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Review Article

Ear, Nose and Throat Section

Pathophysiology of Allergic Rhinitis with Future Therapeutic Targets- An Update

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ABSTRACT

Rhinitis is defined by a combination of two or more nasal symptoms (running, blocking, itching, and sneezing). Allergic Rhinitis (AR) occurs when these symptoms are due to Immunoglobulin E (IgE)-mediated inflammation following exposure to the allergen. The current review article has attempted to revisit the pathophysiologic basis of this disease in order to understand the likely therapeutic targets. Controlling histone acetylation with histone deacetylase inhibitors, Deoxyribonucleic acid (DNA) hypermethylation with DNA methyl transferase inhibitors and post-transcriptional gene expression with micro Ribonucleic Acid (miRNA) mimetics which target epigenetic changes, may aid in the treatment of AR. The allergen-induced nasal hypersecretion in allergic patients can also be definitively blocked by vidian neurectomy. Probiotics are non pathogenic microorganisms that are assumed to exert a positive influence on host health and physiology which may aid in the treatment of AR. Reversing or targeting the epigenetic changes in susceptible individuals can help prevent sensitisation of the individual and better treatment outcome in patients with AR, help cure the symptoms and lack of drug dependance.

Keywords: Allergens, Antibody, Autoimmunity, Inflammation, Sensitisation

INTRODUCTION

Rhinitis is defined by a combination of two or more nasal symptoms (running, blocking, itching, and sneezing). AR occurs when these symptoms are due to IgE mediated inflammation following exposure to allergen. Allergens are mixtures of molecules, typically proteins, glycoproteins, lipoproteins, or protein-conjugate chemicals or drugs that have been solubilised from a defined (usually biological) source, a portion of which can elicit an IgE antibody response in exposed and genetically predisposed individuals [1]. AR has become a pandemic of the modern era, with social and health related impacts [2]. Various factors have been attributed to its rising incidence to 11.3% in children aged 6-7 years, and 24.4% in children aged 13-14 years [3], which include, growing industrialisation, urbanisation and global warming. However, there is lot of difference between fact and fiction which can be rightly said about AR as a disease entity. Its pathophysiology is not yet fully understood. The current review article has attempted to revisit the pathophysiologic basis of this disease in order to understand the mechanism of rise in the incidence and also to understand the therapeutic targets.

DIAGNOSIS OF ALLERGIC RHINITIS (AR)

The AR may be characterised by clinical diagnosis like nasal symptoms (running, blocking, itching, and sneezing). Co-morbidities history or associated family history of atopy or simply clinical diagnosis of appearance of symptoms following exposure of allergens like dust, mites etc., [4]. It can have close differential diagnosis with certain conditions as listed in [Table/Fig-1] [5,6].

Allergic	Intermittent (seasonal)
	Persistent (perennial)
Infectious	**Acute**
	Chronic
	Specific
	Non specific
Other	**Occupational**
	NARES (Non Allergic Rhinitis (AR) with Eosinophilia)
	Atopic
	Drug-induced
	Irritant
	Food
	Stress induced
	Atrophic
	Gastro-oesopahegal reflux
	Idiopathic
	Hypothyroidism
	Hormonal
	Premenstrual

[Table/Fig-1]: Close differential diagnosis of AR with certain conditions [5,6].

Diagnostic Tests

It would be pertinent to discuss the diagnostic test battery available as summarised in [Table/Fig-2], as diagnosis of AR is still done on clinical grounds by many as there are no set guidelines for the same. These tests are relevant for diagnosis and to target the treatment according to the allergen sensitivity [7].

1. **Nasal smear:** It demonstrates a high number of eosinophils in AR. A nasal smear should be taken when the disease is clinically active or after a nasal challenge test. Nasal eosinophilia can also be seen in non AR [6,7]. According to Pal I et al., and Singhvi P et al., nasal smear is a highly specific criterion for the diagnosis of AR with a 100% positive predictive value [5,7]. The sensitivity and specificity were observed to be 54% and 100%, respectively. The test is best suited for confirmation of the diagnosis of AR. e.g., Non AR with eosinophilic syndrome.
2. **Nasal provocation test:** A simple method is to challenge the nasal mucosa with a small amount of allergen placed on the end of a toothpick and ask the patient to sniff into each nostril to see if allergic symptoms are reproduced [8]. According to de Blay F et al., nasal provocation test has a positive predictive value of 100% with however negative predictive value was found to be 54% [9]. More advanced methods are now available. The test is best suited for confirmation of diagnosis of AR.
3. **Skin Tests (Skin prick test):** Skin-prick testing is reasonably accurate for identification of patients with suspected symptoms of AR. The level of accuracy reported in metanalysis by Nevis IF

et al., ranged from sensitivity of 68 to 100% and specificity of 70 to 91% [2]. Test is useful in identification of specific allergen. Fallacies were to check cross-reactivity [4], spontaneous loss of potency of allergen over time extract due to inappropriate storage and to see non match ability between severity of test results and symptoms.

4. **Specific IgE:** Allergen-specific IgE antibody testing Radioallergosorbent Assay (RAST) is an in-vitro test to find the specific allergen. There is a good correlation ranging from 0.84 to 0.94 between the skin tests and specific IgE measurements [10]. However, both false positive and false negative results can occur. RAST, is highly specific but not as sensitive as skin testing [1]. This test is especially useful in primary care if percutaneous testing is not feasible (e.g., due to reagent storage issues, expertise, frequency of use, staff training) or if a patient is taking a medication that interferes with skin testing (e.g., tricyclic antidepressants, antihistamines). According to Nevis IF et al., this can be undertaken by RASTs or by fluorescent assays and Enzyme-linked Immunosorbent Assays (ELISA) [2]. RAST tests are more expensive, delayed and take longer to complete, and they are no more sensitive or specific than skin prick tests. They should be used in situations where skin prick tests are contraindicated. The tests are either unavailable or difficult to interpret [8]. Lack of standardised diagnostic protocols lead to difficulties in accurate diagnosis of patients with AR and can be one of the reasons for inadequate treatment benefit [11].

PATHOGENESIS OF AR AND POTENTIAL THERAPEUTIC TARGETS

The reaction can be considered in four phases:

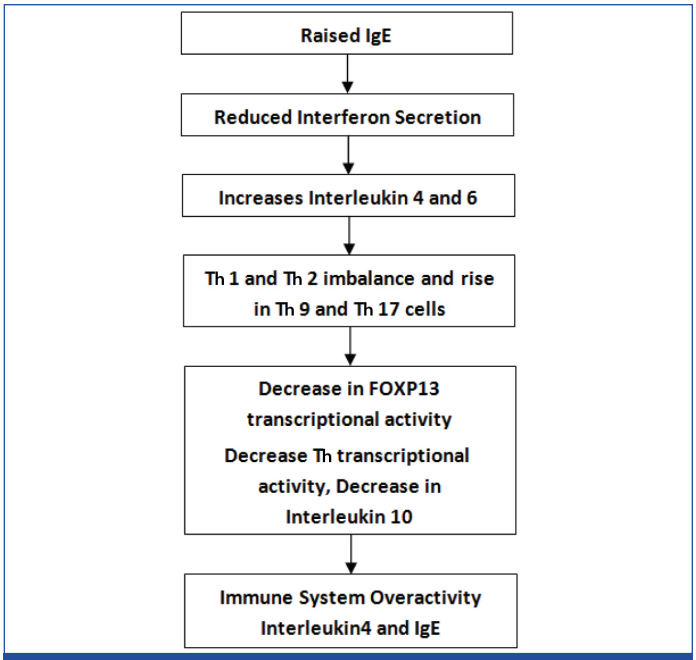
1. Sensitisation

Sensitization is a very important phase as it is the first step in development of frank AR which is more common in genetically predisposed individuals and/or individuals with likely epigenetic changes over their lifespan. Sensitization of atopic subjects occurs following exposure to a relevant allergen. On pre-exposure to the particular allergen as shown [Table/Fig-3], soluble antigens are eluted from the pollen by nasal secretions and pass through the mucosa to react with Ig E bound to mast cells [12], Following the sensitization there is an increase reactivity of nasal membrane following repeated exposure to pollens known as a priming effect [13]. This is followed by mast cell degranulation and release of chemical mediators, which then result in immediate symptoms of rhinorrhea, itch, sneezing and nasal congestion. Continual allergen exposure results in invasion of the nasal mucosa by migratory cell such as eosinophils, lymphocytes, neutrophils, and mast cells and release of inflammatory and immunologic mediators. The released mediators as shown in flow chart below act both directly and indirectly on target cells in the nose, the nasal vasculature, nerves, and submucosal glands [14].

Role of atopy: To develop allergic rhinitis, a patient must have a special predilection for becoming immunologically sensitive to common environmental allergens. This atopic state tends to be familial and may manifest as eczema, rhinitis, asthma alone or in combination [5].

Immune imbalance in Atopic individuals:

Study by Yang et al.[15] on the regulation of Ig-E synthesis in humans show that T cells play a critical role in both mediating and enhancing suppressor signals to the IgE-producing B cells. In the normal subject the suppression overshadows enhancement, and in the atopic person the influence of the helper T cell exceeds that of the suppressor T cells on Ig E synthesis. Although there is no specific therapy currently available to modulate the T cell effects in allergic patients, the present level of understanding of the system



[Table/Fig-2]: Response to sensitisation [10-12].

points toward the potential isolation of suppressor factors that might affect the regulation of Ig E synthesis.

The effect of these active pharmacologic agents in the nose is to produce capillary dilatation, to increase mucous secretion and to attract eosinophils, basophils and leukocytes to the site of reaction. [13].

Role of Genetics and Epigenetics in sensitisation of Individual:

The main feature is the production of a specific immunoglobulin [IgE] directed against normally harmless allergens [11].

1. **Genetics:** Genetics play a significant role in the development of atopic diseases. These underlying genetic risks then react to an environmental trigger to cause the atopic illness. A family history of atopic diseases puts children at risk of developing these conditions [14].
2. **Environment:** While genetics play a role in disease risk, exposure to environmental agents or "triggers" is important in atopic disease.

Atopic patients exposed to the same allergens do not necessarily develop the same patterns of sensitivity. Many patients with allergic rhinitis are clinically and by skin test sensitive to more than one inhalant but the thresholds of reactivity vary considerably with some reacting to very small allergenic challenges and others tolerating heavy doses of allergens before developing symptoms. The pattern and degree of sensitivity are often established in early childhood and change very little after the first decade for those living in the same environment [14].

Immunochemically antibody is identified and classified as Ig-E. Patients with allergic rhinitis have distinctly higher levels of specific Ig-E in the serum than do normal subjects. Artificial immunization experiments through the nose with tetanus toxoid, produce higher levels of Ig-E in the nasal secretions in atopic patients than in non atopic patients. Some Ig-E is produced by non atopic patients, but high levels of Ig E antibody sufficient to mediate allergic reactions are only found among atopic patients [14].

The development of allergic rhinitis is the result of a complex interaction between genetic predisposition and environmental exposure to various factors, the most important of which is the allergen in question. A number of genomic searches have been conducted, yielding various chromosomal associations, the most common of which involve chromosomes 2, 3, 4, and 9 [13].

Therapeutic target: Immunotherapy reduces seasonal increases in allergen-specific IgE, increases [blocking] IgG antibodies, and

inhibits the recruitment and activation of inflammatory cells such as mast cells and basophils to mucosal surfaces. The underlying events that orchestrate these changes are thought to involve T-lymphocyte function modulation.

Mechanisms of Allergic Sensitisation and Allergen Immunotherapy (AIT)

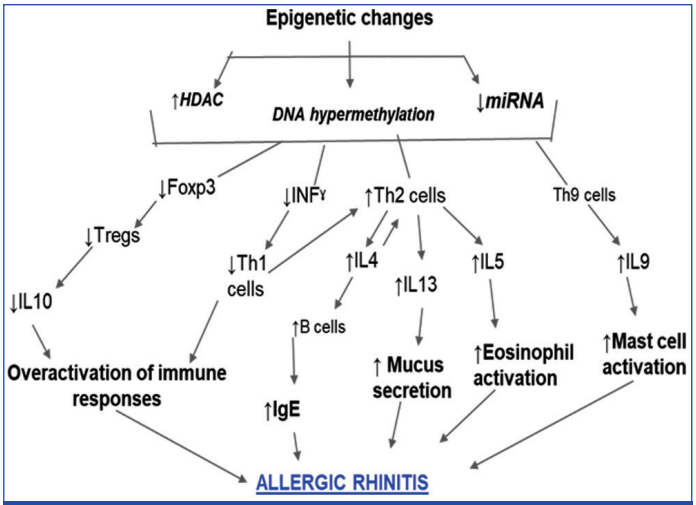
AIT suppresses the development of DC2 phenotype and promotes naïve T cell differentiation to regulatory phenotypes (iTregs, FOXP3+Tregs, T_{FR} cells). These subsets in turn suppress T_H2, T_H2A and T_{FH} responses and favor the differentiation of T_H1. Inhibition of T_H2 responses results in reduced local eosinophilia and prevents the development of IgE+ plasma cells. AIT also induces Bregs and IgG^+/IgA^+ plasma cells which produce blocking antibodies that compete with IgE for binding to the allergen, preventing the cross-linking of high-affinity receptors on mast cell and basophil surfaces and inhibiting their degranulation. Thus, immunotherapy has been shown to induce immune deviation from a Th2-type T-lymphocyte response to a protective Th1-type response as well as to induce a distinct population of T regulatory cells that produce the inhibitory cytokines 1L- 1O and TGF, both of which may downregulate Th2 responses to allergens [14].

Role of Epigenetics

Epigenetic changes produce dysregulation of the immune response. According to preclinical studies [14,16,19], the primary outcome of epigenetic changes during allergic rhinitis is dysregulation of immune response in terms of Th1/Th2 imbalance, changes in cytokine profile, increase in IgE, and decrease in the number of T regulatory cells. In the absence of IFN-, naive CD4+ cells normally convert into Th1 cells. During allergic rhinitis, epigenetic changes reduce IFN secretion while increase IL-4 and IL-6 secretion resulting in a Th1/Th2 imbalance. It is also linked to a rise in the number of Th9 and Th17 cells. Furthermore, there is a decrease in Foxp3 transcriptional activity which results in a decrease in the number of T regulatory cells and IL-10 secretion and immune system overactivation [15]. As the number of Th1 cells decreases, the number of Th2 cells increases which leads to an increase in the secretion of IL-4 promoting the activation of B cells to release IgE. Increased IL-13 release causes mucus secretion and hyperresponsiveness. IL5 secretion is increased to promote eosinophil recruitment and activation. Increased production of IL-9 [also produced by Th9 cells] promotes mast cell activation.

As a result, as shown in arrow in [Table/Fig-3] inhibition of epigenetic changes in the form of histone deacetylase inhibition, activation of DNA demethylase and miRNA mimetics may be able to overcome allergen-induced immune system overactivation. As a result, they could be potentially useful pharmacological agents compare to currently advocated drugs according to Allergic Rhinitis and its Impact on asthma guidelines for treating allergic rhinitis. because drugs that modulate epigenetic changes have not been evaluated clinically in allergic rhinitis patients, it is impossible to precisely describe the side effects and the efficacy of these drugs in patients with AR [18]. Nonetheless, it is possible to speculate that the clinical effects of epigenetic modulators may be long-lasting and these drugs may normalize hyperactivity to inhibit the pathogenesis of allergic. However, the potential side effects of immune response inhibition must be considered. It may also occur as a result of epigenetic therapy. Clinical studies will be planned in future to investigate the efficacy and safety of these drugs in AR.

Treatment target: Controlling histone acetylation with histone deacetylase inhibitors, DNA hypermethylation with DNA methyl transferase inhibitors and post-transcriptional gene expression with miRNA mimetics may aid in the treatment of AR [1].



[Table/Fig-3]: Epigenetic changes in AR [13-19].

The Th1/Th2 Paradigm

The first major proposed mechanism for explaining the protective effect of infectious pathogens against immunological diseases was Th1–Th2 divergence. Inflammatory cytokines such as IL-2, interferon [IFN]-g, and tumour necrosis factor [TNF]-alpha are produced by Th1 T cells and are involved in cell-mediated immunity (including autoimmune diabetes).

Th2 T cells, on the other hand, which generate IL-4, IL-5, IL-6, and IL-13, have a role in IgE production and allergic responses. Given the reciprocal down-regulation of Th1 and Th2 cells, some writers (okada). Hypothesized at first that the lack of microbial burden in early life, which generally favors a strong Th1-biased immune system, redirects the immune system in industrialised countries [20]. As a result, the host is predisposed to allergy diseases due to a shift in responsiveness to a Th2 phenotype. The problem with this argument is that infections that create a Th1 response protect autoimmune disorders, which are mostly Th1 cell-mediated, while parasites that induce a Th2 response may protect above. These demonstrated above. These findings support the idea that infection-induced protection against allergy and autoimmunity is mediated by a similar mechanism.

Improved Hygiene and Bacterial Exposure

According to the "cleanliness hypothesis", improvements in hygiene have resulted in less early-life exposure to microorganisms, resulting in an increase in the prevalence of allergic illness. [16]. The substantial rise in AR prevalence in Westernized countries from the late 1800s to the mid-1900s coincided with significant advancements in hygiene such as the separation of drinking water and sewage which resulted in a decrease in enteric infections [21]. Reduced exposure to farm animals and horses as transportation, chlorination of water and the eradication of malaria and helminth illnesses were among the other hygiene developments in the period [22,23]. Apart from these hygienic enhancements several epidemiologic studies [24,25] have found a link between AR prevalence and environmental factors that influence bacterial exposure which has coincided with the growth of AR [18]. Early childhood exposure has been shown to protect against AR.

2. Early Phase

The following [Table/Fig-4] had listed the symptoms that are produced subsequent to allergen exposure during the early phase.

Histamine	Sneezing, pruritus, and reflex secretory responses.
Tryptase, cysteinyl leukotrienes (LTC4LTD4, LTE4)	Nasal congestion, mucus secretion (to a lesser extent.
Prostaglandins (primarily PGD2)	Hypertrophic inflammation in the nose, Recruitment of eosinophils.

[Table/Fig-4]: Allergens in early phase reaction [6].

3. Late Phase Reaction

The nature of late symptoms differs from that of acute symptoms in that sneezing and pruritus are absent, whereas nasal congestion is the predominant symptom. The late phase reaction is more cellular with additional mediator release [6].Eosinophila, basophils, and leukocytes create an inflammatory state in the tissues lasting 24 to 48 hours or longer, if the allergic challenge continues to occur.

4. Systemic Activation

Activation of the whole system despite the fact that AR appears to be a local phenomenon, there is evidence of increased production and release of eosinophil and basophil precursors from bone marrow in response to allergen contact in the nose or lung. Selectins and adhesion molecules attract the circulating precursors to the reaction site and other parts of the respiratory tract where they infiltrate and mature. This process is also visible in nasal polyposis and may be responsible for some of the well-documented rhinitis/asthma links [12].

SURGICAL MANAGEMENT

In 1979, Konno A and Togawa K described the successful use of a vidian nerve section to alleviate symptoms of AR in patients [15]. Although histamine induces secretion and transudation through its direct effect on the glands and vasculature of the nasal mucosa, histamine-induced nasal hypersecretion is primarily due to histamine stimulation of sensory receptors and reflexive stimulation of the nasal glands via the afferent and efferent pathways. This is closely related to a nasal itching sensation. This mechanism is similar to the response of salivary secretions from all major and minor salivary glands to localised taste stimulation on the tongue. The allergen-induced nasal hypersecretion in allergic patients can also be definitively blocked by a vidian neurectomy. This suggests that the same mechanism is at work in the onset of nasal hypersecretion in nasal allergy patients [23].

RECENT ADVANCES FOR THERAPEUTIC MANAGEMENT OF AR

Probiotics

Probiotics are non pathogenic microorganisms like *Lactobacillus acidophilus, Lactobacillus rhamnosus GG, Saccharomyces boulardii, Bifidobacterium bifidum* and *Bacillus coagulans* which are assumed to exert a positive influence on host health and physiology [25]. A pilot study in humans, the PRODIA study (probiotics for the prevention of beta cell autoimmunity in children at genetic risk of type 1 diabetes), was begun in 2003 in Finland in children carrying genes associated with disease predisposition [15]. The case of probiotics in inflammatory bowel disease is more complex because of the possible local anti-inflammatory effect, which could explain the relief of symptoms without changes in disease progression, as implicated in the hygiene hypothesis. Probiotics should not be considered as totally harmless particularly in the immunodeficient host and more safety studies are needed. As mentioned by Fijan S, probiotics may have unpredictable behaviour like all microorganisms, such as unanticipated gene expression in non native host environment or acquired mutations occurring spontaneously via bacterial DNA-transfer mechanisms controlling histone acetylation with histone deacetylase inhibitors [27]. DNA hypermethylation with DNA methyl transferase inhibitors and post-transcriptional gene expression with miRNA mimetics may aid in the treatment of AR [16].

Role of Fractional Exhaled Nitrous Oxide (FENO) as a Biomarker in AR

Asthma is one of the most common co-morbidities associated with AR as both of them has a similar pathophysiology characterised by eosinophilic inflammation of respiratory pathway. Synthase enzymes control the amount of NO produced by catalysing the change of L-arginine to L-citrulline. Endothelial, inducible Nitric Oxide Synthase (iNOS), and neuronal are the three different isoforms of these enzymes. Recent research demonstrated that in allergic asthmatics, STAT-6 and the proinflammatory Th2-cytokines IL-4 and IL-13 cause iNOS to be upregulated in the respiratory epithelium, producing increased NO concentrations in exhaled air [28]. FENO has traditionally been considered a proxy marker of eosinophilic airway inflammation, but it is more accurate to think of FENO as a Th2-driven local inflammation. It should be ideal to have biomarkers that may be able to predict asthma development in AR patients because AR may precede asthma. Regarding this, it has been proposed that AR patients with Bronchial Hyper Responsiveness (BHR) may have a series of asthma attacks, or the asthma march [28].

Role of Dupilumab in Allergic Rhinitis (AR)

Dupilumab, an anti-IL-4 receptor monoclonal antibody, blocks IL-4/IL-13 signalling, one of the major initiators of type 2/TH2 immunological disorders (such as atopic and allergy illness). Dupilumab reduced severe exacerbations, enhanced lung function and quality of life, and was generally well tolerated in patients with uncontrolled persistent asthma despite using medium to high doses of inhaled corticosteroids in addition to long-acting 2-agonists in a pivotal phase 2b study (NCT01854047) [29]. In patients with severe asthma and co-morbid PAR, dupilumab improved key asthma related outcomes, asthma control, and health related quality of life specifically related to rhinoconjunctivitis while suppresing type 2 inflammatory biomarkers and perennial allergen specific Ig E. This highlights its dual inhibitory effects on IL-4 and IL-13 and its role in managing asthma and perennial AR.

CONCLUSION(S)

Probiotics are non pathogenic microorganisms that are assumed to positively influence host health and physiology, which may aid in the treatment of AR. A vidian neurectomy can definitively block the allergen-induced nasal hypersecretion in allergic patients. Authors propose that reversing or targeting the disease in the early phase, e.g., changes in sensitisation and early stage in susceptible individuals can help improve treatment outcomes in patients with AR and help cure the symptoms and lack of drug dependence.

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