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Allergic Rhinitis And It's Treatment

Department of Pharmacology, Kandhar College of Pharmacy Kandhar, Balantwadi Ghodaj Road, Kandhar, Kandhar

Miss. Gutte Pooja Vitthal, Mr. Mudhal Prathamesh Dilip, Mr. Sandeep D Gavhane, Mr. Mohd Ameen, Dr. Jameel Ahmad

Corresponding author: Gutte Pooja

ABSTRACT

Allergic rhinitis is a common condition often associated with asthma and conjunctivitis. It is a chronic ailment frequently overlooked in primary care. Clinically, it is defined as a nose disorder triggered by IgE-mediated inflammation following exposure to allergens. Symptoms encompass runny nose, nasal blockage, itching, and sneezing, which can improve spontaneously or with treatment. Allergic rhinitis can be categorized as "intermittent" or "persistent." It's a global health concern, impacting approximately 400 million individuals worldwide. Its prevalence has risen with urbanization and environmental pollutants considered key contributors. While some studies suggest a link between allergic rhinitis and asthma, this connection remains inconclusive.

Keywords: *Allergic rhinitis, Treatment of rhinitis, Immunotherapy for allergens, conjunctivitis.*

INTRODUCTION

Rhinitis, a condition characterized by inflammation of the nasal mucosa, is a prevalent issue affecting a substantial portion of the population, with estimates suggesting it impacts up to 40% of individuals. Among the various forms of chronic rhinitis, allergic rhinitis stands out as the most common, affecting approximately 10-20% of the population. Recent data indicates that the prevalence of this disorder is on the rise. Notably, severe allergic rhinitis has been linked to considerable reductions in the quality of life, disturbances in sleep patterns, and hindered work performance. Allergic rhinitis is a global health concern that leads to significant illness and disability on a worldwide scale. People of diverse backgrounds, ethnicities, and age groups experience its effects, which extend to social activities, sleep quality, educational pursuits, and professional responsibilities. It's worth noting that the economic impact of allergic rhinitis is frequently underestimated due to its relatively low direct cost burden..

Figure No 1: Rhinitis

However, the indirect expenses associated with these conditions are significant. Allergic rhinitis and asthma are systemic inflammatory ailments and often co-occur. It was only in the early 1800s that this disease was meticulously documented, and at that time, it was considered quite rare. During the 19th century, the disease's prevalence coincided with the industrialization of Westernized nations, eventually becoming widespread in both Europe and North America. However, the incidence of allergic rhinitis remained low until the last 50 years, when it has seen a substantial increase, with some countries reporting that over 50% of adolescents exhibit symptoms of allergic rhinitis.

In the past, allergic rhinitis was thought to be a condition confined to the nasal passages, but current research suggests that it may be part of a systemic airway disorder affecting the entire respiratory system. Various physiological, functional, and immunological connections exist between the upper respiratory tract (comprising the nose, nasal cavity, paranasal sinuses, Eustachian tube, pharynx, and larynx) and the lower respiratory tract (encompassing the trachea, bronchial tubes, bronchioles, and lungs). For example, both tracts feature ciliated epithelium with goblet cells that produce mucus to filter incoming air and safeguard the airways' internal structures. Additionally, the submucosa of both upper and lower airways houses blood vessels, mucous glands, support cells, nerves, and inflammatory cells.

Classification

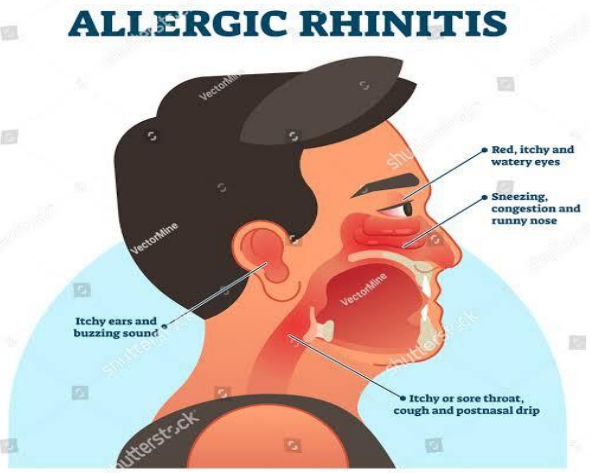

Figure No 2: Allergic rhinitis

Rhinitis can be categorized based on its underlying causes: IgE-mediated (allergic), autonomic, infectious, or idiopathic (of unknown origin). While our main focus here is on allergic rhinitis, let's briefly describe the other types. Traditionally, allergic rhinitis has been divided into seasonal (occurring during specific seasons) and perennial (persistent throughout the year). However, this classification doesn't encompass all cases. For instance, some allergic triggers like pollen may be seasonal in cooler climates but perennial in warmer regions. Additionally, individuals with multiple "seasonal" allergies may experience symptoms throughout most of the year. Consequently, allergic rhinitis is now categorized by symptom duration (intermittent or persistent) and severity (mild, moderate, or severe). According to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, "intermittent" allergic rhinitis includes symptoms present for fewer than 4 days per week or less than 4 consecutive weeks, while "persistent" allergic rhinitis comprises symptoms present more than 4 days per week and lasting for more than 4 consecutive weeks.

CLINICAL SIGNS AND SYMPTOMS OF ALLERGIC RHINITIS

Allergic rhinitis (AR) is characterized by a combination of nasal and non-nasal symptoms. Nasal symptoms encompass issues like anterior or posterior rhinorrhoea, sneezing, nasal congestion, and itching of the nose. These symptoms can persist for hours following exposure to allergens, which induce mucosal inflammation. Consequently, the mucosa becomes more sensitive not only to the triggering allergen but also to other allergens and non-allergenic stimuli, such as strong odors and irritants.

Non-nasal symptoms manifest as ocular symptoms, often termed allergic rhinoconjunctivitis, which includes itching, redness of the eyes, and tearing. Additional symptoms comprise itching of the palate, postnasal drip, and cough. Hypersensitivity reactions can manifest not only in AR but also in conditions like bronchial asthma, allergic conjunctivitis, allergic dermatitis, food allergies, and even anaphylactic shock. It's important to note that more than 30% of AR patients suffer from severe allergic symptoms that can result in significant disability and, in extreme cases, life-threatening conditions like anaphylaxis. In severe instances, individuals may experience intense bronchospasms, laryngeal edema, cyanosis, hypotension, and shock.

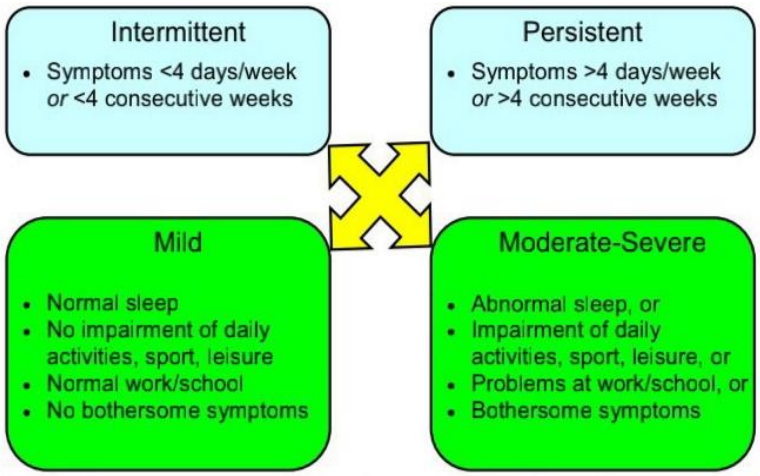

Figure No 3: Classification of allergic rhinitis according to symptom duration and severity

LABORATORY CHARACTERISTICS OF ALLERGIC RHINITIS

To identify the specific allergen responsible for triggering IgE antibody production in Allergic Rhinitis (AR), multiple tests can be employed. These tests include in vivo methods like the skin prick test (SPT) and intradermal skin tests (IDST), as well as in vitro tests such as serum allergen-specific IgE (ssIgE) immunoassays. While there isn't a universally recognized "gold standard" laboratory test for diagnosing AR, SPT is typically considered the primary approach for assessing allergic sensitivities. SPT is not only swift but also cost-effective in diagnosing allergic sensitization. On the other hand, IgE immunoassays involve commercially available test panels, making them comparatively more expensive. Additionally, they are less sensitive for diagnosing allergies caused by inhaled allergens when compared to SPT. However, ssIgE immunoassays can be valuable when skin testing isn't feasible, often due to factors like extensive skin conditions, the inability to discontinue antihistamines or other interfering medications, demographic factors, or other complexities that hinder skin testing.

DIAGNOSTIC CRITERIA OF ALLERGIC RHINITIS

Diagnostic criteria are generally broad and must reflect the different features of a disease (i.e., heterogeneity), with a view to accurately identify as many patients with the condition as possible . Due to the lack of gold standards in diagnosing AR, definitive diagnostic criteria have been challenging to establish. The choice of confirmatory test is a matter of clinical judgment and the results obtained must be considered together with additional risk factors, rather than definitive indicators of disease .

In skin tests, positive result is considered when the wheal-and flare reaction occurs on the skin test site after 20 min of exposure to allergens. For SPT, positive result must demonstrate wheal (i.e., a red and itchy raised bump with surrounding inflammation that indicates the presence of allergic antibodies) size in diameter of ≥4 mm .

PATHO-PHYSIOLOGY

Early and Late Phase of Allergic Rhinitis

Type I hypersensitivity represents an allergic response mediated by IgE antibodies when exposed to allergens (reference 13). This type of reaction unfolds swiftly, typically occurring within 20 minutes of allergen exposure, and it involves the activation of mast cells and inflammatory cells, which then infiltrate tissues (reference 58). Allergic reactions in the case of

allergic rhinitis (AR) can be broken down into two distinct phases: the early phase and the late phase. The early phase initiates within 20 minutes of allergen exposure. Antigen-presenting cells, like dendritic cells on mucosal surfaces, capture, process, and present allergen-derived peptides on the major histocompatibility complex (MHC) class II molecules. This antigen-MHC class II complex serves as a ligand for T cell receptors found on naïve CD4+ T cells, leading to the differentiation of these cells into allergen-specific Th2 cells. These activated Th2 cells release cytokines, such as IL-4 and IL-13, which interact with B cells to produce allergen-specific IgE antibodies. These allergen-specific IgE antibodies then bind to high-affinity Fc receptors for IgE (FcεR) present on mast cells, ultimately resulting in mast cell activation.

Allergens in Allergic Rhinitis

Allergens are typically proteins with molecular weights ranging from 10 to 40 kDa, and they trigger type I hypersensitivity reactions by interacting with specific IgE antibodies. Common allergen types encompass food allergens such as shrimp, soybean, crab, clam, wheat, peanut, egg yolk, and cow's milk, as well as pet allergens like cat and dog dander, along with house dust mites (HDMs). Major indoor allergens, including HDMs, cockroaches, cat and dog dander, have consistently been identified as significant risk factors for allergic rhinitis (AR).

Lifestyle choices play a substantial role in shaping the composition and diversity of the airway and gut microbiotas. The hygiene hypothesis proposes the significance of establishing symbiotic relationships with specific microorganisms to facilitate immune system maturation and promote a shift toward a more tolerogenic immune state, thereby serving as a fundamental factor in the development of allergies.

Concerning HDMs, which are among the leading causes of AR, the protease activity of HDMs triggers an excessive production of IgE. Under normal physiological conditions, the production of IgE by B cells is regulated through a negative feedback mechanism involving the binding of IgE to CD23, also known as the low-affinity receptor for IgE (FceRII). When IgE/allergen complexes bind to CD23, it down-regulates IgE production by B cells. However, in individuals sensitized to HDMs and suffering from AR, Der p 1, a cysteine proteinase allergen from HDMs, disrupts this IgE-feedback mechanism by selectively cleaving CD23. This disruption leads to the overproduction of IgE by B cells. Additionally, in allergic diseases, there are implications for pulmonary surfactant.

T Helper 2 Responses in Allergic Rhinitis

T Helper 2 (Th2) cells activate type 2 responses by stimulating B cells to proliferate and differentiate into plasma cells through the production of Th2 cytokines including IL-4, IL-5, IL-6, and IL-13 . Th2 cells are major contributors of IgE-producing B cells , and Th2 cells play a predominant role I AR pathogenesis. Together with eosinophils and basophils, Th2 cells infiltrate the nasal mucosa tissue, resulting in late phase allergic response (83). IL-4 is a key cytokine in promoting Th2 differentiation from naïve CD4+ T cells . The mechanism is dependent on the activation of signal transducer and activator transcription 6 (STAT6) signalling through IL-4 receptor complex. Th2 cytokines not only enhance inflammatory cell activation but also may deregulate epithelial cell barrier integrity in allergic disease (e.g., AR, eosinophilic esophagitis, asthma, and chronicles rhino sinusitis) . The cytokines may also be releases within the sinonasal microenvironment including sinonasal epithelial cells, causing increased epithelial cell permeability. This is thought to be due to regulation of transmembrane transcription involved in TJ re modelling where the “tight” barrier properties of TJ proteins are switched to “leaky” properties TJ proteins are switched to “leaky” properties Th2 cytokines also hinder the epithelial barrier from resealing which may maintain the inflammation and exposure to inflammatory antigens.

In normal physiological state (left panel), intact epithelial barrier prevents allergens infiltration and hence homeostasis of immune components and functions are maintained. In AR such as HDM-sensitized AR (right panel), proteases released by HDMs disrupt tight junctions leading to disrupted epithelial barrier that allows infiltration of allergens. This triggers a cascade of IgE overproduction by B cells, cleaved CD40 on the surface of DCs disrupts the production of thiols by DCs causing decreased Th1 proliferation and collectively with increased IL-6 secretion leads to biased Th2 proliferation. Th2 cells produce the hallmark AR cytokines IL-4 and IL-13. HDM proteases also cleave the pulmonary surfactants SP-A and SP-D, causing decreased lung clearance of allergens. CLDN, Claudine; DC, Dendritic cell; HDM, House dust mite; IL-4, Interleukin 4; IL-12, Interleukin 12; IL-13, Interleukin 13; IL-25, Interleukin 25; IL-33; Interleukin 33; IFNγ, Interferon gamma; OCLN, Occluding; SP-A, Surface protein A; SP-D, Surface protein D; Th1, T helper type 1; Th2, T helper type 2; Treg, Regulatory T cell; TSLP, Thymes stromal lymphopoietin

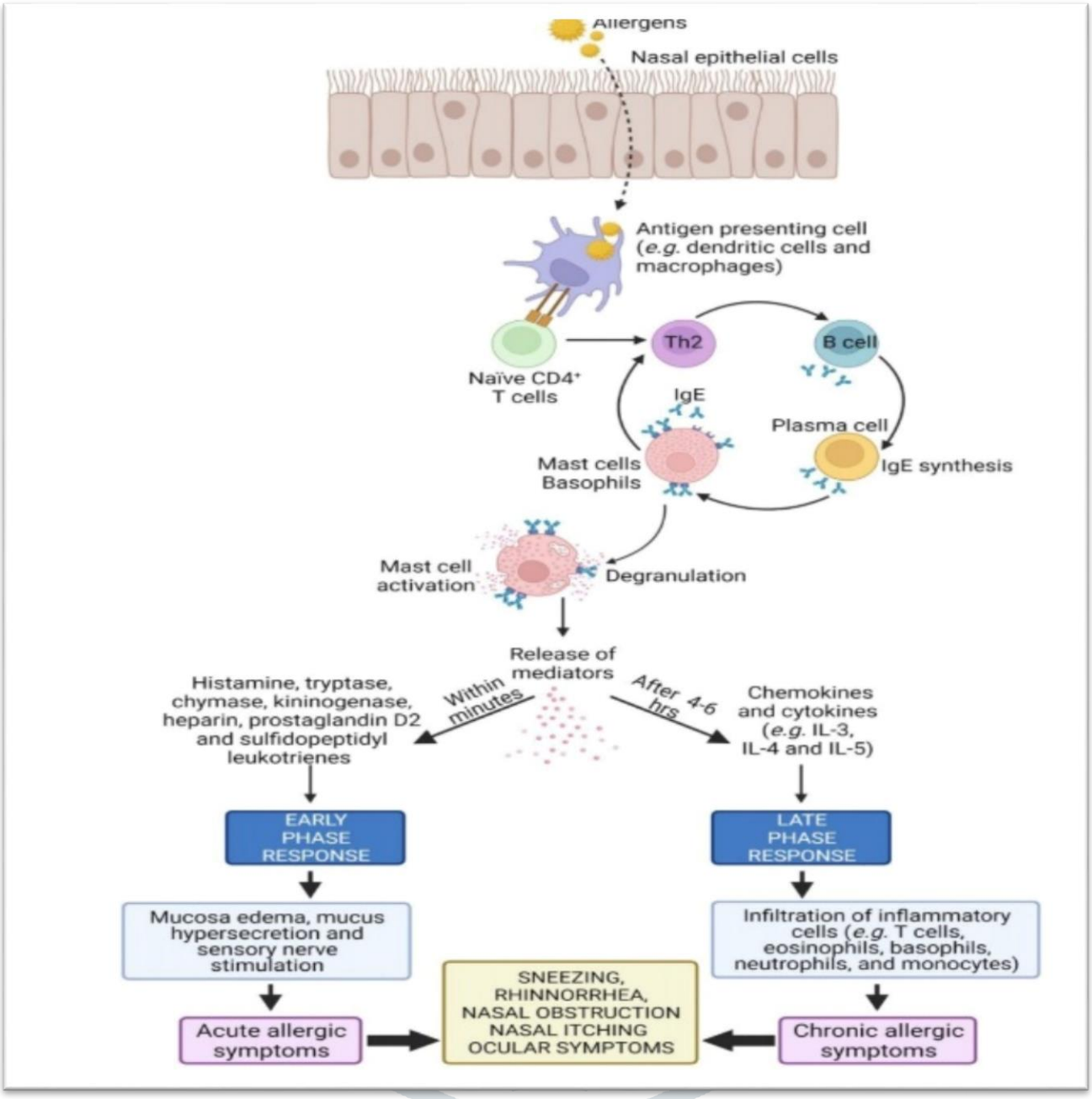

Figure No 4: Pathophysiology

TREATMENT

- The treatment goal for allergic rhinitis is relief of symptoms. Therapeutic options available to achieve this goal include avoidance measures, nasal saline irrigation, oral antihistamines, intranasal corticosteroids, combination intranasal corticosteroid/antihistamine sprays; leukotriene receptor antagonists (LTRAs), and allergen immunotherapy.

- Other therapies that may be useful in select patients include decongestants and oral corticosteroids. If the patient's symptoms persist despite appropriate treatment, referral to an allergist should be considered. As mentioned earlier, allergic rhinitis and asthma appear to represent a combined airway inflammatory disease and, therefore, treatment of asthma is also an important consideration in patients with allergic rhinitis.

- The first-line treatment of allergic rhinitis involves the avoidance of relevant allergens (e.g., house dust mites, moulds, pets, pollens) and irritants (e.g., tobacco smoke). Patients allergic to house dust mites should be instructed to use allergen-impermeable covers for bedding and to keep the relative humidity in the home below 50% (to inhibit mite growth).

- Pollen and outdoor mould exposure can be reduced by keeping windows closed, using window screen filters, using an air conditioner, and limiting the amount of time spent outdoors during peak pollen seasons.

- For patients allergic to animal dander, removal of the animal from the home is recommended and usually results in a significant reduction in symptoms within 4–6 months.

- However, compliance with this recommendation is poor and, therefore, the use of high-efficiency particulate air (HEPA) filters and restricting the animal from the bedroom or to the outdoors may be needed to attempt to decrease allergen levels.

- Measures for reducing exposure to mould allergens include cleaning with fungicides, dehumidifcation to less than 50%, remediation of any water damage, and HEPA filtration. avoidance strategies can effectively improve the symptoms of allergic rhinitis, and patients should be advised to use a combination of measures for optimal results.

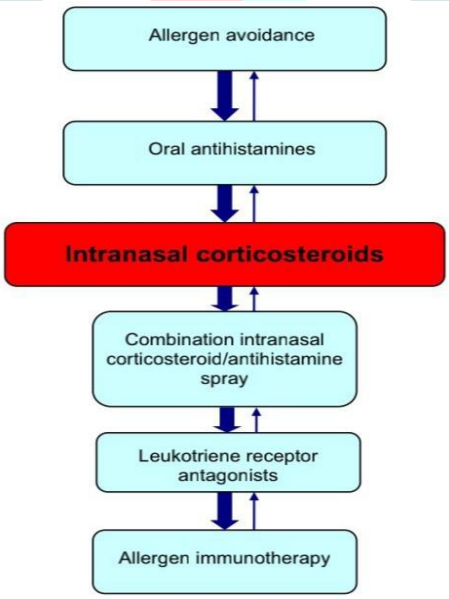

Figure No 5: Treatment

Allergen immunotherapy

Allergen immunotherapy entails the subcutaneous delivery of gradually increasing amounts of the relevant allergens to induce immunologic tolerance. It proves effective in treating allergic rhinitis, particularly in cases of intermittent (seasonal) allergic rhinitis caused by various pollens like tree, grass, and ragweed. Moreover, it has demonstrated efficacy in addressing allergic rhinitis stemming from house dust mites, Alternaria, cockroach, and cat and dog dander. However, it's essential to reserve allergen immunotherapy for patients when standard avoidance measures and pharmaceutical treatments prove inadequate or intolerable. Given the potential risk of

anaphylactic reactions, this therapy should only be recommended by trained physicians capable of managing life-threatening anaphylaxis.

Other therapeutic options

Oral and intranasal decongestants, such as pseudoephedrine and phenylephrine, prove valuable in alleviating nasal congestion in individuals with allergic rhinitis. Nevertheless, the side effect profile linked with oral decongestants, such as restlessness, sleep disturbances, headaches, and palpitations, can restrict their extended usage. Additionally, these medications are unsuitable for patients dealing with uncontrolled hypertension and severe coronary artery disease. Prolonged reliance on intranasal decongestants can lead to a condition known as rhinitis medicaments, characterized by rebound nasal congestion. Therefore, it is recommended not to utilize these agents for more than 3–5 days. Oral corticosteroids have demonstrated effectiveness in cases of severe allergic rhinitis that does not respond well to oral antihistamines and intranasal corticosteroids. Although not as potent as intranasal corticosteroids, intranasal sodium cromoglycate (Cromolyn) has been proven to reduce sneezing, nasal discharge, and nasal itching, making it a reasonable treatment option for specific patients. The anti-IgE antibody omalizumab has also shown efficacy in seasonal allergic rhinitis and asthma, but it currently lacks approval for allergic rhinitis treatment.

Complementary and alternative medicines (CAM)

Given the popularity of complementary and alternative medicines (CAM) in the general population, it is reasonable for physicians to ask patients about their use of CAM in a non-judgmental manner. Given the limited number of well-designed clinical trials examining the efficacy of CAM in allergic rhinitis, it is difficult for clinicians to evaluate these therapies and provide guidance. Nonetheless, since there will be patients who wish to pursue CAM for the management of allergic rhinitis, it is advisable to provide some information about these therapies including a discussion of the lack of high-quality studies evaluating some of these therapies . Various CAM have been used for the management of allergic rhinitis, including traditional Chinese medicines, acupuncture, homeopathy, and herbal therapies [52]. In a number of studies, acupuncture has been shown to provide modest benefits for patients with allergic rhinitis.

CONCLUSIONS

Allergic rhinitis is a prevalent condition that can significantly impact a patient's quality of life. Diagnosis typically involves a thorough review of the patient's medical history and a comprehensive physical examination. Additional diagnostic measures, such as skin-prick tests or allergen-specific IgE tests, are often necessary to confirm that allergies are the underlying cause of the rhinitis. The treatment options available for allergic rhinitis are effective in alleviating symptoms and are generally well-tolerated and safe. Primary treatments include second-generation oral antihistamines and intranasal corticosteroids. In specific cases, allergen immunotherapy and other medications, such as decongestants and oral corticosteroids, may be beneficial

REFERENCES

1. Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. World Allergy Organ J. (2014) 7:12. doi: 10.1186/1939-4551-7-12

2. Licari A, Manti S, Ciprandi G. What are the effects of rhinitis on patients with asthma? Expert Rev Respir Med. (2019) 13:503–5. doi: 10.1080/17476348.2019.1604227

3. Steelant B, Farre R, Wawrzyniak P, Belmans J, Dekimpe E, Vanheel H,et al. Impaired barrier function in patients with house dust mite-induced allergic rhinitis is accompanied by decreased occludin and zonula occludens1 expression. J Allergy Clin Immunol. (2016) 137:1043–53.e5. doi: 10.1016/j.jaci.2015.10.050

4. Steelant B, Seys SF, Boeckxstaens G, Akdis CA, Ceuppens JL, Hellings PW. Restoring airway epithelial barrier dysfunction: a new therapeutic challenge in allergic airway disease. Rhinology. (2016) 54:195–205. doi: 10.4193/Rhin15.376

5. Steelant B, Seys SF, Van Gerven L, Van Woensel M, Farre R, Wawrzyniak P, et al. Histamine and T helper cytokine-driven epithelial barrier dysfunction in allergic rhinitis. J Allergy Clin Immunol. (2018) 141:951–63.e8. doi: 10.1016/j.jaci.2017.08.039

6. Nur Husna SM, Tan H-TT, Md Shukri N, Mohd Ashari NS, Wong KK. Nasal epithelial barrier integrity and tight junctions disruption in allergic rhinitis: overview and pathogenic insights. Front Immunol. (2021) 12:663626.doi: 10.3389/fimmu.2021.663626

7. Nur Husna SM, Siti Sarah CO, Tan HT, Md Shukri N, Mohd Ashari NS, Wong KK. Reduced occludin and claudin-7 expression is associated with urban locations and exposure to second-hand smoke in allergic rhinitis patients. Sci Rep. (2021) 11:1245. doi: 10.1038/s41598-020-79208-y

8. Siti Sarah COS, Shukri NM, Ashari NSM, Wong KK. Zonula occludens and nasal epithelial barrier integrity in allergic rhinitis. PeerJ. (2020) 8:e9834.doi: 10.7717/peerj.9834

9. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the world health organization, GA(2)LEN and AllerGen).Allergy. (2008) 63(Suppl. 86):S8–160. doi: 10.1111/j.1398-9995.2007.01620.x

10. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. (2017) 140:950–8. doi: 10.1016/j.jaci.2017.

11. Carr W, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012;129(5):1282–1289.e10.

12. Hampel FC, et al. Double-blind, placebo-controlled study of azelastine and fluticasonein a single nasal spray delivery device. Ann Allergy Asthma Immunol. 2010;105(2):168–73.

13. Meltzer EO. Pharmacotherapeutic strategies for allergic rhinitis: matching treatment to symptoms, disease progression, and associated conditions. Allergy Aasthma Proc.2013;34(4):301–11.

14. Seidman MD, et al. Clinical practice guideline: allergic rhinitis executive summary. Otolaryngol Neck Surg.

2015;152(2):197–206.

15. Seidman MD, et al. Clinical practice guideline: allergic rhinitis executive summary. Otolaryngol Neck Surg.

2015;152(1 Suppl):S1–S43.

16. Bachert C, Bousquet J, Hellings P. Rapid onset of action and reduced nasal hyperreactivity: new targets in allergic rhinitis management. ClinTranslAllergy. 2018;8:25

17. Lenfant C. Introduction. In: Corren J, Togias A, Bousquet J, editors. Upper and lower respiratory disease lung biology in health and disease, Vol. 181. NY: Marcel Dekker, 2004:iii–iv.

18. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. Allergy 2003;58:691–706.

19. Bousquet J, Jacquot W, Vignola AM, Bachert C, Van Cauwenberge P. Allergic rhinitis: a disease remodeling the upper airways? J Allergy Clin Immunol 2004;113:43–49.

20. Bachert C, Vignola AM, Gevaert P,Leynaert B, Van Cauwenberge P, Bousquet J. Allergic rhinitis, rhinosinusitis, and asthma: one airway disease. Immunol Allergy Clin North Am 2004;24:19–43.

21. Price D, Bond C, Bouchard J, Costa R, Keenan J, Levy ML, et al. International Primary Care Respiratory Group (IPCRG) Guidelines: management of allergic rhinitis. Prim Care Respir J 2006;15:58–70.

22. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S,et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.

23. Schunemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 13. Applicability, transferability and adaptation. Health Res Policy Syst 2006;4:25.

24. Custovic A, Wijk RG. The effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma: ARIA update (in collaboration with GA(2)LEN). Allergy 2005;60:1112–1115.

25. Peshlakai G, Bousquet PJ, Carlsen KH, Kemp J, Lockey RF,Niggemann B, et al. ARIA update: I.Systematic review of complementary and alternative medicine for rhinitis and asthma. J Allergy Clin Immunol 2006;117:1054–1062.

26. Bousquet J, van Cauwenberge P, Ait Khaled N, Bachert C, BaenaCagnani CE, Bouchard J, et al. Pharmacologic and anti-IgE treatment of allergic rhinitis ARIA update (in collaboration with GALEN). Allergy 2006;61:1086–1096.

27. Allen DB, Meltzer EO, Lemanske RF Jr, Philpot EE, Faris MA, Kral KM, Prillaman BA, Rickard KA. No growth suppression in children treated with the maximum recommended dose of futicasone propionate aqueous nasal spray for one year. Allergy Asthma Proc. 2002;23(6):407–13.

28. Agertoft L, Pedersen S. Efect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med. 2000;343(15):1064–9.

29. Schenkel EJ, Skoner DP, Bronsky EA, Miller SD, Pearlman DS, Rooklin A, Rosen JP, Ruf ME, Vandewalker ML, Wanderer A, Damaraju CV, Nolop KB, Mesarina-Wicki B. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. Pediatrics. 2000;105:E22.

30. Bousquet J, Lund VJ, van Cauwenberge P, Bremard-Oury C, Mounedji N, Stevens MT, El-Akkad T. Implementation of guidelines for seasonal allergic rhinitis: a randomized controlled trial. Allergy. 2003;58(8):733–41.

31. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, Munzel U, Bousquet J. A novel intranasal therapy of azelastine with futicasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012;129(5):1282–9.

32. Meltzer E, Ratner P, Bachert C, Carr W, Berger W, Canonica GW, Hadley J, Lieberman P, Hampel FC, Mullol J, Munzel U, Price D, Scadding G, Virchow JC, Wahn U, Murray R, Bousquet J. Clinically relevant efect of a new intranasal therapy (MP29-02) in allergic rhinitis assessed by responder analysis. Int Arch Allergy Immunol. 2013;161(4):369–77.

33. Price D, Shah S, Bhatia S, Bachert C, Berger W, Bousquet J, Carr W, Hellings P, Munzel U, Scadding G, Lieberman P. A new therapy (MP29-02) is efective for the long-term treatment of chronic rhinitis. J Invest Allergol Clin Immunol. 2013;23(7):495–503.

34. Berger WE, Shah S, Lieberman P, Hadley J, Price D, Munzel U, Bhatia S. Long-term, randomized safety study of MP29-02 (a novel intranasal formulation of azelastine hydrochloride and futicasone propionate in an advanced delivery system) in subjects with chronic rhinitis. J Allergy Clin Immunol Pract. 2014;2(2):179–85.

35. Pullerits T, Praks L, Skoogh BE, Ani R, Lötvall J. Randomized placebocontrolled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. Am J Respir Crit Care Med. 1999;159(6):1814–8.