 32 patients with poorly controlled asthma to either BT or a control group.The results showed that while the BT group experienced an initial rise in short-term morbidity, their pre-bronchodilator FEV1 and asthma symptom scores considerably improved.[75] The AIR2 study, which was conducted after these trials, also showed a significant reduction in asthma symptoms and exacerbations in individuals who were randomly assigned to BT.[74] Therefore, in patients with severe asthma who are not responding to medication, BT may be a useful non-pharmacologic treatment. However, there are serious side effects connected to BT, including potentially fatal severe exacerbations.[74, 75]

ACCEPTABLE CIRCUMSTANCES:-In order to effectively manage asthma, comorbid illnesses must be treated, and environmental and allergy triggers must be avoided. Asthma symptoms have been linked to a number of conditions, including obesity, acid reflux, depression and anxiety, sinusitis and rhinitis, and seasonal and chronic allergies.[8,15, 76–79]More medications that address these comorbidities can greatly enhance asthma control, particularly in people with severe asthma

IV. CONCLUSION

Asthma is a long term inflammatory illness of the respiratory tract that is caused by the release of several inflammatory mediators by mast cells, eosinophils, and T-lymphocytes . It is well accepted that both hereditary and environmental variables have a role in the development of asthma ,even though the exact cause of the condition is still unknown . The three main goals of treating asthma are to dilate the lung's restricted bronchi, prevent exposure to antigens and reduce inflammation and hyperactivity in the bronchi. The best medications for treating acute bronchospasm and avoiding exercise-induced bronchospasm (EIB) are beta2 agonists, which are inhaled.Glucocorticoids inhibit inflammation, which lessens asthma symptoms. Glucocorticoids have specific anti-inflammatory effects, such as : (1) reducing the release and production of inflammatory mediators (eg: histamine, prostaglandins and leukotrienes); (2) reducing the infiltration and activity of inflammatory cells (eg: leukocytes and esinophils); and (3) reducing mucosal edema in the airways (due to a reduction in vascular permeability) The usage of LABAs alone has the following benefits:(i) it can reduce the number of inhalations; (ii) it can result in excellent adherence; and (iii)it can avoid using LABAs alone

REFERENCES

[1] World Health Orgnization. Asthma. 2017. Available at:http://www.who.int/respiratory/asthma/en/. Last accessed: 11September 2018..

[2] Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. J Allergy Clin Immunol. 2011;127(1):145-52.

[3] S Ragab, et al. Treatment of chronic rhinosinusitis and its effects on asthma.

[4] Eur Respir J. 2006; 28: 68-74.

[5] Buist AS. Similarities and differences between asthma and chronic obstructive pulmonary disease: Treatment and early outcomes. Eur Respir J. 2003;21(Suppl 39):30S-5s.

[6] Neukirch F et al. Prevalence of asthma and asthma-like symptoms in three French cities. Respir Med. 1995;89(10):685-92.

[7] Sistek D et al. Clinical diagnosis of current asthma: Predictive value of respiratory symptoms in the SAPALDIA study. Swis study on air pollution and lung disease in adults. Eur Respir J. 2001;17(2):214-9.

[8] Global Initative for Asthma. GINA. 2018. Available at: https://ginasthma.org/gina-reports/. Last accessed: 11 September 2018.

[9] McCracken JL et al. Diagnosis and management of asthma in adults: A review. JAMA. 2017;318(3):279-90.

[10] Tanabe T et al. Cardiac asthma: New insights into an old disease. Expert Rev Respir Med. Ward C et al. Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma. Thorax. 2002;57(4):309-16. 2012;6(6):705-14.

[11] Jorge S et al. Cardiac asthma in elderly patients Incidence,clinical presentation and outcome. BMC Cardiovasc Disord. 2007;7(1):16.

[12] Kenn K, Balkissoon R. Vocal cord dysfunction: What do we know? Eur Respir J. 2011;37(1):194-200.

[13] Ward C et al. Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma. Thorax. 2002;57(4):309-16.
[14] Miravitlles M et al. Clinical outcomes and cost analysis of exacerbations in chronic obstructive pulmonary disease. Lung. 2013;191(5):523-30.
[15] Bateman ED et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31(1):143-78.
[16] National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. 2007. Available at: https://www.nhlbi.nih.gov/files/docs/guidelines/asthgdln.pdf. Last accessed: 12 September 2018
[17] Coates AL et al.; Bronchoprovocation Testing Task Force. ERS technical standard on bronchial challenge testing: General considerations and performance of methacholine challenge tests. Eur Respir J. 2017;49(5).
[18] Anderson SD et al.; A305 Study Group. Comparison of mannitol and methacholine to predict exerciseinduced bronchoconstriction and a clinical diagnosis of asthma. Respir Res. 2009;10:4.
[19] Mustafina M et al. Comparison of the sensitivity and specificity of the methacholine challenge test and exercise test for the diagnosis of asthma in athletes. Eur Respir J. 2014;42(Suppl 57)
[20] Bousquet J et al. Eosinophilic inflammation in asthma. N Engl J Med. 1990;323(15):1033-9.
[21] Dweik RA et al.; American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications. An official ATS clinical practice guideline: Interpretation of exhaled nitric oxide levels (eENO) for clinical applications. Am J Respir Crit Care Med. 2011;184(5):602-15.
[22] Zacharasiewicz A et al. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. Am J Respir Crit Care Med. 2005;171(10):1077-82.
[23] Stirling RG et al. Increase in exhaled nitric oxide levels in patients with difficult asthma and correlation with symptoms and disease severity despite treatment with oral and inhaled corticosteroids. Asthma and Allergy Group. Thorax. 1998;53(12):1030-4.
[24] Shaw DE et al. The use of exhaled nitric oxide to guide asthma management: A randomized controlled trial. Am J Respir Crit Care Med. 2007;176(3):231-7.
[25] Szefler SJ et al. Management of asthma based on exhaled nitric oxide in addition to guidelinebased treatment for inner-city adolescents and young adults: A randomised controlled trial. Lancet. 2008;372(9643):1065-72.
[26] Chung KF et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73.
[27] Parsons JP et al. An official American Thoracic Society clinical practice guideline: Exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 2013;187(9):1016-27.
[28] Juniper EF et al. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902-7.
[29] Nathan RA et al. Development of the asthma control test: A survey for assessing asthma control. J Allergy Clin Immunol. 2004;113(1):59-65.
[30] Juniper EF et al. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J. 1999;14(1):32-8.
[31] Ignacio-Garcia JM, GonzalezSantos P. Asthma self-management education program by home monitoring of peak expiratory flow. Am J Respir Crit Care Med. 1995;151(2 Pt 1):353-9.
[32] Lahdensuo A et al. Randomised comparison of guided self management and traditional treatment of asthma over one year. BMJ. 1996;312(7033):748-52.
[33] Haldar P et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008;178(3):218-24.
[34] Douwes J et al. Non-eosinophilic asthma: Importance and possible mechanisms. Thorax. 2002;57(7):643-8.
[35] Bonsignore MR et al. Advances in asthma pathophysiology: Stepping forward from the maurizio vignola experience. Eur Respir Rev. 2015;24(135):30-9.
[36] Siroux V et al. Identifying adult asthma phenotypes using a clustering approach. Eur Respir J. 2011;38(2):310-7.
[37] Moore WC et al. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. Am J Respir Crit Care Med. 2010;181(4):315-23.
[38] Wilson SR et al. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. Am J Respir Crit Care Med. 2010;181(6):566-77.
[39] Partridge MR, Hill SR. Enhancing care for people with asthma: The role of communication, education, training and self-management. 1998 World Asthma Meeting Education and Delivery of Care Working Group. Eur Respir J. 2000;16(2):333-48.
[40] Sylvester JT. The tone of pulmonary smooth muscle: ROK and Rho music? Am J Physiol Lung Cell Mol Physiol.2004;287(4):L624-30.
[41] U.S. Department of Health and Human Services. Albuterol – Medical Countermeasures Database. 2014. Available at: https://chemm.nlm.nih.gov/countermeasure_albuterol.htm. Last accessed: 11 September 2018.
[42] O'Byrne PM et al. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med. 2018;378(20):1865-76.
[43] Rosen JP et al. Duration of action of oral albuterol in an asthmatic population. Ann Allergy. 1986;56(1):28-33.
[44] U.S. Food and Drug Administration. PROAIR HFA (albuterol sulfate) inhalation aerosol indications and

usage. 2008. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021457s013lbl.pdf. Published Last accessed: 11 October 2018.

[45] Goodman LS et al., "Pharmacotherapy of Asthma," Brunton L et al. (eds.), Goodman & Gilman's the Pharmacological Basis of Therapeutics (2006) 11th edition, McGraw-Hill, pp.720-5.

[46] Nelson HS et al. The salmeterol multicenter asthma research trial: A comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006;129(1):15-26.

[47] Peters SP et al. Serious asthma events with budesonide plus formoterol vs. budesonide alone. N Engl J Med. 2016;375(9):850-60.

[48] O'Byrne PM et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: The OPTIMA randomized trial. Am J Respir Crit Care Med. 2001;164(8 Pt 1):1392-7.

[49] Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. Am Rev Respir Dis. 1993;148(4 Pt 2):S1-26.

[50] Haahtela T et al. Comparison of a β2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. N Engl J Med. 1991;325(6):388-92.

[51] Lorentzson S et al. Use of inhaled corticosteroids in patients with mild asthma. Thorax. 1990;45(10):733-5.

[52] Kerstjens HAM et al. A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. N Engl J Med. 1992;327(20):1413-9.

[53] Juniper EF et al. Effect of longterm treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroiddependent asthmatics. Am Rev Respir Dis. 1990;142(4):832-6.

[54] Kavuru M et al. Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: A randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2000;105(6 Pt 1):1108-16.

[55] Shapiro G et al. Combined salmeterol 50 microg and fluticasone propionate 250 microg in the diskus device for the treatment of asthma. Am J Respir Crit Care Med. 2000;161(2 Pt 1):527-34.

[56] Reddel HK et al. An official American Thoracic Society/European Respiratory Society statement: Asthma control and exacerbations: Standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180(1):59-99.

[57] Szefler SJ, Nelson HS. Alternative agents for anti-inflammatory treatment of asthma. J Allergy Clin Immunol. 1998;102(4 Pt 2):S23-35.

[58] Moulton BC, Fryer AD. Muscarinic receptor antagonists, from folklore to pharmacology; Finding drugs that actually work in asthma and COPD. Br J Pharmacol. 2011;163(1):44-52.

[59] Barnes PJ. Muscarinic receptor subtypes in airways. Life Sci. 1993;52(5-6):521-7.

[60] Guyer AC, Long AA. Long-acting anticholinergics in the treatment of asthma. Curr Opin Allergy Clin Immunol. 2013;13(4):392-8.

[61] Peters SP et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med. 2010;363(18):1715-26.

[62] Boehringer Ingelheim. Evaluation of tiotropium 5 µg/day delivered via the Respimat® inhaler over 48 weeks in patients with severe persistent asthma on top of usual care (Study I). NCT00772538. https://clinicaltrials.gov/ct2/show/NCT00772538.

[63] Boehringer Ingelheim. evaluation of tiotropium 5 µg/day delivered via the Respimat® inhaler over 48 weeks in patients with severe persistent asthma on top of usual care (Study II). NCT00776984.

[64] Kerstjens HAM et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012;367(13):1198-207.

[65] Humbert M et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005;60(3):309-16.

[66] Ortega HG et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371(13):1198-207.

[67] Bel EH et al. Oral glucocorticoidsparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371(13):1189-97.

[68] Castro M et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: Results from two multicentre, parallel, double-blind, randomised, placebocontrolled, Phase 3 trials. Lancet Respir Med. 2015;3(5):355-66.

[69] Bleecker ER et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): A randomised, multicentre, placebo-controlled Phase 3 trial. Lancet. 2016;388(10056):2115-27.

[70] Nair P et al. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. N Engl J Med. 2017;376(25):2448-58.

[71] R. Guelfi, D., dos A. Reis Jr, R., & F. T. Chagas, W. (2021). Enhanced efficiency phosphorous fertilizers on the coffee crop in sandy soil. In International Journal of Horticulture, Agriculture and Food science (Vol. 5, Issue 1, pp. 19–26). AI Publications. https://doi.org/10.22161/ijhaf.5.1.3

[72] Castro M et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. 2018;378(26):2486-96.

[73] Rabe KF et al. Efficacy and safety of dupilumab in

glucocorticoiddependent severe asthma. N Engl J Med. 2018;378(26):2475-85.
[74] Corren J et al. Tezepelumab in adults with uncontrolled asthma. N Engl J Med. 2017;377(10):936-46.
[75] Laxmanan B et al. Advances in bronchial thermoplasty. Chest. 2016;150(3):694-704.
[76] Castro M et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: A multicenter, randomized, doubleblind, sham-controlled clinical trial. Am J Respir Crit Care Med. 2010;181(2):116-24.
[77] Pavord ID et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. Am J Respir Crit Care Med. 2007;176(12):1185-91.
[78] Dhakal, T., Khanal, B., & Maharjan, S. (2023). Performance of Exotic Cucumber Varieties under Local Cultivation Practices in Kapilvastu District of Nepal. In International Journal of Environment, Agriculture and Biotechnology (Vol. 8, Issue 5, pp. 067–073). https://doi.org/10.22161/ijeab.85.11
[79] Beuther DA et al. Obesity and asthma. Am J Respir Crit Care Med. 2006;174(2):112-9.
[80] Thomas AD et al. Gastroesophageal reflux-associated aspiration alters the immune response in asthma. Surg Endosc. 2010;24(5):1066-74.
[81] Harding SM, Richter JE. The role of gastroesophageal reflux in chronic cough and asthma. Chest. 1997;111(5):1389-1402.
[82] Ten Brinke A et al. Psychopathology in patients with severe asthma is associated with increased health care utilization. Am J Respir Crit Care Med. 2001;163(5):1093-6.