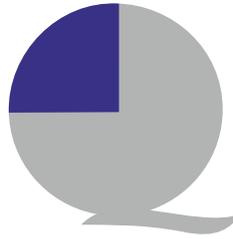


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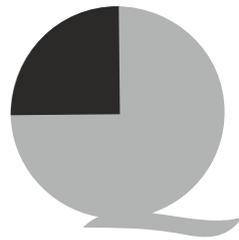
Review:
**Allergic
Rhinitis -
An Overview**

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

Problems relating to allergies		Particles in air (allergens)		Allergic symptoms	
	Swollen sinus linings				
Trapped fluid in the sinuses can cause sinus infections	Eye inflammation	Pollen		Watery eyes	
Blocked eustachian tube may cause ear congestion and infection	Stuffy or runny nose	Dust mite debris		Runny nose	
	Itchy or sore throat	Animal dander		Itchy throat	

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ALLERGIC RHINITIS - AN OVERVIEW

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Introduction

The immune system is a system of many biological structures and processes within an organism that protects against disease. It consists of two components, innate immunity and the adaptive immunity. The innate immune system which is pre-existing resistance characterized by physiologic barriers to entry of pathogenic organisms and very fast host defense responses while the adaptive immune system which is acquired consists of cells displaying antigen recognition molecules, and is mediated through cells (T lymphocytes) and humoral (B lymphocytes producing the antibodies) and has the capacity for long-term memory.

Normally the immune system helps the body fight against a wide variety of agents, ranging from bacteria, viruses, parasites to other foreign body. However when these responses are exaggerated or inappropriate they may result in causing harm to the body. These reactions are called hyper-sensitivity reactions.

There are four main types of hypersensitivity reactions.

Types I, II, and III are antibody-mediated; type IV is T-cell-mediated.

Type I: Immediate Hypersensitivity (Allergy)

Type II: Hypersensitivity (antibody mediated)

Type III: Immune Complex Hypersensitivity

Type IV: Cell-Mediated (Delayed) Hypersensitivity

There are four main types of hypersensitivity reactions:

Type I: Immediate

Hypersensitivity (Allergy)

Type II: Hypersensitivity (antibody mediated)

Type III: Immune Complex Hypersensitivity

Type IV: Cell-Mediated (Delayed)

Type I hypersensitivity manifests itself in tissue reactions occurring within seconds after the antigen combines with the matching antibody. It may occur as a systemic reaction (anaphylaxis) or local reaction (asthma, rhinitis, urticaria and eczematous dermatitis) alone or in combination in presence of Ig E. It may or may not be associated with atopy. Atopic hypersensitivity disorders exhibit a strong familial predisposition and are associated with elevated IgE levels.

Predisposition to atopy is clearly genetic, but symptoms are induced by exposure to specific allergens. The induction of allergic diseases requires sensitization of a predisposed individual to a specific allergen. The greatest propensity for the development of atopic allergy is in childhood and early adolescence when the immune system is hyperactive. The allergen is processed by the antigen presenting cells located throughout the body at surfaces that contact the outside environment, such as the nose, lungs, eyes, skin and the intestine. These antigen presenting cells present the antigens to the T helper cells via the Major Histocompatibility Complex (MHC). Depending upon the genetic constitution of an individual and the cytokine response generated by the antigen itself, either a TH1 subset (protective immunity) or TH2 subset (allergic immunity) gets activated. The TH2 response is

associated with activation of specific B cells that can present allergens or that transform into plasma cells for antibody production. Synthesis and release into the plasma of allergen specific IgE results in sensitization of the mast cells which is the key effector cells in the response to the specific allergen. It is a component of the innate immunity and is distributed at cutaneous and mucosal surfaces and in the sub mucosal tissues around the blood vessels and influence the entry of foreign substances by their rapid response capability.

Synthesis and release into the plasma of allergen specific IgE results in sensitization of the mast cells and release of the granules containing histamine, proteoglycans, tryptase, chymase and carboxypeptidase

Following sensitization, when the individual is re exposed to the allergen, activation of the effector cells and release of the granules containing the preformed mediators which include histamine, proteoglycans, tryptase, chymase and carboxypeptidase A occurs. In addition to exocytosis, aggregation of the Ig E to the mast cell initiates two other pathways for generation of bioactive products, namely, lipid mediators with subsequent release of arachidonic acid. It is converted by the cyclooxygenase pathway to prostaglandins (predominantly PGD₂) and by the lipoxygenase pathway to leukotriene LTB₄ and LTC₄ while platelet activating factor (PAF) is formed as a byproduct. Also there are a number of cytokines including interleukins, TNF, interferon and various other chemokines. The cellular component of the mast cell- mediated inflammatory response would be augmented and sustained by cytokines and chemokines of mast cell origin.

The allergic inflammation has two phases, a mediator induced immediate phase which is characterized by pruritus with a wheal and flare response, watery discharge from the nose, and bronchospasm and mucus secretion from the lung which are manifested in isolation or simultaneously. The reduced nasal patency, reduced pulmonary function test, or evident erythema with swelling at the skin site are manifestations of the cell mediated late response.⁽¹⁾

Now let us take a brief overview of the allergic diseases involving the respiratory tract in detail and their implication and correlations with each other.

Allergic Rhinitis

Epidemiology:

Allergic rhinitis(AR) is the most common atopic disease, with an increasing prevalence worldwide, ranging between 10-30% in both European as well as American studies.⁽²⁾ The prevalence varies according to the definition used and whether it is based on physician diagnosis alone or in combination with allergy testing. In a recent study involving 1200 subjects IN Delhi, India, the prevalence of AR was reported to be 11% (132 subjects) and out of them, 33.3% (44 patients) had concomitant asthma. Because more than 50% of

Americans are skin test positive for common allergens, skin testing does not always accurately confirm the diagnosis in the absence of a definitive history. However accurate estimates of allergic rhinitis are difficult to obtain secondary to variability of geographic pollen counts, misinterpretation of symptoms by patients and inability of both patient as well as the physician to recognize the disorder.⁽³⁾

Incidence of onset is greatest in children at adolescence with peak occurring at ages 13 to 14 years, with a decrease in incidence seen in advancing age. Although it may be seen in infants, in most of the cases an individual requires two or more seasons of exposure to a new antigen before exhibiting the clinical manifestations of allergic rhinitis.⁽⁴⁾

Definition

It is clinically defined as a symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation of the membranes lining the nose. The symptoms of which include rhinorrhea, nasal obstruction, nasal itching, sneezing and at times itching of the eyes, ear and throat which are reversible spontaneously or with treatment. The stuffy nose is the most burdensome symptom to patients, but the itch and sneeze are the most characteristic.

A symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation of the membranes lining the nose.

Burden of the disease:

Although it is not a fatal disease, AR has a negative impact on the quality of life (QOL). Sleep, absenteeism and presenteeism, mood and cognition and participation in sports and leisure activities are all affected, causing a great physical and financial burden on the patient. Hidden direct cost includes treatment of asthma, upper respiratory infection, chronic sinusitis, otitis media, nasal polyposis and obstructive sleep apnea.

In a survey of 8,267 U.S. employees, 55% experienced allergic rhinitis symptoms for an average of 52.5 days, were absent from work for 3.6 days/year because of their condition, and were unproductive 2.3 hours/workday when experiencing symptoms. The mean total productivity (absenteeism and presenteeism) losses were \$593/employee per year.⁽⁵⁾ In total, allergic rhinitis results in an estimated 3.5 million lost work days and 2 million lost school days.⁽⁶⁾ Approximately 10,000 children are absent from school on any given day secondary to allergic rhinitis. Depending on a child's age, absence from school may also affect parent's productivity or absence from work.

Classification:

Previously, allergic rhinitis was sub divided into seasonal, perennial and occupational depending upon the time and place of exposure. Perennial allergic rhinitis is most

frequently caused by indoor allergens such as dust mites, mold spores, animal dander and cockroaches, while seasonal allergic rhinitis is related to a variety of pollens and molds. This classification works best as an attempt to identify the allergens causing the disease, particularly in certain parts of the world where there are distinct seasons. However this created confusion among the treating clinician as there was frequent overlap between the two, hence for better understanding, and management it is now classified by the Allergic Rhinitis and its Impact on Asthma (ARIA) workshop 2008 guidelines⁽²⁾:

1) Depending upon the duration as “intermittent” i.e. IAR and “persistent” i.e. PER.

And

2) Depending upon the severity of the symptoms and their impact on social life, school and work allergic rhinitis can be also classified as “mild” and “moderate/severe”

Table 1- Classification of allergic rhinitis according to ARIA

1	“Intermittent”	Means that the symptoms are present <ul style="list-style-type: none"> ● Less than 4 days a week ● Or for less than 4 consecutive weeks
2	“Persistent”	Means that the symptoms are present <ul style="list-style-type: none"> ● More than 4 days a week ● Or more than 4 consecutive weeks
3	“Mild”	Means none of the following are present <ul style="list-style-type: none"> ● Sleep disturbance ● Impairment of daily activities, leisure, and/or sport ● Impairment of school or work ● Symptoms present but not troublesome
4	“Moderate/severe”	Means that one or more are present <ul style="list-style-type: none"> ● Sleep disturbance ● Impairment of daily activities, leisure, and/or sport ● Impairment of school or work ● Symptoms troublesome

Risk Factors

Allergic rhinitis is a multifactorial disease with interplay of genetic as well as environmental factors influencing the disease development.

1. Atopy: It commonly occurs in atopic individuals, and has been linked to multiple genetic loci.⁽⁷⁾ A family history therefore represents a major risk factor for allergic rhinitis. However it may also occur in those no atopy or family history.

2. Early life risk factors: Early life events are essential in shaping the immune answer towards the Th1 or Th2 profile. The hygiene hypothesis⁽⁸⁾ suggests that an early life environment primes the immune system in the Th1 direction while a sterile environment tends to promote the development of allergic diseases. Infectious diseases such as

hepatitis or salmonellosis can be inversely associated with allergy.

A family history represents a major risk factor for allergic rhinitis

3. Ethnic groups: prevalence of atopy and allergic rhinitis is higher in urban than in rural areas, suggesting that countryside lifestyle could possibly protect children from the development of allergy.

This protective farm effect was related to livestock farming and thus exposure to microbial antigens.

4. Allergen: Allergens are antigens inducing and reacting with specific IgE antibodies. They originate from a wide range of animals, insects, plants, fungi or occupational sources.

They are usually classified as indoor (principally mites, pets, insects or from plant origin e.g. ficus), outdoor (pollens and molds) or occupational agents.

- i. House dust mites make up a large of house dust allergens, most important ones being Dermatophagoides in both tropical and subtropical regions. They are associated with enzymatic activities, which directly potentiate Th2 cell response. They are present abundantly in mattresses, bed bases, pillows, carpets, furniture or fluffy toys. They maximally grow in hot(above 20°) and humid conditions(80%), and die out when the humidity falls. Many patients present symptoms all year round but with a recrudescence during humid periods. Airborne exposure occurs with the active disturbance of contaminated fabrics and settles rapidly after disturbance. The sensitized patient shows a greater risk of developing asthma at a later date. Storage mites are present in stocked grains and flour and are usually associated with agricultural allergies.



Fig. 1 : Environmental allergens

Storage mites are present in stocked grains and flour and are usually associated with agricultural allergies.

- ii. Pollens are the male sex of the vegetable kingdom are emitted in large quantities and liberated into the atmosphere. The pollens important in causing allergic rhinitis are from plants that depend on the wind (anemophilous). The size of the pollen varies from 10 μm to 100 μm , and this explains their deposition in the nostrils and more particularly in eyes. The pollination season of various plants depends on the individual plant and various geographic locations. Though most of the pollens are seasonal some of the plants may pollinate over a very long period and are considered as perennial. Weather conditions, such as temperature and rainfall, influence the amount of pollen produced.

- iii. Animal Dander is powerful allergens which are capable of causing allergic reactions and they remain air borne for long periods and stick to the clothing and can be carried to the

areas in which the pets have no access. The saliva and the sebaceous glands also represent allergens. Schools are a risk environment for children allergic to cats as they may develop symptoms or worsen; and are a site of transfer of cat allergen to homes.

Mold spores released from fungi and penetrate deeply into the respiratory track and provoke both rhinitis and asthma

- iv. Molds spores are most important allergens, released from fungi and molds growing on organic putrefying matter. Outdoor molds generally first appear in the spring and become most significant during the warmer months while the indoor molds are abundantly found in bathrooms and kitchens all year round. They are small in size particularly 3 to 10 and penetrate deeply into the respiratory track and provoke both rhinitis and asthma. They are significantly related to an increase in the hospitalization of asthmatics.
- v. Insects are indoor allergens, particularly cockroaches in low income housing where they are frequently found in large numbers. The cockroach allergens are found in their stools as well as their chitin shell.
- vi. Nonspecific irritants and infections may influence the course of persistent allergic rhinitis. Children with this condition appear to have a higher incidence of respiratory infections that tend to aggravate the condition and may lead to the development of complications.
- vii. Tobacco smoke and air pollutants such as sulfur dioxide, ozone, exhaust particles, nitrogen dioxide and particulate matter increases the sensitization to the allergens and as well as the severity and persistence of symptoms.
- viii. Foods as direct cause of allergic rhinitis are difficult to correlate, however rarely hypersensitivity to dietary proteins may induce symptoms of non-seasonal rhinitis. Cross reactivity exists between food and inhalant allergens, i.e. those allergic to pollen frequently develop symptoms with fruits, nuts, vegetables.⁽⁹⁾
- Occupational agents are a major cause of persistent allergic rhinitis however symptoms are not constant because there is clear, temporal association with workplace exposure. Some causes of occupational rhinitis include laboratory animals (rats, mice, guinea pigs etc.), grains (bakers and agricultural workers), medications (penicillin), wood dust, latex and chemicals (acid anhydrides, platinum, glues, solvents).⁽¹⁰⁾

Clinical features

Major symptoms of allergic rhinitis are sneezing, rhinorrhea, nasal pruritus and nasal congestion

The major symptoms of allergic rhinitis are sneezing, rhinorrhea, nasal pruritus and nasal congestion although patients may not have the entire symptom complex.

Sneezing most characteristic symptom, and one may have

paroxysms of 10 to 20 sneezes in rapid succession particularly in mornings.

Rhinorrhea is typically a thin discharge which may be profuse and continuous. Due to copious nature, patients classically may have a “nasal allergic salute”. Purulent discharge is never seen and if present indicates secondary bacterial infection.

Nasal congestion and obstruction resulting from swollen turbinate’s is a frequent complaint. Owing to severe nasal obstruction interference with aeration of Eustachian tubes and sinuses may occur resulting in headache and earache. Hearing may also be muffled, and continuous nasal obstruction may result in loss of smell and taste. It may also worsen obstructive sleep apnea.

Pruritus particularly in children and may induce frequent rubbing of the nose.

Eye symptoms (pruritus, erythema and lacrimation) often accompany nasal symptoms. Irritation of the throat and post nasal discharge results in a non-productive cough, aggravated on lying down. A constricted feeling of the chest with associated dyspnea occurs suggesting coexisting hyper reactive airway or asthma.

A characteristic feature of the symptom complex is the periodicity of its appearance. Symptoms usually recur each year for many years in relation to the duration of the pollinating season of the causative plant. The intensity of the symptoms tends to follow the course of pollination, becoming more severe when the pollen concentration is highest and waning as the season ends. These symptoms may also exhibit periodicity within the season. Many patients tend to have more intense symptoms in the morning because most windborne pollen is released in greatest numbers between sunrise and 9am. Some specific factors such as rains may decrease symptoms or dry winds may increase the symptoms due to the influence on pollen concentration.

There may be increased reactivity of the nasal mucosa after repeated exposure to the pollen. This local and non-specific increased reactivity has been termed as priming effect. Owing to this non-specific irritants may also potentiate and prolong the symptoms of allergic rhinitis. Also because patients may be sensitized to several allergens, symptoms may persist beyond the pollination season.

General ENT examination

The nasal cavity must be examined for congestion, hypertrophied turbinates, deviated septum, polyps and secretions.

Sinus tenderness

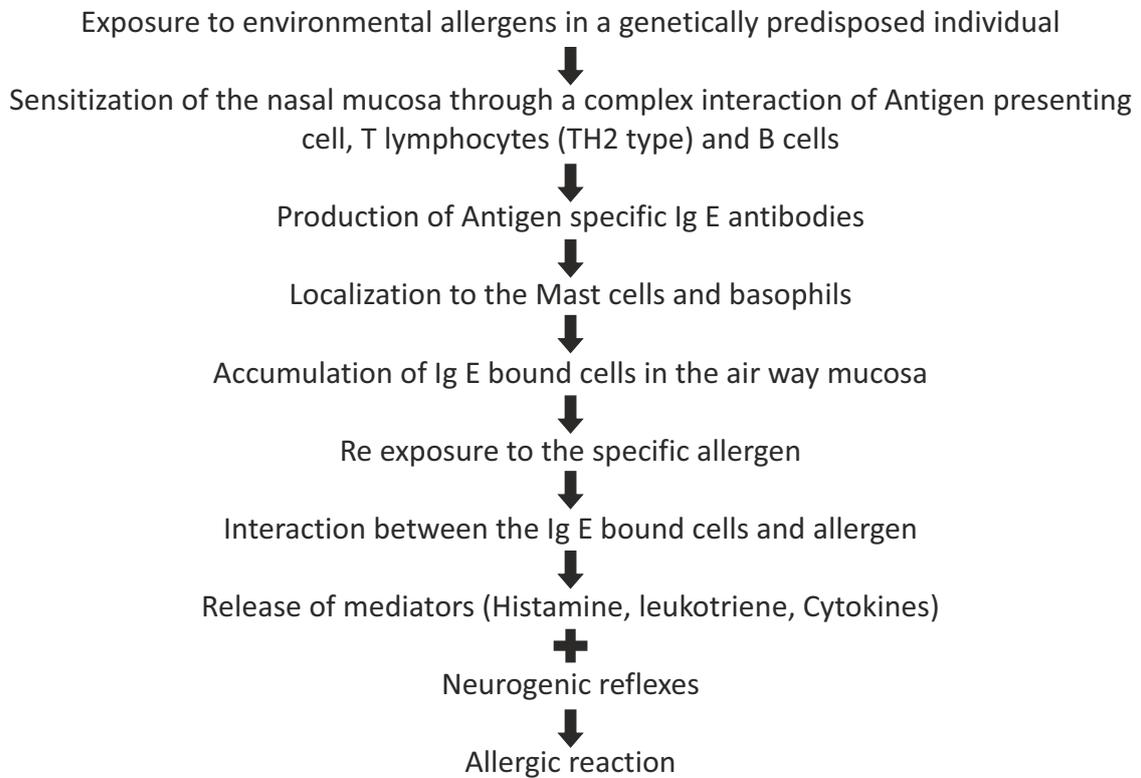
Oral cavity must be checked for pharyngeal wall congestion, enlarged tonsils and dryness due to mouth breathing.

Eyes must be examined for hyperemia, edema and lacrimation.

Ear for discharge, perforated tympanic membrane.

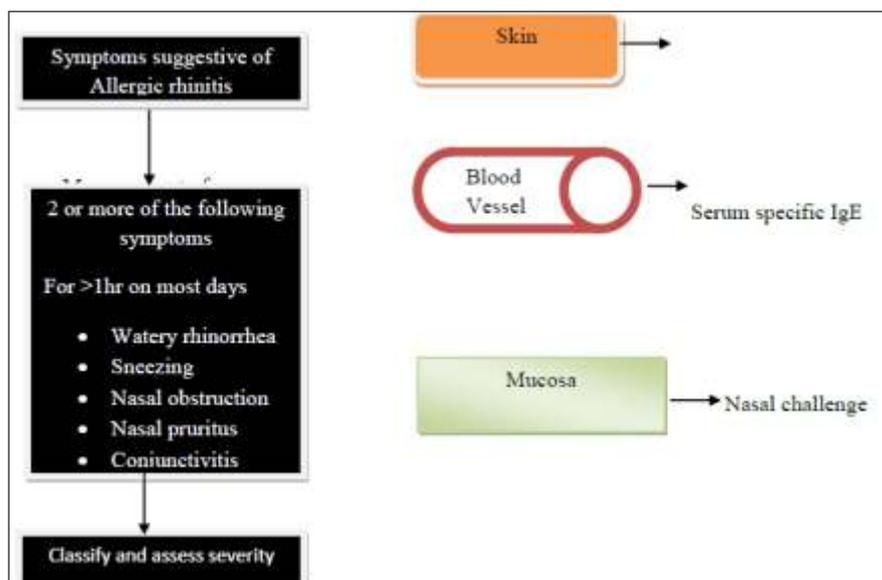
Chest auscultation for signs of airway obstruction

Pathophysiology of Allergic Rhinitis



Diagnosis

The diagnosis of allergic rhinitis depends on a combination of history, physical examination, and diagnostic test.



When taking a history, one should record the specific characteristics of the symptoms, as follows:

(a) Define the onset and duration of symptoms and emphasize any relationship to seasons of life events, such as changing residence or occupation, or new hobby.

(b) Define the current symptoms including secretions, degree of congestion, sneezing and nasal itching or sinus pressure and pain. Obtain a history regarding ocular symptoms, such as itching, lacrimation, puffiness and chemosis; pharyngeal symptoms of a mild sore throat, throat clearing and itching of the palate and throat; associated systemic symptoms of malaise, fatigue or sleep disturbances.

(c) Identify exacerbating factors, such as indoor and outdoor allergens and non-specific irritants (e.g. cigarette smoke, chemical fumes, cold air etc.)

(d) Identify other associated allergic diseases such as asthma or atopic dermatitis or a family history of allergic diathesis.

(e) Complete medication history.

Skin testing methods

Immediate hypersensitivity skin tests are widely used to demonstrate an Ig E mediated allergic reactions of the skin. These tests represent a major diagnostic tool in field of allergy.⁽¹¹⁾ Out of the various methods available, prick and puncture method is widely employed as recommended by the US joint council of Allergy Asthma and Immunology.

Immediate hypersensitivity skin tests are widely used to demonstrate an Ig E mediated allergic reaction. Prick and puncture method is widely employed

The skin test is available for a wide range of allergens including molds as aspergillus, house dust mites, pollens and animal dander.

Skin test should be read at the peak of their reaction by measuring the wheal and the flare approximately 15mins after the performance of the test.

Carefully performed and correctly interpreted skin test with high quality allergen vaccines and a battery that includes all the relevant allergens of the patient's geographic area are a simple, painless and highly efficient method. Therefore, skin testing represents one of the primary tools for allergy diagnosis by the trained physicians.

Both false positive and false negative skin tests may occur due to improper technique or material. False positive skin tests may result from dermographism or may be caused by irritant reactions or a non-specific enhancement from a nearby strong reaction.

False negative skin tests can be caused by:

Extracts of poor initial potency or subsequent loss of potency

Drugs modulating the allergic reaction

Diseases attenuating the skin response

Improper technique(no or weak puncture)

Even after false positive and false negative tests have been eliminated, the proper interpretation of results requires a thorough knowledge of the history and physical findings. A positive skin test alone does not confirm a definite clinical reactivity to an allergen.

Serum total Ig E

Serum total Ig E is measured using radio- or enzyme immune assays. In normal subjects, levels of Ig E increase from birth (0-1KU/l) to adolescence and then decrease slowly and reach a plateau after the age of 20-30 years. In adults, levels of over 100-150KU/l are considered to be above normal. Allergic and parasitic diseases as well as many other conditions increase the levels of total Ig E in serum.

Serum total Ig E is measured using radio-or enzyme immune assays. In adults, levels of over 100-150KU/l are considered to be above normal.

Serum specific Ig E

Serum allergen specific Ig E measurement is of significance. The first technique to accurately measure was the RAST (radioallergosorbent test),⁽¹²⁾ newer techniques are now available using either radio or enzyme labeled anti Ig E. The cut off level above which the test is considered positive is 0.35KU/l. It is of particular importance of diagnosis of allergic broncho pulmonary aspergillosis or fungal sinusitis.

Nasal mucosal challenge

These tests are done more for research purpose and to a lesser extent for clinical practice.

Radio imaging⁽¹³⁾

CT has become the principal radiological investigation for major Sino – nasal disorders but is of limited use in the diagnosis of allergic rhinitis, CT scans can be done to

- (a) To eliminate other conditions
- (b) To exclude CRS
- (c) To eliminate complications in rhinitis
- (d) In patients who do not respond to treatment
- (e) Unilateral rhinitis.

Treatment of Allergic Rhinitis

(a) Avoidance therapy

In the primary prevention of the development of allergy, no specific measure has been recommended by the ARIA guidelines.

However in those suffering from allergic rhinitis complete avoidance of an allergen results in a cure but provided there is only a single allergen of limited and clearly defined distribution. Hence attempts should be made to minimize contact with any important allergens regardless of what other mode of treatment is instituted.

In those suffering from allergic rhinitis complete avoidance of an allergen results in a cure

In most of cases of allergic rhinitis, complete avoidance therapy is not possible because aeroallergens are so widely distributed.

There is little doubt that removal of the pet from the house will achieve improvement.

Attempts to eradicate sources of pollens or mold have also not proven to be significantly effective. However mold sensitive patients should avoid damp, musty basements, raked or burning leaves, barns, moldy hay and straw as also avoidance of certain foods having high mold content. Avoiding sites where demolition is taking place.

A comprehensive program for house dust mite control may result in a decreased exposure to the allergens. Recommendations include washing bed linen in very hot water (104°) and encasing both the mattress and box spring in mite proof casings. Eliminating upholstered furniture, wall to wall carpeting and stuff toys. Steam cleaning or acaricides help reduce mite number in the carpets. Use of a dehumidifier to reduce the humidity in the houses may be an effective measure. However effect associated with this is very mild and extremely costly affair.

Approaches to the extermination of cockroaches are based on eliminating suitable environment which favors the breeding of these vectors. Extensive cleaning and repair of the crevices and cracks in houses may be of help.

(b) Pharmacological treatment

With mild intermittent AR, the suggested initial pharmacotherapy consists of oral anti histaminic, an intranasal antihistaminic or an oral decongestant. When intermittent AR is moderate- severe, intranasal steroids provide an alternative.

In persistent AR both mild and moderate-severe intranasal corticosteroids are first line of therapy. Leukotriene antagonist act as an add on therapy when symptoms are not adequately controlled by intranasal steroids and in concomitant asthma.

An overview of the other comorbidities must also be taken into consideration to optimize the treatment.

(I) Intranasal corticosteroids

Guidelines recommend intranasal steroids as the first line treatment for the management of moderate to severe allergic rhinitis.⁽¹⁴⁾ They represent the single most effective class of medications for allergic rhinitis and improve all nasal symptoms including nasal congestion, rhinorrhea, itching and sneezing.

The suggested initial pharmacotherapy consists of oral anti histaminic, an intranasal antihistaminic, an oral decongestant or Intranasal steroids

In addition they may also be of value in relieving throat pruritis, associated cough, watery eyes. Corticosteroids have specific effects on the inflammatory cells and chemical mediators through multiple pharmacological actions by reducing the influx of the cells, reducing their survival, reducing the release of preformed and newly generated mediator and also reducing the levels of IgE.

Currently mometasone furoate and fluticasone furoate aqueous solutions are the available. These drugs are quickly metabolized to less active metabolites, have quick onset of action and are associated with a few systemic side effects (i.e. no suppression of HPA axis or bone fractures). Long term use of intranasal corticosteroid does not appear to cause significant risk for adverse morphological effects in mucosa.

The major side effects of intranasal steroids include local dryness or irritation, nasal crusting and bleeding rarely. Perforation of septum is uncommon side effect in patients who improperly point the spray towards the septal wall. This complication can be reduced by tilting the head downwards.

It is suggested that patients must be informed that intranasal steroids should be used prophylactically as the maximum benefit is not immediate and may take weeks. The optimal effectiveness is only achieved with regular use.

Initially, some patients may require topical decongestants before administering intranasal steroids. In some patients, the congestion is so severe that a 3 to 5 day course of oral corticosteroids is required to allow delivery of intranasal steroids for maintenance. The systemic steroids must only be reserved for severe cases that cannot be controlled by routine measures. They must be used for a limited period and never on chronic basis.

(ii) Antihistaminics

Stimulation of H₁ receptor produces many of the symptoms of rhinitis and asthma, including smooth muscle contraction, increased vascular permeability, increased mucous production and activation of sensory nerves that cause itching and sneezing. Antihistaminics are the foundation of symptomatic therapy and are most useful in controlling the symptoms of sneezing, rhinorrhea and pruritus. They have a property of antagonizing some of the actions of histamine by occupying the receptor sites.

The first generation anti histaminics (eg chlorpheniramine, diphenhydramine) are effective

H₁ receptor antagonists. Problems associated with their use are their side effects, the most common and most important being anticholinergic (dry mouth and eyes, urinary retention), CNS effects (sedation and impairment of motor and cognitive functions) and in large doses they are reported to cause cardiotoxicity.

Most useful in controlling the symptoms of sneezing, rhinorrhea and pruritus. newer second generation anti histaminics lack sedation, also free of anticholinergic side effects and also not associated with cardiac toxicity

Because the newer second generation anti histaminics do not appreciably penetrate the blood-brain barrier, they lack sedation. They are also free of anticholinergic side effects and also not associated with cardiac toxicity (newer agents loratidine, fexofenadine, cetirizine and levocetirizine). Second generation anti histaminics have been associated with a rapid onset of action that allows them to be taken as needed.

Azelastine is a selective H₁ receptor antagonist in form of intranasal spray. It is 10 times more potent and has a fast onset of action. In addition to H₁ blocking property it also has inhibitory effect on the cells and mediators. Azelastine is free of drug interaction and a possible alternative to oral anti histaminics. It demonstrates synergism when combined with an intranasal steroid.⁽¹⁵⁾ An unpleasant taste is its most common side effect.

(iii) Sympathomimetic agents

They are used as vasoconstrictors for the nasal mucous membrane. By taking advance of the drugs that stimulate a receptors, the edema of the nasal mucus membranes in allergic rhinitis can be reduced by topical or systemic administration. They are frequently combined with antihistaminic in oral preparations to synergize the effect and decrease the drowsiness that accompanies antihistaminics.

Nasal drops or nasal spray containing sympathomimetic agents are frequently overused as they are quick in onset of action. However they are followed by a "rebound" phenomena in which the nasal mucosa becomes even more congestion and edematous. This results in patient to use the drops or spray more frequently and in higher doses to obtain relief. The condition is called rhinitis medicamentosa. The patient must abruptly discontinue their use to alleviate the condition.

In large doses they induce elevated blood pressure, nervousness and insomnia.

Hence it is best to minimize the use of these agents.

(iv) Leukotriene receptor antagonist

The leukotriene receptor antagonist montelukast is superior to placebo in relieving nasal symptoms in patients with AR.⁽¹⁶⁾ They are relatively weak as monotherapy.

However it is used as an adjunct in the treatment of a patient who does not have an adequate response to an antihistaminic, a nasal corticosteroid or both.

They are very effective in aspirin sensitive rhinitis⁽¹⁷⁾ and in those who have a combination of seasonal allergic rhinitis with mild asthma.⁽¹⁸⁾

c) Immunotherapy

Allergen immunotherapy is defined as the repeated administration of specific allergens to patients with IgE mediated conditions to provide protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens.⁽¹⁹⁾

Immunotherapy using inhalant allergens is clinically effective to treat allergic rhinitis and asthma. It induces clinical and immunological tolerance as long terms efficacy⁽⁴⁾ and may prevent the natural progression of allergic diseases, also improves the quality of life.

The quality of allergen vaccine is critical for both diagnosis and treatment. Standardized vaccine of known potency and shelf life should be used.

Allergen immunotherapy is defined as the repeated administration of specific allergens to patients with IgE mediated conditions to provide protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens.

Subcutaneous immunotherapy (SCIT)

The clinical efficacy is well established, however optimal dosing is recommended as under dosing may result ineffective therapy while over dosing results in adverse systemic reactions. Clinical efficacy has been demonstrated with pollen, birch, grass, cat, ragweed and mite allergens both in terms of reduction of symptoms and treatment required.

The total duration of the therapy is for 3 years with using standardized allergen.

Subcutaneous immunotherapy alters the natural course of the disease. Long term efficacy persists after it has been stopped. In monosensitized children it prevents the development of new sensitizations and may prevent the development of asthma in patients with rhinitis. It is a very cost effective therapy.

Indications for subcutaneous immunotherapy-

1. Patients with symptoms induced predominantly by allergen exposure.
2. Patients with prolonged season or with symptoms induced by succeeding pollen seasons.
3. Patients with rhinitis and symptoms from the lower airways during the peak allergen exposure.
4. Insufficient control of symptoms despite optimal pharmacotherapy.
5. Undesirable side effects.

Contraindication –

1. Treatment with b blockers.
2. Other immunological diseases.
3. Instability of the patient to comply.
4. Pregnancy

Sublingual immunotherapy (SLIT)

Allergen immunotherapy can be also administered sublingually in form of tablets or drops. Although mild oral and sublingual itching and swelling occurs, systemic reactions are rare. A recent review of SCIT versus SLIT determined that although sublingual is safer than subcutaneous therapy, SLIT is only about one half as effective.⁽²⁰⁾ It would be potentially beneficial in those who have adverse reactions to SLIT.

Omalizumab

The recombinant humanized monoclonal anti- Ig E antibody forms complexes with free IgE, lowering its levels and preventing its interaction with mast cells and basophils.

Recombinant humanized monoclonal anti-Ig E antibody forms complexes with free IgE, lowering its levels and preventing its interaction with mast cells and basophils.

It has been found to be effective in both allergen challenge studies and clinical trials. Multiple studies have shown its efficacy in seasonal and perennial allergic rhinitis with significant reduction of the nasal symptoms.⁽²¹⁾ Unfortunately the cost of the therapy is prohibitive for allergic rhinitis. It is primarily indicated in treatment of severe persistent allergic asthma not controlled despite high dose oral glucocorticosteroids.

In view of the common comorbidities and shared pathophysiological mechanisms of asthma and AR, common therapeutic approach seems to be optimal for better management of patients.

ARIA guidelines⁽²⁾ recommend

Patients with allergic rhinitis should be evaluated for asthma

Patients with asthma should be evaluate for allergic rhinitis

A strategy should combine the treatment of upper and lower airways in terms of efficacy and tolerability

The effect on asthma symptoms by treating AR has been well documented.

Intranasal glucocorticosteroids, improved asthma symptoms and significantly reduced the bronchial hyper responsiveness. Though the role of intra bronchial steroids on nasal symptoms is unclear, circulating levels of eosinohils are reduced. Oral steroids have beneficial role in both, however their use is limited by side effects.

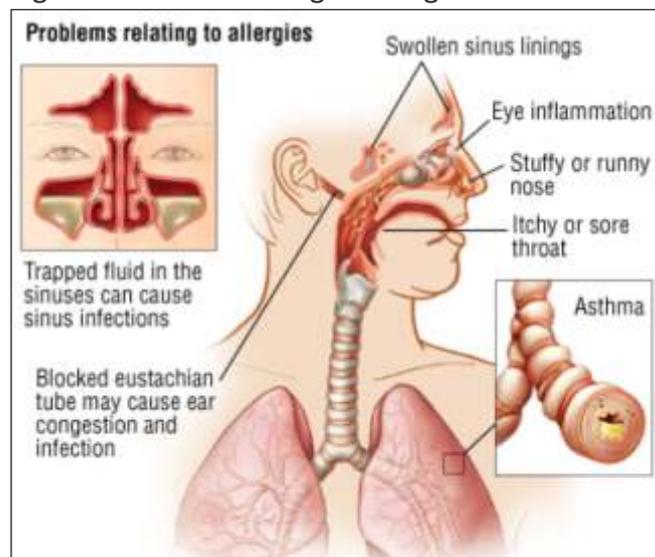
Although antihistaminics are not used in the treatment for asthma, they may have beneficial effects in presence of concomitant AR. In a placebo controlled study of patients with seasonal allergic rhinitis and seasonal asthma, cetirizine 100mg was able to significantly reduce asthma symptoms during pollen season.

In many ways, leukotriene receptor antagonist represent a rational approach to such 'one airway' disease management. They are an established treatment option for asthma, with evidence to support their use in mild persistent disease, paediatric, exercise induced bronchoconstriction and also in tapering of inhaled steroids. Evidence is also accumulating in AR to suggest that both alone or in combination with an anti histamine, LTRAs such as montelukast can alleviate the signs and symptoms of AR.

Comorbidities

Besides causing symptoms and a negative impact on QOL, AR is associated with a variety of comorbid conditions.

Fig. 2: Problems relating to allergies



1. Conjunctivitis

Although often referred to as AR, this disease usually involves the eye as well as nasal symptoms; hence the more appropriate name may be "allergic rhinoconjunctivitis."

Data suggest ocular symptoms not only affect about 40% of the adult population but about 75% have severely bothersome disease.

Eye symptoms specifically does not require any treatment with topical steroids as the Intranasal steroids and even oral anti histaminics affect the eye symptoms

The pathophysiologic mechanisms involved in generation of ocular symptoms in patients with AR are:

- Direct effects of allergen deposition onto conjunctiva
- Naso ocular reflexes(predominant mechanism
- Release of mediators and up regulation of the inflammatory cells from the nasal mucosa attracted to the eye.

The eye symptoms specifically does not require any treatment with topical steroids as the Intranasal steroids and even oral anti histaminics affect the eye symptoms, that is they reduce the inflammation, which primes the reflex.

2. Sleep

The impact of AR on sleep, which includes trouble falling asleep, difficulty staying asleep, and not feeling that one had a good night's sleep is a major problem.

Microarousals during sleep caused by nasal obstruction contributes to sleep associated problems. Problems with sleep architecture negatively affects the QOL, and treatment with INS helps correct sleep disturbances in patients who have AR.

Nasal obstruction and AR contribute minimally to sleep apnea.

3. Acute and chronic rhinosinusitis

A significant clinical overlap exists between AR and chronic rhinosinusitis, in the manner that patients undergoing sinus surgery are found to have a incidence of atopy between 50% and 94% and about 60% of the patients with AR have sinus disease. AR and chronic rhinosinusitis share similar inflammatory cell infiltrate

About 60% of the patients with AR have sinus disease

The classic explanation is that AR alters the sinus physiology, leading to ostial obstruction. Blockage then prevents normal drainage and ventilation of the sinuses, causing accumulation of the mucus, exudation of serum and decreased oxygenation with resultant impairment o mucociliary transport, stasis of secretions and susceptibility to bacterial overgrowth.

The direct effects of pollen on the sinus mucosa, because of the problems of access to paranasal sinuses are conceptually difficult to understand. Because allergens deposited near the ostia are cleared away into nose.

4. Eustachian tube dysfunction and otitis media

Nasal inflammation due to allergic rhinitis is a confirmed contributing factor in development of Eustachian tube dysfunction. 40 to 50% of children older than 3 years with Eustachian tube dysfunction have allergic rhinitis. Air pressure must be equal on both sides of the eardrum. Nasal mucosal edema and inflammation blocking the opening of the

Eustachian tube at the pharynx, which creates an imbalance of the pressures with increased negative pressure in the middle ear and improper ventilation.

Middle ear effusion occurs due to protein exudation, which is accentuated by inflammatory mediators and cytokines.

Studies linking the viral infections to airway disease support the theory that these infections predispose to chronic mucosal inflammation which promote secondary bacterial infections by enhancing the bacterial adherence and altering the host immune response.

5. Asthma

An epidemiological association between AR and asthma has been consistently demonstrated across the patient populations, including children and adults. Estimates show that up to 80% of asthmatics are affected by AR and conversely, upto 40% of patients with AR have concomitant asthma.⁽²²⁾

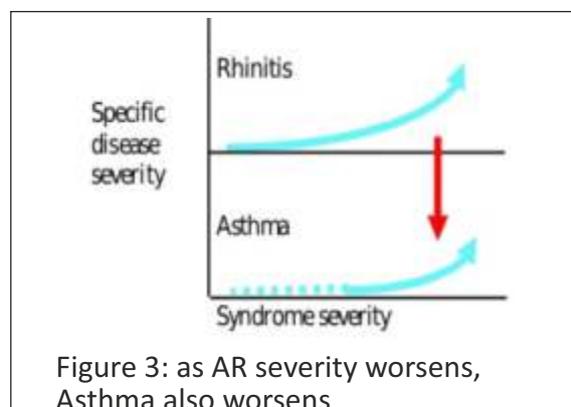
Besides epidemiological association, the concept of “unified airway” is supported by the link between AR and asthma which is present at the anatomic, physiologic, pathologic and therapeutic levels.

Asthma patients with significant rhinitis are over four times more likely to have poor asthma control than those without.⁽²³⁾ Prior studies have shown that AR may complicate asthma management and lead to poor asthma control and outcomes.

Epidemiological Link

Whether AR precedes asthma, triggers asthma or precipitates asthma is still unexplained, there are multiple schools of thoughts one of which is the “atopic march theory” an entity which refers to the sequential development of allergic diseases in childhood supports the concept that atopic dermatitis which occurs in infancy following cutaneous sensitization leads to migration of inflammatory cells to the nose and airways leading to allergic rhinitis and asthma. The prognosis of atopic dermatitis in is good however the risk of developing AR and asthma is very high.

Also some studies believe that AR is an independent risk factor for the development of asthma. Multiple studies have supported the fact that individuals with AR are about three times likely to develop asthma as compared to the negative controls. Whichever may be the cause, the current concept is that AR precedes asthma in most of the cases and when AR worsens, it negatively affects the course of asthma.



Functional Link

1. Anatomy

The respiratory tract can be considered as a single morpho-functional unit. It is entirely covered, up to the smaller bronchi, by ciliated epithelium and mucinous glands and an extensive vasculature and innervation (similar in both upper and lower airways).⁽²⁴⁾

The respiratory mucosa is rich in mast cells, which are important effector and immune-regulatory units and these cells are thought to significantly contribute to nose- bronchi connection via cytokine release. Moreover, the lymphoid tissue constitutes the bronchial (mucosal) associated lymphoid tissue (BALT or MALT), which is largely represented in both the nose and the bronchi. Although these similarities exist between the nose and the lungs, cardinal differences also exist in that the nose and paranasal sinuses are rigid cavities, whereas the lower airways have an elastic parenchyma, rich in peribronchial smooth muscles. This anatomic diversity accounts for the differential clinical features or symptoms to the same offending allergens such as sneezing, rhinorrhea and blockage in the nose and bronchoconstriction in the lung

2. Common allergens

Most of the inhaled allergens are associated with nasal and bronchial symptoms. This includes both environmental as well as occupational agents.

3. Common inflammatory pathway

The inflammation of the nasal and the bronchial mucosa is sustained by the similar inflammatory infiltrate, including mast cells, eosinophils, TH2 lymphocytes, cells of the monocytic lineage and similar pro inflammatory mediators as histamine, leukotrienes , cytokines and chemokines.⁽²⁴⁾

Allergens challenging the nose will induce the influx of inflammatory cells in the lower airways and vice versa. This is evident by the fact that

(A) An eosinophilic inflammation, bronchial hyper responsiveness, increased cough sensitivity and lower airway remodeling is seen in non asthmatics with nasal allergy.

(B) Nasal mucosal eosinophilia is present in asthmatics with or without nasal symptoms.

Thus the inflammatory response is similar for both AR and asthma with Early Allergic and Late Allergic response manifesting in both.

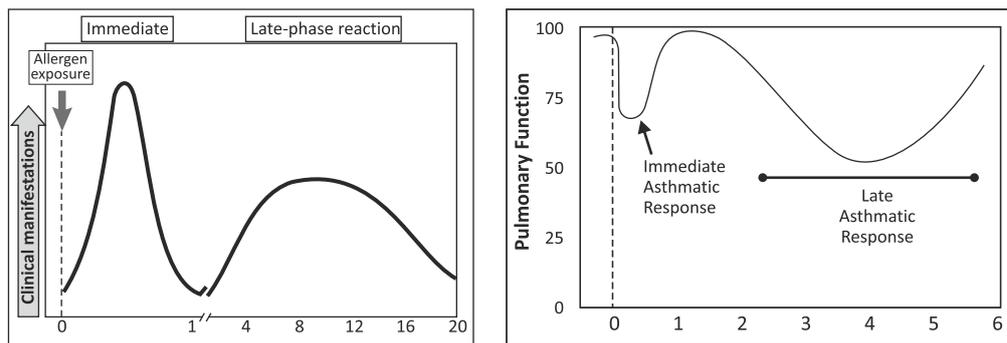
During the early- phase response, symptoms in patients with AR typically consist of sneezing, rhinorrhea and conjunctivitis, whereas patients with asthma experience wheezing, coughing and shortness of breath, in addition to objectively demonstrable changes in lung function.

There is a similar pattern and time course of early and late phase responses in AR and

asthma. Approximately 1 hour after allergen provocation, patients with AR experience a peak in symptoms, while patients with asthma experience a steep decline in lung function, measured by the forced expiratory volume in 1 sec (FEV1).

During the late-phase response, nasal congestion is sustained in patients with AR, whereas a prolonged fall in lung function is again observed in patients with asthma. Within 12-24 hours, both types of reactions typically resolve.⁽²⁵⁾

Figure 4: Shared pathophysiology of allergic rhinitis and asthma

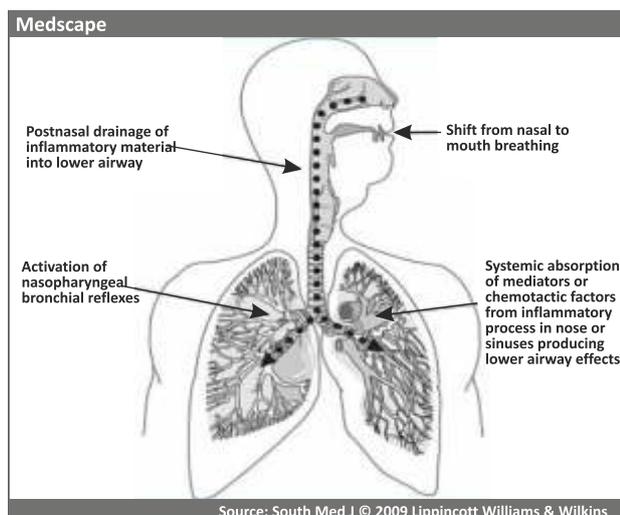


Time in hours post allergen challenge

Possible Mechanisms for the Link

1. The upper airway tract acts as a filter, resonator, heat exchanger and humidifier for the inhaled air. The inhaled air is processed and enters into the bronchi with a temperature of about 37°C and almost completely saturated in humidity. The foreign particles greater than 5-6microns are efficiently removed and therefore, filtered off from entering the lower airways. In allergic rhinitis there is a shift from nasal to mouth breathing. Thus homeostasis becomes function of the lower respiratory airways, whereby evaporative water losses induce a bronchospasm. This theory holds true for exercise induced bronchospasm.

2. Nasal bronchial reflex, in this paradigm nasal stimulation promotes bronchoconstriction through a reflex arc, with afferent arm located in pharyngolaryngeal area, a Centre in hypothalamus and efferent as vagus. This theory is supported by the finding that in asthmatics but not healthy individuals provocation with cold air in the nose causes bronchoconstriction



while cold air causes bronchodilatation.

3. Post nasal drip of inflammatory material Aspiration of upper airway secretions into the lower airways can trigger cough and wheezing.

4. Immunological theory Allergic inflammation in the nose releases cytokines that affect cells in the bone marrow and systemic circulation. These cytokines can prime the circulating cells so that when they are recruited into the lungs, they release more inflammatory mediators, thus exacerbating asthma.

5. Therapeutic links Nasal therapy with intranasal steroids and antihistaminics in AR patients with asthma has beneficial effect on asthma symptoms, bronchial hyper responsiveness and airway inflammation. Further more it reduces the risk of asthma exacerbations.

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