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Review on Moderate to Severe Asthma in Primary Care

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Asthma is a chronic condition characterized by wheezing, coughing, and shortness of breath due to airway inflammation and hyper-responsiveness. Severe asthma accounts for a considerable amount of asthma-related costs, although being less common than milder asthma. According to a review of US studies, the expenses for people with severe asthma are roughly 1.7- to 5-fold higher than for people with mild asthma. A subspecialized severe asthma services provides the benefit of an organized, variety of approaches to validate the diagnosis, asthma severity and phenotype, and risk factors and comorbidities management. This multimodal approach frequently comprises a team of respiratory physicians, nurses, and support health specialists, such as physiotherapists, speech therapists, nutritionists, and clinical psychologists. In addition to evaluation and monitoring for common comorbidities, they provide physician review, lung function testing, blood tests, inhaler optimization, and general illness awareness. This review aims to overview approach to diagnosis and management of moderate to severe asthma in primary care settings.

Keywords: Asthma; wheezing; comorbidities management; primary care.

1. INTRODUCTION

Asthma is a chronic condition characterized by wheezing, coughing, and shortness of breath due to airway inflammation and hyper-responsiveness. The term "asthma" refers to a group of illnesses that have similar symptoms but differ in their underlying etiology and prognosis. Depending on the age of onset, clinical signs might indicate one of several phenotypes of the disease, each with its own set of diagnostic, management, and therapy problems. It is hoped that a better understanding of the various subtypes of asthma will help us better evaluate, manage, and cure the symptoms [1-3].

Asthma is often assumed to be an illness that starts in childhood. Despite the fact that asthma is most typically diagnosed in children, it can manifest clinically at any age. Indeed, according to a national survey, 3.1 percent each year who diagnosed with asthma are over 65 years old which is not significantly different from those between the ages of 18 and 34 where 4.0 percent are diagnosed per year. Asthma occurrence in adults over 65 years of age is reported to be 7%, which is comparable to the total prevalence. Prematurity, early lung infections, sinusitis, tobacco consumption, and obesity are linked to diagnosis of asthma in adults. As a result, an older patient's beginning of chronic cough should not prevent the physician from examining asthma [4-7].

According to the National Health Interview Survey–2012, roughly 40 million people in the USA have had asthma at some point in their lives, this comprises about 13 % of the total population .and 8% are currently having asthma which includes about 26 million patient . Incidences for young adults aged 18-24 years are higher (10.3 percent) when compared to older people. 5% to 10% of the entire adult asthma populations are diagnosed with severe asthma [8,9]. Severe asthma accounts for a considerable amount of asthma-related costs, although being less common than milder asthma. According to a review of US studies, the expenses for people with severe asthma are roughly 1.7- to 5-fold higher than for people with mild asthma [10-12]. Asthma is substantially more common in women (10.4%) than in men (6.2%), in those living in poverty (11.8%), and in those who identify as an ethnic or racial minority, particularly black race (10.2%) and Puerto Rican Hispanic ethnicity (14.9 percent). The incidence varies greatly per state, ranging from 4.9 percent to 12.7 percent. Despite the availability of a wide range of treatment options, over half of individuals with asthma report having one or more attacks in the previous year, emphasising the significance of symptom management and disease control [13].

Severe asthma is a diverse condition that is described as a treatment-resistant disease characterized by persistent symptoms or recurrent acute episodes despite the use of standard medications. It means patients with "difficult-to-treat" asthma, in which a variety of factors contribute to poor management of the disease , as well as patients with "biologically severe" asthma, who remain to have poor control yet after alternative diagnoses have been ruled out and contributory factors have been optimized. There are now successful, focused biological medicines aimed at targeting the underlying pathogenic pathways for some people

with physiologically severe asthma. Many individuals with difficult-to-treat asthma, on the other hand, have risk factors that exacerbate symptoms, and by carefully managing these variables, they can achieve significant enhancement. As a result, it's critical to establish care models that best address the complex and varied needs of people with severe asthma, with the overall goal of enhancing patient outcomes for all [14-19].

The vast number of asthma patients is treated by primary care physicians, placing them at the forefront of asthma management, allowing them to identify at-risk patients and give appropriate medication and awareness. In a 2012 survey, reported that just 22% of asthma patients were managed by a specialist on a regular basis, and 48% of patients had never seen a specialist. As a result, it's critical for healthcare professionals to conduct routine asthma management evaluations and ask patients the right questions in order to keep track of asthma severity. Patients with asthma should be referred to specialists by primary care providers who do not do pulmonary function testing on a regular basis [20-23]. According to an Australian survey, up to 45 percent of community members had uncontrolled asthma, resulting in frequent hospitalizations and unscheduled medical visits. However, just half of the patients had seen a general practitioner in the previous year, and only 10% had had a specialist evaluation [24].

A subspecialized severe asthma services provides the benefit of an organized, variety of approaches to validate the diagnosis, asthma severity and phenotype, and risk factors and comorbidities management. This multimodal approach frequently comprises a team of respiratory physicians, nurses, and support health specialists, such as physiotherapists, speech therapists, nutritionists, and clinical psychologists. In addition to evaluation and monitoring for common comorbidities, they provide physician review, lung function testing, blood tests, inhaler optimization, and general illness awareness. It expands educational and self-management opportunities, as well as access to modern biological medicines. These services are now encouraged as they showed positive results on improving the Symptoms of the illness, life expectancy and decreased incidences of disease exaggeration [25-29].

The word "asthma" originates from the Greek meaning short of breath, meaning that any patient with breathlessness was asthmatic. The term was refined in the latter part of the 19th Century with the publication of a treatise by Henry Hyde Salter entitled "On Asthma and its Treatment". In this scholarly work Salter defined asthma as "Paroxysmal dyspnoea of a peculiar character with intervals of healthy respiration between attacks", a description that captures his concept of a disease in which the airways narrow due to contraction of their smooth muscle [72]. His book contains remarkably accurate illustrations of the airways in asthma and bronchitis as well as the cellular appearance of asthmatic sputum some 30 years before Paul Ehrlich described aniline stains for eosinophils (eosin) and mast cells (toluidine blue). He also described black coffee as a treatment for asthmatic spasms, a drink with a high content of theobromine, a derivative of theophylline and theophylline itself. This extraordinary insight into asthma stems from Dr Salter himself suffering from asthma himself. Thus, by the late nineteenth century, physicians adopted the view that asthma was a distinct disease which had a specific set of causes, clinical consequences, and requirements for treatment [73-74].

2. DEFINITION AND PATHOGENESIS OF SEVERE ASTHMA

Historically, asthma was thought to be a condition caused by increase in the activity of the airway smooth muscle, or bronchoconstriction, in reaction to environmental stimuli. Even in people with just occasional symptoms or new-onset asthma, chronic airway inflammation is now regarded a characteristic of the condition. The incidence of symptoms, the extent of functional disability, and the rate of asthma attacks were all used to determine the severity of asthma. More recent practice guidelines reflect increased knowledge of the basic pathophysiology of asthma, so the previous factors are considered only as elements of asthma management, and the severity of asthma disease is categorized by the type and dosage of medicines a patient needs to maintain proper disease control. As a result, symptom control is evaluated separately from and then incorporated into the criteria of asthma severity [30,31].

The International European Respiratory Society (ERS) and the American Thoracic Society (ATS) updated the concept of severe asthma in 2014.

Severe asthma in people aged 6 and up is defined by the ERS/ATS guidelines as either (1) asthma that needs treatment with medium- to high-dose inhaled corticosteroids (ICS) and one or more additional medicines (eg, long-acting 2-agonist, , leukotriene modifier, and theophylline) or systemic corticosteroids for minimum 6 months According to these criteria, uncontrolled asthma requires at least one of the following symptoms: unsatisfactory symptom control, recurrent acute exacerbations, major exacerbation (requiring hospitalization), or airflow limitation [32]. Although asthma has a bigger influence on physical than mental functioning, poorly controlled asthma is linked to poor school performance, attention, and focus, as well as an increase in depression and anxiety symptoms. Furthermore, airway remodeling can result in airway functional impairment and the evolution of chronic obstructive pulmonary disease (COPD). Taking oral corticosteroids to treat severe uncontrolled asthma has its own set of side effects, including osteoporosis, slowed growth in children, and increased risk of cataract and inflammation [30,31,33,34].

3. ASSESSMENT AND EVALUATION OF ASTHMA

The combination of patient symptoms and respiratory function testing is required for a reliable diagnosis of asthma [35]. As the symptoms of asthma are sometimes ambiguous and can be triggered by other diseases, it's crucial to rule out disorders that resemble asthma, especially in older people who are more subjected to have other illnesses [36].

4. HISTORY

Asthma symptoms include wheezing, tightness of the chest, and coughing. These symptoms are frequently recurrent in nature and can vary in strength. Changes in stimulators such as allergens, irritants, or respiratory illnesses are related to changes in symptoms. Bronchoconstriction in reaction to exercise can cause symptoms of asthma. At rest, people with uncontrolled illness may experience persistent symptoms. The presence of chest tightness as the primary presenting symptom should raise suspicions of heart illness. Asthmatics frequently suffer from rhinitis and sinusitis, where allergic rhinitis is a predisposing factor for developing asthma. Upper airway symptoms should be assessed, as they are regarded to represent diverse presentations of a shared allergic pathogenesis [35,36].

Any possible exposures that aggravate the patient's respiratory problems should be tested by physician. The presence of identifiable triggers raises the likelihood of underlying asthma. Allergens are well-known triggers that might be seasonal (usually outdoors) or persistent (typically indoor). Outdoor allergen exposure is widely different across the United States in terms of distribution and timing. Outdoor allergies are primarily pollen-based and can come from a variety of sources, including trees, and weeds, and can be detected at different periods throughout the year. Dust mites, cockroaches, molds, and animal dander from pets are examples of perennial allergies. Cigarette smoking, secondhand smoke exposure, perfumes or strong scents, excess heat or cold , exercise, or psychosocial strain are among non-allergic triggers. Occupational exposures can cause the onset of asthma or exacerbate the symptoms of asthma that already exist . It's crucial to ask about employment exposures in relation to asthma diagnosis and symptom variation by asking about changes in symptoms between weekdays and weekends. Environmental sensitivity is suggested by changes in respiratory symptoms while travel, which supports an asthma diagnosis [37-40].

5. PHYSICAL EXAMINATION

The physical examination is most helpful in determining whether or not there are any concomitant or mimicking conditions. A pulmonary examination in an asthmatic patient is frequently unremarkable. Expiratory wheezing is possible; however it is neither sensitive nor unique to this disease. Inspiratory wheeze is unusual and could indicate a different or additional condition. Crackles, on the other hand, should prompt you to examine other possibilities. Patients may exhibit symptoms of rhinitis or postnasal drip. Eczema can be discovered with a skin examination. Finally, to check for evidence of heart failure, a cardiac examination should be conducted [37-40].

6. TESTS

Spirometry is an essential diagnostic tool used when both the history of the patient and its physical evaluation point to asthma as a potential diagnosis. Spirometry should be performed before and after administration of

bronchodilator to check for the two major criteria for asthma diagnosis: expiratory airflow obstruction and airflow variability. Spirometry that shows both airflow obstruction and complete reversal of airflow obstruction after bronchodilator delivery confirms an asthma diagnosis. Spirometry is typically normal when asthma is adequately treated since variability in symptoms and airflow limitation is a significant aspect of asthma. Additionally, due of increased disease symptoms during presentation, some individuals with asthma who present with expiratory airflow obstruction may not entirely reverse following bronchodilator administration. These other illnesses should be examined because partial reversibility is also a characteristic of COPD or asthma-COPD overlap. In such cases, spirometry is unable to reliably differentiate between asthma and COPD.

A ratio of fractional exhaled volume in the first second (FEV1) to total volume forcefully expelled (FVC) less than the lower limit of normal (LLN) indicates the presence of airflow blockage. Because the LLN compensates for the projected fall in FEV1/FVC that happens with ageing, it is preferable over adopting a set threshold (e.g., 70%). The term "post-bronchodilator response" refers to an increase in FEV1 or FVC of more than 12% and more than 200 mL after using a bronchodilator. These limits are set by guidelines that emphasize that the clinical situation should be considered when evaluating test results. For example, a patient who improves their FEV1 by 10% after a bronchodilator and also improves their FEV1 before the bronchodilator following a trial of inhaled corticosteroids (ICS) would have had a clinically meaningful response that is highly compatible with a diagnosis of asthma [41-43].

When spirometry indicates normal results but physician still consider the diagnosis of asthma, spirometry must be repeated at a later time point, because minimally single episode of obstruction must be documented to confirm the conclusion of asthma. If reversibility on spirometry cannot be determined, sequential testing with a peak flow meter can be used to establish variability in airflow limitation. Over the course of two weeks, the patient is told to record the best of three attempted peak flows twice daily (usually in the morning and late evening) or more frequently during periods of respiratory discomfort. Variable airflow limitation can be diagnosed by a 7-day average of each day's largest to smallest recorded value, divided by the day's average [42].

Bronchoprovocation tests, such as a methacholine challenge, for measuring the hyper-responsiveness of airways has a poor sensitivity for asthma, as other respiratory disorders, such as COPD, and the general population, where the prevalence has ranged from 4% to 37%, have been linked to airway hyper-responsiveness. As a result, this test is no longer used to verify asthma, although it does have a function in excluding asthma in some groups due to its high negative predictive value, which has been observed to approach 100% [44-46].

A progressive diagnostic strategy involving spirometry or peak flow testing to determine blockage and variable airflow limitation is used mainly unless the patient shows exaggerated symptoms on administration. When patients are already using asthma drugs, identifying asthma-related blockage might be difficult. According to a recent Canadian study, up to one-third of those who have been diagnosed with asthma by a doctor do not actually have it. These patients were less likely to have received formal testing for airflow limitation, and the outcomes of the study highlight the importance of objective testing in asthma diagnosis [47].

In most cases, radiographic studies and blood tests are not required in the diagnostic process until there is a suspicion of a different diagnosis. Elevations in eosinophils, immunoglobulin E (IgE), or allergen-specific IgE, while useful in detecting allergic illness and evaluating advanced therapy, are neither sensitive nor specific for the initial diagnosis of asthma. Although fractional exhaled nitric oxide (FeNO) is a sign of eosinophilic airway inflammation, it is rarely used in asthma diagnosis [47].

7. MANAGEMENT

To enhance disease control and address underlying inflammation while reducing side effects from prescribed drugs, successful care necessitates ongoing review over time. Symptoms, risk of worsening, drug tolerance and adherence, and comorbidities should all be assessed at each appointment.

Respiratory function, symptom recurrence, and frequency of exacerbations can all be used to determine the severity of asthma before starting

medical treatment. Severity is defined as frequent, mild - to - moderate persistent or severe persistent, and can guide first therapy decisions. Mild intermittent symptomatology is no longer advised since it suggests that other severities cannot be symptomatic. Importantly, asthma severity is not a static attribute and should be reclassified at each visit based on the quantity of medication required to manage or relieve asthma symptoms. Changes in asthma severity might signal new environmental exposures, comorbidities, or disease progression [52].

8. NON-PHARMACOLOGICAL MANAGE-MENTS

Asthma care relies heavily on avoiding triggers. Common triggers and techniques for dealing with them are listed below [56]:

- Ambient air pollution :Remain indoors during poor air quality days [56].
- Certain foods :Test for food-specific allergies, avoidance [51].
- Cigarette smoke :Smoking cessation assistance, home smoking ban [51].
- Cockroaches: Sweep and vacuum regularly, use roach traps [52].

During periods of high pollen counts or poor outdoor air quality, patients with sensitivity to air pollution are advised to stay home. Pollen avoidance should be timed according to each patient's sensitivity profile, which should be established if the patient has a strong history of seasonal allergies and necessitates a referral to an allergist. The importance of avoiding secondhand smoke and quitting smoking is underlined. Indoor allergen avoidance, focusing on specific allergens to which the patient is allergic, is recommended but difficult to put into practice due to the difficulty of attaining total allergy remediation and the high cost of therapies [48-50]. Overweight or obese patients should be counseled on weight loss as part of general health maintenance, and all patients should be urged to eat a balanced diet. Weight loss of 10 to 15 kgs has been shown to enhance asthma severity [51].

Picrorrhiza kurroa (P kurroa)

P kurroa is a small herb with tuberous roots that is used in Ayurvedic medicine for the treatment of various conditions including lung diseases such as asthma and bronchitis [65].

Solanum xanthocarpum/trilobatum

S xanthocarpum and*S trilobatum* as a powder of the whole dried plant or decoction are widely used to treat respiratory disorders by practitioners of the Sidda system of medicine in Southern India [66].

Boswellia serrata (B serrata)

The gum resin of *B serrata* is known in the Indian Ayurvedic system of medicine as Salai guggal and contains boswellic acids which have been shown to inhibit leukotriene biosynthesis [67].

Tylophora indica (T indica)

T indica *is a plant indigenous to India and reputed to be able to provide relief to patients with bronchial asthma [68].*

Tsumura saiboku-to (TJ-96)

TJ-96 is the one of the most popular and best studied anti-asthmatic Kampo herbal medicines and is used both in Japan and China [65]. It is a combination of two herbal preparations containing 10 herbs[69]. and has been used in China for steroid dependent asthma resulting in a steroid sparing effect. Despite its intensive use [70].

9. MARIHUANA

Marihuana was used for the treatment of asthma in the last century [71].

Dried Ivy Leaf Extract

10. PHARMACOLOGICAL MANAGEMENTS

Medication for controlling asthma

The main goal of such medications is to block the inflammatory process that causes asthma and thus preventing any non-reversible airway remodeling. The backbone of controller therapy is inhaled corticosteroids. Oral thrush, which can be alleviated by using a spacer device and cleaning the mouth after ICS use, and dysphonia, which can be managed by switching to a different delivery system, are two common side effects. If control is inadequate, long-acting beta agonists (LABA) or leukotriene modifiers can be added to ICS, with the former being more

successful than the latter. Long-acting muscarinic antagonists, which are routinely used to treat COPD, do not appear to be superior to LABA and are normally reserved for patients with severe disease. LABA mono-therapy is unsuitable and should never be given for a patient with asthma, as it was associated with an elevated asthma -related mortalities [52-56].

Beta-2 agonists help mucociliary clearance by relaxing bronchial smooth muscle, reducing mast cell degranulation and histamine release, inhibiting microvascular leakage into the airways, and increasing mucociliary clearance. Short-acting, long-acting, or ultra–long-acting beta-2 agonists are available (see tables Drug Treatment of Chronic Asthma and Drug Treatment of Asthma Exacerbations).

Beta-2 agonists with a short half-life (eg, albuterol) The medicine of choice for treating acute bronchoconstriction and avoiding exercise-induced asthma is 2 puffs every 4 hours breathed as needed. They should not be used to treat persistent asthma on their own for lengthy periods of time. They start working within minutes and can last up to 8 hours, depending on the medicine. The most prevalent acute side effects of inhaled beta-2 agonists are tachycardia and tremor, both of which are dose-dependent. Mild hypokalemia is a rare occurrence. Although the use of levalbuterol (a solution containing the R-isomer of albuterol) is thought to reduce side effects, its long-term effectiveness and safety have yet to be proven. Oral beta-2 agonists have higher systemic effects and should be avoided if possible.

Long-acting beta-2 agonists (such as salmeterol) can last up to 12 hours in the body. They're used to treat moderate and severe asthma, but never as a stand-alone treatment. They work in tandem with inhaled corticosteroids, allowing for lower corticosteroid doses.

Long-acting beta-2 agonists (e.g., indacaterol) are used for moderate to severe asthma, and ultra-long-acting beta-2 agonists (e.g., indacaterol) are used for moderate to severe asthma, but should never be taken alone. They work in tandem with inhaled corticosteroids, allowing for lower corticosteroid doses. The safety of using beta-2 agonists on a regular basis for an extended period of time is unknown. When administered as monotherapy, long-acting beta-2 agonists may raise the risk of asthma-related mortality. As a result, these drugs (salmeterol, formoterol, vilanterol) should only be used in combination with an inhaled corticosteroid for patients whose condition is not adequately controlled with other asthma controllers (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants additional maintenance therapies when treating patients with asthma. Usage of short-acting beta-2 agonists on a daily basis or with declining effects, or use of less than one canister per month, indicates insufficient control and the need to start or strengthen additional medications.

11. ANTICHOLINERGICS

Anticholinergics relax bronchial smooth muscle by inhibiting muscarinic (M3) cholinergic receptors in a competitive manner. When combined with short-acting beta-2 agonists, ipratropium may have an additive impact. Pupilary dilation, hazy vision, and dry mouth are some of the side effects. Tiotropium soft mist inhaler (1.25 mcg/puff) is an inhaled anticholinergic that can be used by asthma sufferers for up to 24 hours. Clinical studies using tiotropium combined with inhaled corticosteroids or a combination of an inhaled long-acting beta-2 agonist and a corticosteroid in asthma patients showed better respiratory function and fewer asthma exacerbations.

12. CORTICOSTEROIDS

Corticosteroids reduce airway inflammation, reverse beta-receptor downregulation, and prevent the generation of cytokines and the activation of adhesion proteins. They inhibit the late (but not the early) allergic reaction to inhaled allergens. Oral, IV, and inhaled delivery are all options. Early administration of systemic corticosteroids in acute asthma exacerbations frequently stops the exacerbation, reduces the need for hospitalisation, avoids relapse, and promotes recovery. Both the oral and intravenous methods are equally effective.

Inhaled corticosteroids have little effect on acute exacerbations, but they are used to suppress, regulate, and reverse inflammation and symptoms over time. They significantly minimise the requirement for oral corticosteroid maintenance medication. Dysphonia and oral candidiasis are two adverse local effects of inhaled corticosteroids that can be avoided or mitigated by having the patient wear a spacer, gargle with water after corticosteroid inhalation, or both. Systemic effects are dose-dependent,

can occur in either oral or inhaled forms, and are most common at inhaled dosages more than 800 mcg/day. The adrenal-pituitary axis is suppressed, osteoporosis, cataracts, skin atrophy, hyperphagia, and bruisability are among them. It's unknown if inhaled corticosteroids slow down growth in youngsters. Most children who are given inhaled corticosteroids grow to their full adult height. Tuberculosis that has been dormant for a long time might be resurrected.

13. STABILIZERS FOR MAST CELLS

Mast cell stabilisers diminish airway hyperresponsiveness and limit the early and late reactions to allergens by inhibiting histamine release from mast cells. Patients with exercise- or allergen-induced asthma are given them via inhalation as a preventative measure. Once symptoms have appeared, they are ineffectual. They're the safest antiasthmatics, but they're also the least effective.

14. MODIFIERS OF LEUKOTRIENES

Orally administered leukotriene modifiers can be utilised for long-term symptom management and prevention in individuals with mild to severe persistent asthma. The primary side effect is an increase in liver enzymes (which occurs with zileuton). Patients have acquired a clinical condition that resembles eosinophilic granulomatosis with polyangiitis, despite the fact that this is an uncommon occurrence.

15. METHYLXANTHINES

Methylxanthines relax bronchial smooth muscle (likely by blocking phosphodiesterase) and, through unknown mechanisms, may increase cardiac and diaphragmatic contractility. Methylxanthines appear to reduce intracellular calcium release, microvascular leakage into the airway mucosa, and the late allergic reaction. They reduce eosinophil infiltration into the bronchial mucosa and T cell infiltration into the epithelium.

Theophylline, a methylxanthine, is used in conjunction with beta-2 agonists for long-term management. Theophylline with an extended release helps with nocturnal asthma. Because of its numerous side effects and interactions as compared to other medications, theophylline has gone out of favour. Headache, vomiting, cardiac arrhythmias, seizures, and worsening of gastric reflux are some of the side effects (by reducing lower esophageal sphincter pressure). Methylxanthines have a restricted therapeutic index; methylxanthine metabolism and elimination are affected by a variety of medicines (including macrolide antibiotics) and circumstances (such as fever, liver illness, and heart failure). Theophylline levels in the blood should be checked on a regular basis and kept between 5 and 15 mcg/mL (28 and 83 micromole/L).

16. IMMUNOMODULATORS

Immunomodulators include omalizumab, an anti-IgE antibody, three IL-5 antibodies (benralizumab, mepolizumab, reslizumab), and duplilumab, a monoclonal antibody that suppresses IL-4 and IL-13 signalling. Omalizumab is used to treat individuals with severe allergic asthma and high IgE levels. Omalizumab has been shown to reduce asthma exacerbations, corticosteroid use, and symptoms. A dosing plan based on the patient's weight and IgE levels determines the dosage. Every 2 to 4 weeks, the medication is given subcutaneously.

Mepolizumab, reslizumab, and benralizumab are monoclonal antibodies that inhibit IL-5 and were developed for treatment in patients with eosinophilic asthma. The cytokine IL-5 increases eosinophilic inflammation in the lungs.

In individuals with asthma who are on chronic systemic corticosteroid medication, mepolizumab improves exacerbation frequency, asthma symptoms, and the requirement for systemic corticosteroid therapy. According to data from clinical studies, effectiveness is achieved when blood absolute eosinophil counts are more than 150/microL (0.15 109/L); however, the efficacy threshold for patients on prolonged systemic corticosteroid treatment is unknown. Every four weeks, 100 mg of mepolizumab is given subcutaneously.

Reslizumab also appears to lessen the number of asthma exacerbations and symptoms. Patients had blood absolute eosinophil concentrations of about 400/microL (0.4 109/L) in clinical studies. The eosinophil count threshold for effectiveness in individuals treated with prolonged systemic corticosteroids is unknown. Every four weeks, patients are given 3 mg/kg of Reslizumab IV over 20 to 50 minutes.

Benralizumab is an IL-5 receptor-binding monoclonal antibody. It's for the maintenance

treatment of severe asthma in those over the age of 12 who have an eosinophilic phenotype. It has been demonstrated to lessen the frequency of exacerbations and reduce or eliminate the usage of oral corticosteroids. 30 mg subcutaneously once every 4 weeks for 3 doses, then 30 mg once every 8 weeks is the suggested dosage. Participants in clinical studies (1, 2 references) were given a combination of high-dose inhaled corticosteroids and long-acting beta-2 agonists, with or without additional controls. Eosinophil counts in the blood were usually > 300/microL (>0.3 109/L).

Dupilumab is a monoclonal antibody that inhibits both IL-4 and IL-13 signalling by blocking the IL-4R-alpha subunit. It's for people with moderate-to-severe asthma who are 12 years or older and have an eosinophilic phenotype or who are taking oral corticosteroids. A 400 mg subcutaneous dosage followed by 200 mg every other week, or a 600 mg subcutaneous dose followed by 300 mg every other week, is the suggested dose. Patients who require concurrent oral corticosteroids or who have co-morbid moderate-to-severe atopic dermatitis should take the larger dose.

Clinicians who use these immunomodulators should be aware of the signs and symptoms of anaphylaxis and allergic hypersensitivity responses. Even if earlier doses of dupilumab, benralizumab, omalizumab, or reslizumab were well tolerated, anaphylaxis can develop after any dose. Mepolizumab has been linked to allergic hypersensitivity responses. Mepolizumab usage has been linked to herpes zoster infection; consequently, unless contraindicated, zoster immunisation is recommended prior to starting medication [76-77].

17. RESCUE MEDICATIONS

All patients should be provided with an albuterol rescue inhaler. In individuals with acute symptoms, this short-acting drug delivers rapid bronchodilator and can be used up to four times per day. Albuterol administered by metered-dose inhaler (MDI) without spacer, MDI with spacer, or nebulizer is equally effective in an adult patient with appropriate guidance. In practice, though, spacers and nebulizers are more reliable at delivering medication. Patients with episodic asthma may be able to manage their symptoms with just a short-acting beta-agonist; however, those with chronic asthma (those who use their albuterol inhaler more than twice weekly to relieve symptoms) will require the addition of an inhaled corticosteroid (ICS) [57,58].

18. OTHER TREATMENT OPTIONS IN SEVERE ASTHMA

A typical target is the allergic inflammatory pathway. Omalizumab is an anti-IgE antibody that interacts with mast cells, eosinophils, and basophils in the allergic pathway. It's approved for people with mild to severe asthma who don't respond to ICS and have confirmed allergen sensitivity. It's given every 2 to 4 weeks. Antibodies such as mepolizumab, reslizumab, and benralizumab target the interleukin-5 pathway, which is implicated in eosinophil recruitment and activation [59-62]. Bronchial thermoplasty (BT) is an endoscopic technique that uses radiofrequency heat radiation to ablate airway smooth muscle, diminishing its ability to cause bronchoconstriction. In people with severe asthma, data shows that BT lowers exacerbations, minimizes asthma-related health-care utilization, and enhances the quality of life [63,64].

- Asthma affected an estimated 262 million people in 2019 and caused 461000 deaths (1).

19. WHO STRATEGY FOR PREVENTION AND CONTROL OF ASTHMA

Asthma is included in the WHO Global Action Plan for the Prevention and Control of NCDs and the United Nations 2030 Agenda for Sustainable Development.

WHO is taking action to extend diagnosis of and treatment for asthma in a number of ways.
The WHO Package of Essential Noncommunicable Disease Interventions (PEN) was developed to help improve NCD management in primary health care in low-resource settings. PEN includes protocols for the assessment, diagnosis, and management of chronic respiratory diseases (asthma and chronic obstructive pulmonary disease), and modules on healthy lifestyle counselling, including tobacco cessation, and self-care.

Reducing tobacco smoke exposure is important for both primary prevention of asthma and disease management. The Framework Convention on Tobacco Control is enabling

progress in this area as are WHO initiatives such as MPOWER and mTobacco Cessation [78].

20. CONCLUSION

Asthma is one of the most known respiratory disorders that require long-term managements. Diagnosis of asthma is complicated by the common features between asthma and other respiratory diseases. Severe asthma is considered when the patient is not responding to the normal medication, where inhaled corticosteroids are the main management technique beside avoidance of the trigger that causes case exacerbation. Patient awareness about the disease and adequate methods for its management is an important step in the management of this disorder.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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