

Allergic Rhinitis: Diagnosis and Management Revisited

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Authors' contributions

This work was carried out in collaboration among all authors. Author KKD designed the study, performed the literature search and wrote the first draft of the manuscript. Authors CSV and MNNH managed the literature search and prepared the final manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Allergic rhinitis (AR) is the commonest allergic disease affecting approximately 400 million people worldwide. It is associated with a reduced quality of life, low productivity in the work place, and poor school performance. On the other hand, medical cost increases. Allergic rhinitis has a considerable effect on quality of life and can have significant consequences if left untreated. Many patients downplay rhinitis symptoms as an inconvenience rather than a disease. The majority of the patients start visiting their local physician, when the problem becomes chronic, especially when it is associated with complications. There is a huge economic burden associated with allergic rhinitis. It is the fifth costliest chronic disease in the United States with 75% of the costs coming from decreased productivity. Diagnosis of allergic rhinitis is important because it can become a chronic

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condition, which might predispose patients to chronic sinusitis or chronic middle ear infection and hearing impairment. This review discussed the background of rhinitis and allergic rhinitis, the burden of disease, differentiating characteristics of allergic rhinitis from non-allergic rhinitis, diagnosis, complications and management.

Keywords: *Allergic rhinitis; non-allergic rhinitis; diagnosis of allergic rhinitis; pharmacological management of allergic rhinitis.*

1. INTRODUCTION

Rhinitis is a very common disorder caused by inflammation or irritation of nasal mucosa. Rhinitis is classified as acute, recurrent, or chronic. Dominant symptoms are nasal obstruction. However, in some patients, runny nose, excessive sneezing or nasal itch may be the most bothersome symptoms [1]. Rhinitis may present with other symptoms like recurrent throat cleaning, itchy throat, and palate [2,3], headaches, facial pain depending on the sinuses involved. Frequent snoring, as well as sleep disturbances, are common complaints in patients with poorly managed chronic rhinitis [4]. In recent years, allergic rhinitis is frequently blamed for symptoms related to nasal inflammation, especially in patients with chronic symptoms. It is important to consider a comprehensive list of differential diagnosis in these patients. This includes at least 9 subtypes of non-allergic rhinitis [5]: namely drug-induced rhinitis, gustatory rhinitis, hormonal-induced rhinitis, infectious rhinitis, non-allergic rhinitis with eosinophilia syndrome, occupational rhinitis, senile rhinitis, atrophic rhinitis, and non-allergic rhinopathy. This article focuses on some of the most common types of chronic rhinitis, including mixed rhinitis (allergic and non-allergic presenting simultaneously), rhinitis medicamentosa, hormonal rhinitis, rhinitis of the elderly, and gustatory rhinitis [5]. In this review article, we tried to explain the common causes of inflammation of mucoepithelial lining of the nasal cavity, its presentation, the significance of diagnosing rhinitis, the pathophysiology involved, the basis of its diagnosis, and treatment. Ultimately, we hope that the primary physician, who is the first line of medical professionals in treating the patients, will accurately arrive at the diagnosis of allergic rhinitis.

2. REVIEW OF LITERATURE

2.1 Allergic Rhinitis

Allergic rhinitis is defined as symptoms of sneezing, nasal pruritus, airflow obstruction, and

mostly clear nasal discharge caused by IgE-mediated reactions against inhaled allergens. It results in mucosal inflammation driven by type 2 helper T (Th2) cells [6]. Allergic rhinitis which shows increased in prevalence over the last several decades, now affects 10–30% of the population, mostly involving children and adolescents [7]. Since children's immune systems develop between the first and fourth year of life, those with atopic predisposition begin to express allergic condition with a clear Th2 response to allergen exposure, resulting in symptoms, often begin with atopic dermatitis (AD) and later progress to asthma and rhinitis (the allergic march) [7]. However, after early childhood years, allergic rhinitis is the first manifestation to be seen in the majority of patients [8]. In the United States, allergic rhinitis is the fifth most common chronic disease [9].

2.2 Burden of Allergic Rhinitis

Allergic rhinitis (AR) is one of the most common allergic condition affecting approximately 400 million people worldwide. It can lead to lower quality of life, work productivity and school learning performance. On the other hand, medical cost multiplies.

Formerly regarded as a nuisance disease, allergic rhinitis (AR) has a considerable effect on the quality of life. There are significant detrimental consequences if left untreated. The total burden of this disease lies not only in impaired physical and social functioning but also in increasing the financial burden, especially considering that there is ample evidence to suggest that AR is a possible causal factor in comorbid diseases, such as asthma or sinusitis [3].

Allergic rhinitis has become a common condition affecting people of different races, countries, and age groups around the world [10]. In the United States, it affects 10-30% of the adult general population and up to 40% of children. This accounts for 30-60 million people in the United States [11]. A self-report study conducted in

China showed that the prevalence rates of AR were 14.46%, 20.42%, and 7.83% in Beijing, Chongqing, and Guangzhou, respectively. About 10.73% of AR patients suffered from asthma [12]. It is estimated that 44% to 87% of people with rhinitis have mixed allergic and non-allergic rhinitis [1], and therefore all that sneezes are not necessarily allergy-related [13]. Symptoms like runny nose, nasal obstruction, nasal itching, could be due to many other conditions that result in inflammation of mucopithelial lining of the nasal cavity. Many patients downplay rhinitis symptoms as an inconvenience rather than a disease. They only come to realize the seriousness of the problem when the condition becomes chronic, especially when complications develop, accompanied by frequent visits to the hospital and clinics. There is a huge economic burden associated with this chronic disease. In the United States, the direct medical costs (physician services, diagnostics, medications, etc.) nearly doubled from US\$6.1 billion in 2000 to US\$11.2 billion in 2005 [14]. In Europe, it was estimated that by the late 1990s, €1.0-1.5 billion was spent on direct costs [15]. These data are decade old but it clearly gives us an idea the financial problem involved with the rhinitis and its diagnosis, not to mention, the indirect costs (travelling cost for physician visits, decreased work productivity, missed school-days and loss of parents' income from missed-work-day to care for their children, etc.) incurred. In the US, there are 3.5 million lost workdays and 2 million lost school days due to allergic rhinitis. It is estimated that productivity decreases by US\$600 per affected employee per year, which is a greater loss compared to asthma, diabetes, and coronary heart disease [13]. Furthermore, chronic rhinitis is associated with other complications which further increase both the direct and indirect costs involved in its management. Overall, allergic rhinitis was the fifth costliest chronic disease in the United States with 75% of the costs related to decreased productivity [3, 14].

2.3 Differential Diagnosis of Allergic Rhinitis (AR) From Non-allergic Rhinitis (NAR)

Various other conditions present with symptoms similar to allergic rhinitis. These are classified as non-allergic rhinitis. This is shown in Table 1. This includes medical conditions with symptoms that are similar to rhinitis, as given in Table 2.

NAR affects 25% of the adolescent and adult population with rhinitis. Women have NAR twice as frequent as men. In general, patients with NAR have more persistent but equally severe symptoms, as compared to patients with AR. However, individuals with AR experience more sneezing and itchy eyes, which is usually seasonal, as compared to those with NAR [16].

Table 1. Nonallergic Rhinitis (NAR): Specific syndromes classified as NAR [17]

Nonallergic rhinitis syndromes
Drug-induced rhinitis, including rhinitis medicamentosa
Gustatory rhinitis
Hormonal-induced rhinitis, including the rhinitis of pregnancy
Infectious rhinitis
NARES
Occupational rhinitis
Senile rhinitis
Atrophic rhinitis
Vasomotor or idiopathic rhinitis

Table 2. Medical conditions associated with or present similarly to non allergic rhinitis [18]

Medical conditions associated with or present similarly to Nonallergic rhinitis
Metabolic
Acromegaly
Pregnancy
Hypothyroidism
Autoimmune
Sjogren syndrome
Systemic lupus erythematosus
Relapsing polychondritis
Churg-Straus syndrome
GPA formerly known as Wegner granulomatosis
Other
Cystic fibrosis
Kartagener syndrome
Sarcoidosis
Immunodeficiency

2.4 Diagnosis of Allergic Rhinitis

Basic requirements in diagnosis include history, clinical examination, investigation that includes Serum IgE, with or without Skin tests. American Academy of Otolaryngology—Head and Neck

Surgery Foundation 2014 Development Group Panel made the following recommendations:

(1) Clinicians should make the clinical diagnosis of AR when patients present with a history and physical examination consistent with an allergic cause with 1 or more of the following symptoms: nasal congestion, runny nose, itchy nose, or sneezing. Findings of AR consistent with an allergic cause include, but are not limited to, clear rhinorrhea, nasal congestion, pale discoloration of the nasal mucosa, and red watery eyes.

(2) Clinicians should perform and interpret or refer the patients to a clinician who can perform and interpret, specific IgE (skin or blood) allergy testing for patients with a clinical diagnosis of AR who do not respond to empiric treatment, or when the diagnosis is uncertain, or when knowledge of the specific causative allergen is needed for target therapy [19].

2.4.1 Clinical diagnosis on history:

ARIA Workshop Group 2001 classified allergic rhinitis into following subtypes, depending on the following symptoms [20]:

Intermittent symptoms:

- < 4 days a week
- Or < 4 weeks

Persistent symptoms:

- > 4 days a week
- > 4 weeks

Mild symptoms:

- Normal sleep
- Normal daily activities, sports, and leisure
- Normal number of school-day
- No troublesome symptoms

Moderate/Severe symptoms (one or more):

- Abnormal sleep
- Impairment of daily activities, sports, and leisure
- Problems of attendance in school-day
- Troublesome symptoms

2.4.2 Clinical examination findings in typical allergic rhinitis

The typical facial features of affected children may include a long, pale face, and allergic

'shiners' or Dennie-Morgan folds under the eyes. The child may be mouth-breathing with dry, cracked lips and has associated lip-licking eczema. There may be halitosis, dental malocclusion, and postnasal drip.

2.4.3 Rhinoscopy examination

The nasal examination may reveal an external nasal crease due to persistent rubbing and a boggy nasal bridge. A metal speculum may be used to demonstrate reduced nasal airflow. Typical mannerisms such as the 'allergic salute' – a habitual rubbing of the nose with the hand – reflect the intensity of the nasal itch. Internal examination of the nose via an auriscope is sufficient in the paediatric population whilst the adult population requires nasal endoscopic examination. This will reveal a pale purple or pink, swollen inferior turbinate with narrowing of the nasal airway. An important differential diagnosis is nasal polyps, which are pale, non-tender and mobile. In children, nasal polyps should be considered due to cystic fibrosis until proven otherwise [21].

2.4.4 Serum IgE and nasal secretions Eosinophil level

Eosinophilia in peripheral blood and nasal secretion are indirect indicators of allergy but with low sensitivity and specificity. The presence of intestinal helminthiases, which still exists in many parts of the world, is responsible for the diagnosis of tropical pulmonary eosinophilia (TPE) in which patients commonly presenting with symptoms similar to allergic rhinitis and bronchial asthma. This diagnostic dilemma limits the diagnostic value of elevated levels of eosinophils in the peripheral blood. Non-allergic rhinitis with eosinophilia syndrome (NARES) is a clinical syndrome comprising of symptoms that are consistent with allergic rhinitis, but with the absence of allergy demonstrated by negative allergen skin testing, and failure of nasal cytology analysis to demonstrate more than 20% of eosinophils. Anosmia is a prominent feature not shared with allergic rhinitis. The pathophysiology of NARES is poorly understood [22].

Nevertheless, some studies have proven that nasal eosinophilia is a useful diagnostic test in allergic rhinitis, with moderately high sensitivity and high specificity [23].

Immunoglobulin E (IgE) was first described in 1967. It has the lowest serum concentration among all circulating immunoglobulin isotypes.

Serum IgE concentration at birth is low. It continues to rise until the age of 10-15 years. The increase of serum IgE in children with a predisposition to atopic reactions is usually more abrupt than those who are not. Total serum IgE levels decline from the second to the eight decades of life. Usually, elevated IgE concentration is related to atopic diseases but many other disorders result in elevated serum IgE (for example: infections, neoplasms, immunodeficiency syndromes, skin disorders, and inflammatory diseases) [24]. Relying on the measurement of IgE as the only screening test for the allergic disease is unreliable, with the predictive value of an elevated IgE in patient population was found to be 50%, whereas misclassification of asymptomatic as allergic was low (4%). In conclusion, total IgE is highly influenced by allergen skin reactivity [25]. In addition, it is important to mention that 35% to 50% of patients with allergic rhinitis present within normal total IgE levels, whereas 20% of non-atopic individuals present with high total IgE levels [26]. Food allergens have been most comprehensively studied to determine the clinical sensitivity of tests for specific IgE antibodies. Likewise, IgE thresholds help to define 95% probability of negative challenges [27]. The concept is unclear. Yet, we have routinely, undoubtedly opined that allergy is a hypersensitivity reaction mediated by IgE.

2.4.5 Skin testing for the diagnosis of allergies

Skin tests in patients with IgE-mediated immediate-type allergy are performed to establish contact between allergens and skin mast cells. The latter carry specific IgE antibodies on their surface. If mast cells get activated, mediators (mainly histamine) are released which induce a visible skin reaction (wheal and erythema) [28]. Skin tests are used in addition to a directed history and physical examination to exclude or confirm IgE-mediated diseases such as allergic rhinitis, asthma, and anaphylaxis to aeroallergens, foods, insect venoms, and certain drugs. There are two types of skin testing used in clinical practice. These include percutaneous testing (skin prick or puncture) and intra-cutaneous testing (intradermal). Prick testing involves introducing a needle into the upper layers of the skin through a drop of allergen extract, devices are available for prick testing. Intra-cutaneous (intradermal) testing involves injecting a small amount of allergen (0.01-0.02 mL) into the dermis. The

release of preformed histamine from mast cells causes increased vascular permeability via smooth muscle contraction and development of a wheal; inflammatory mediators initiate a neural reflex causing vasodilatation, leading to erythema (the flare) [29]. Skin prick tests are the preferred choice of investigation. However, intradermal tests are more sensitive than skin prick tests. As intradermal tests are more convenient, testing can also be done at a less susceptible site of the body (i.e. upper back). The reaction is read after 15 to 20 minutes. Skin tests are regarded as positive if the mean wheal diameter is ≥ 3 mm for the prick test, and ≥ 5 mm for the intradermal test. However, skin test results may be negative although patients are allergic [28].

2.4.6 Skin testing or Ig E level: Which is better in the diagnosis of allergy disorder?

Few studies with better statistics have attempted to address the above confusion so that timely diagnosis can be made. It is important to note that both in vivo assays (typically skin-prick tests) and in vitro assays have sufficient sensitivity to provide comparably useful clinical information for allergic rhinitis. Skin-prick testing is moderately more sensitive but less specific than radioallergosorbent testing. Recently, newer variants of the radioallergosorbent test like FEIA and the enzyme-linked immunosorbent assay (ELISA) have been developed that are more sensitive than the original radioallergosorbent test. These newer in vitro tests are slightly less sensitive than skin tests [30] but they provide greater specificity [31].

Other less frequently used assays for IgE-mediated reactions include: [32]

- histamine release from basophils and plasma tryptase secondary to mast cell degranulation (useful in the detection of anaphylaxis and mastocytosis)
- eosinophils and their generated products, such as eosinophilic cationic protein (ECP in sputum)
- basophil activation test, as detected by the expression of CD63 and/or CD203C surface markers by flow cytometry (for both diagnosis and serial monitoring of therapeutic efficacy)
- application of Rapid test for the allergic conjunctival disease to nasal diseases by applying immunochromatography to tear fluid.

2.5 Complications of Allergic Rhinitis

Establishing the diagnosis of allergic rhinitis is important as numerous complications may develop with chronic rhinitis. The complications are as follows:

- (1) Severe chronic upper-airway disease.
- (2) Subjects with AR have an increased risk of developing asthma.
- (3) May constitute a suitable population for secondary intervention to interrupt the “allergic march” [33].
- (4) The development of other syndromes or diseases: acute or chronic rhinosinusitis, nasal polyps, otitis media with effusion, and hearing impairments [3].
- (5) There is an association between allergic or nonallergic rhinitis with obstructive sleep apnea:
- (6) In children, these are considered to be independent predictors for sleep-disordered breathing (SDB) and failure of adeno-tonsillectomy, which is the recommended first-line therapy for children with OSA [34].

The fact that the respiratory infections, commonly of viral origin, occur frequently in young children and produce similar symptoms, it is very difficult to diagnose allergic rhinitis in the first 2 or 3

years of life. The prevalence of allergic rhinitis peaks in the second to fourth decades of life and then gradually diminishes [35-37].

The MeDALL (Mechanisms of the Development of Allergy) study [38], which includes both canonical epidemiological methods [39] and unsupervised cluster analysis [40] has shown that coexistence of asthma, eczema, and rhinitis in the same child is more common than expected by chance alone. This supports the existence of a multi-morbidity cluster. We should never take lightly the diagnosis of rhinitis specifically allergic rhinitis, which chronic inflammation is a rule if exposure to the allergen is not prevented.

2.6 Management

The goal of treatment is to minimize or eliminate symptoms in order to decrease suffering and increase the quality of life (Figs. 1, 2). Patients need to be counselled on the most appropriate medications or safe combination of medications for optimal management. In addition, advice on alternative treatment options should be provided, especially when medications fail or if unwanted side effects occur.

The pharmacological treatment options of allergic rhinitis and eye manifestations are shown in Table 3 and 4.

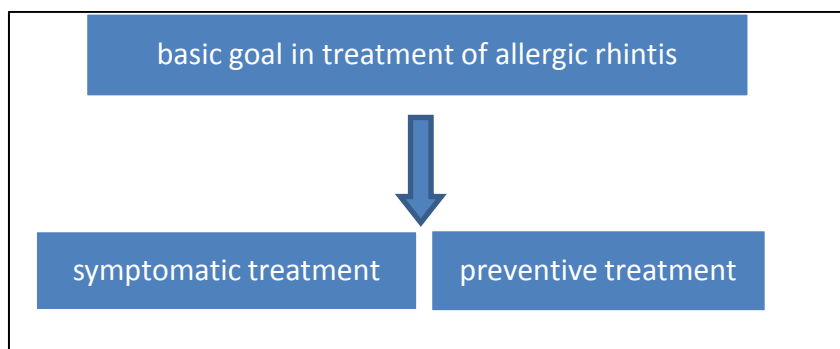


Fig. 1. Some basic approaches in treatment of allergic rhinitis

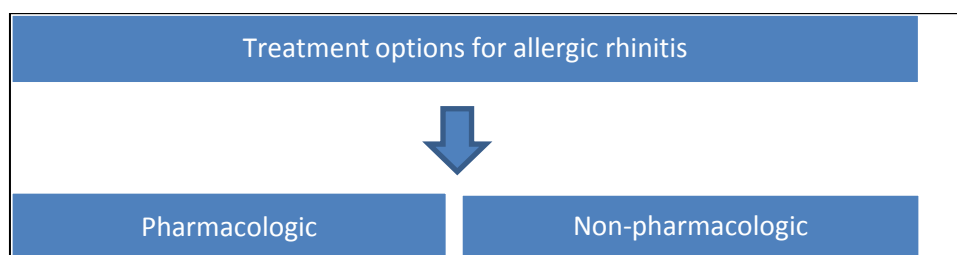


Fig. 2. Treatment options for allergic rhinitis: Pharmacologic treatment options

Table 3. Pharmacologic options for treatment of allergic rhinitis [41]

Class of drugs	Common dosage	Known side effects
Anti-histaminic	loratadine tablet 10 mg solution 5mg/5ml disintegrating tab 10 mg chewable tabs 5 mg cetirizine syrup 5 mg/5ml chewable tab 5,10 mg disintegrating tab 10 mg tablet 10 mg levocetirizine solution 2.5 mg/5ml tablet 5 mg	1st generation: Anticholinergic effects • blurred vision • dry mouth • urinary retention Central nervous system • drowsiness (increased accidents) • cognitive impairment (any age) Gastrointestinal • constipation • GI upset • nausea Sensory • taste: bitter taste, loss of taste 2 nd generation: • GI upset • headache • drowsiness (1-3%) • myalgia
Intranasal Antihistamine	azelastine hydrochloride spray: 5 to 11 yrs: 1 spray EN 2x/day ≥ 12 yrs: 1-2 sprays EN 2x/day olopatadine hydrochloride spray: 6 to 11 yrs: 1 spray EN 2x/day ≥ 12 yrs: 2 sprays EN 2x/day	Nasopharyngeal • nasal irritation • epistaxis • pharyngitis, coughing • septal perforation Sensory • smell: reduced sense of smell • taste: unpleasant taste, loss of taste
Intranasal Corticosteroids	fluticasone propionate spray: 1 spray each nostril (EN) 2x/day or 2 sprays EN 1x/day mometasone spray: 2 sprays EN 1x/day	Nasopharyngeal • nasal irritation • epistaxis • pharyngitis, coughing • septal perforation Sensory • smell: reduced sense of smell • taste: unpleasant taste, loss of taste • global: headache with intranasal steroids Same like above
Intranasal Anticholinergic	ipratropium bromide spray: 2 sprays EN 2-3x/day 2 sprays EN 4x/day (max. 3 weeks)	
Leukotriene Inhibitors	montelukast sodium: 6 months to 5 yrs: 4 mg daily 6 to 14 yrs: 5 mg daily ≥ 15 yrs: 10 mg daily	• headache • rash (uncommon) • dream abnormalities • gastritis, dyspepsia • dental pain • respiratory tract infections
Intranasal Mast Cell Stabilizers	cromolyn sodium spray: ≥ 2 yrs: 1 spray EN 3-6 x/day	Similar like other intranasal products

Table 4. Medicines for eye complaints in allergic rhinitis

Class of drugs	Common dosage	Known side effects
Ocular Antihistamines	ketotifen fumarate solution: 1 drop into affected eye every 8- 12 h (max. 8 weeks) azelastine solution: 1 drop into affected eye 2x/day (max. 8 weeks)	• headache • ophthalmic irritation: burning, dryness, pruritus, stinging • possible contact lens irritation (consult with eye care provider)
Ocular Mast Cell Stabilizers	nedocromil sodium 2% solution: 1-2 drops into affected eye 2x/day lodoxamide tromethamine solution: 1-2 drops into affected eye 4x/day	• headache • ophthalmic irritation: burning, dryness, pruritus, stinging • possible contact lens irritation (consult with eye care provider)

3. CONCLUSION

Allergic rhinitis is mainly triggered by inhaled allergens, which caused the IgE-mediated reactions and lead to mucosal inflammation. Common presenting symptoms of allergic rhinitis are sneezing, nasal pruritus, airflow obstruction, and nasal discharge, and it is important to differentiate from the non-allergic rhinitis (NAR).

Patients with allergic rhinitis generally experience more sneezing and itchy eyes, which are usually seasonal compared to NAR. The diagnosis of allergic rhinitis is based on history and physical examination. Further investigations of specific IgE (skin or blood) allergy testing may proceed for the patients who do not respond to empiric treatment, or when the diagnosis is uncertain, or when knowledge of the specific causative

allergen is needed for target therapy. Management of allergic rhinitis aims to minimize or eliminate symptoms to reduce suffering and improve the quality of life. Antihistamines, intranasal corticosteroids, intranasal anticholinergic, leukotriene inhibitors, and Intranasal Mast Cell Stabilizers can be used for the treatment of allergic rhinitis. Ocular antihistamines and ocular mast cell stabilizer eye drops may reduce the eye symptoms of allergic rhinitis cases.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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