Reeaction of the body's immune system (Allergic Rhinitis).

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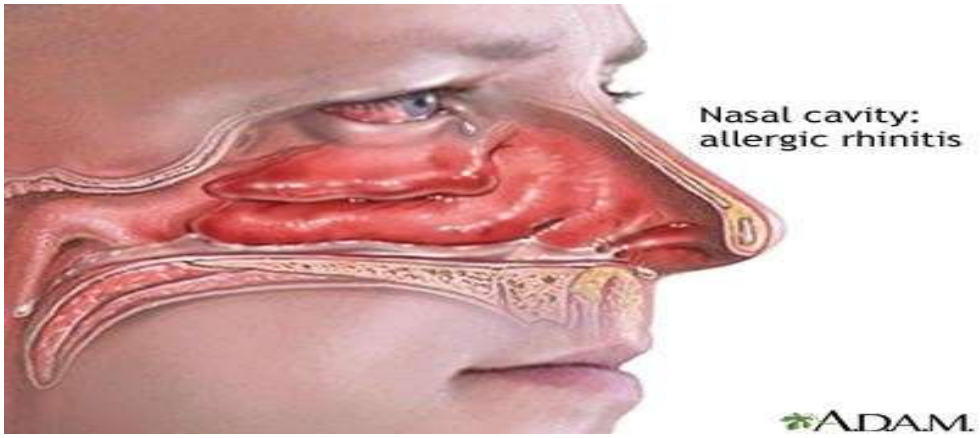
ABSTRACT

Allergic rhinitis is caused by a reaction of the body's immune system to an environmental irritant. The most common environmental irritants include dust, mold, pollen, hay, trees, and animals. Both seasonal allergies and year-round allergies can cause allergic rhinitis. Symptoms of allergic rhinitis include itching, sneezing, nasal congestion, runny nose, itching, and watery eyes. The patient may also suffer from headache, swollen eyelids, coughing, and wheezing, and the doctor can diagnose allergic rhinitis based on a history of medical symptoms. In many cases, the patient has The person has a family history of allergies. The doctor may be able to obtain more detailed information from blood tests or skin tests.

Keywords: Allergic, rhinitis, dust, mold, pollen.

Allergic rhinitis also known as hay fever, is a type of inflammation in the nose which occurs when the immune system overreacts to allergens in the air.[6] Signs and symptoms include a runny or stuffy nose, sneezing, red, itchy, and watery eyes, and swelling around the eyes.[1] The fluid from the nose is usually clear.[2] Symptom onsetis often within minutes following allergen exposure and can affect sleep, and the ability to work or study.[2][8] Some people may develop symptoms only during specific times of the year, often as a result of pollen exposure.[3] Many people with allergic rhinitis also have asthma, allergic conjunctivitis, or atopic dermatitis.[2]



(Fig. 1-1)

Allergic rhinitis is typically triggered by environmentalallergens such as pollen, pet hair, dust, or mold.[3] Inherited genetics and environmental exposures contribute to the development of allergies.[3]

The underlying mechanism involves IgE antibodies that attach to an allergen, and subsequently result in the release of inflammatory chemicals such as histamine from mast cells.[2] Diagnosis is typically based on a combination of symptoms and a skin prick test or blood tests for allergen-specific IgE antibodies.[4] These tests, however, can be falsely positive.[4] The symptoms of allergies resemble those of the common cold; however, they often last for more than two weeks and typically do not include a fever.[3]

Several different types of medications reduce allergic symptoms: including nasal steroids, antihistamines, such as diphenhydramine, cromolyn sodium, and leukotriene receptor antagonists such as montelukast.[5] Oftentimes, medications do not completely control symptoms, and they may also have side effects.[2] Exposing people to larger and larger amounts of allergen, known as allergen immunotherapy (AIT), is often effective.[6] The allergen can be given as an injection under the skin or as a tablet under the tongue.[6] Treatment typically lasts three to five years, after which benefits may be prolonged.[6] Allergic rhinitis is the type of allergy that affects the greatest number of people.[9] In Western countries, between 10 and 30% of

people are affected in a given year.[2][7] It is most common between the ages of twentyand forty.[2] The first accurate description is from the 10th-century physician Rhazes.[10] In 1859, Charles Blackley identified pollen as the cause.[11] In 1906, the mechanism was determined by Clemens von Pirquet.[9]
The link with hay came about due to an early (and incorrect) theory that the symptoms were brought aboutby the smell of new hay.[12]

Literature review

2- 1 Allergic rhinitis

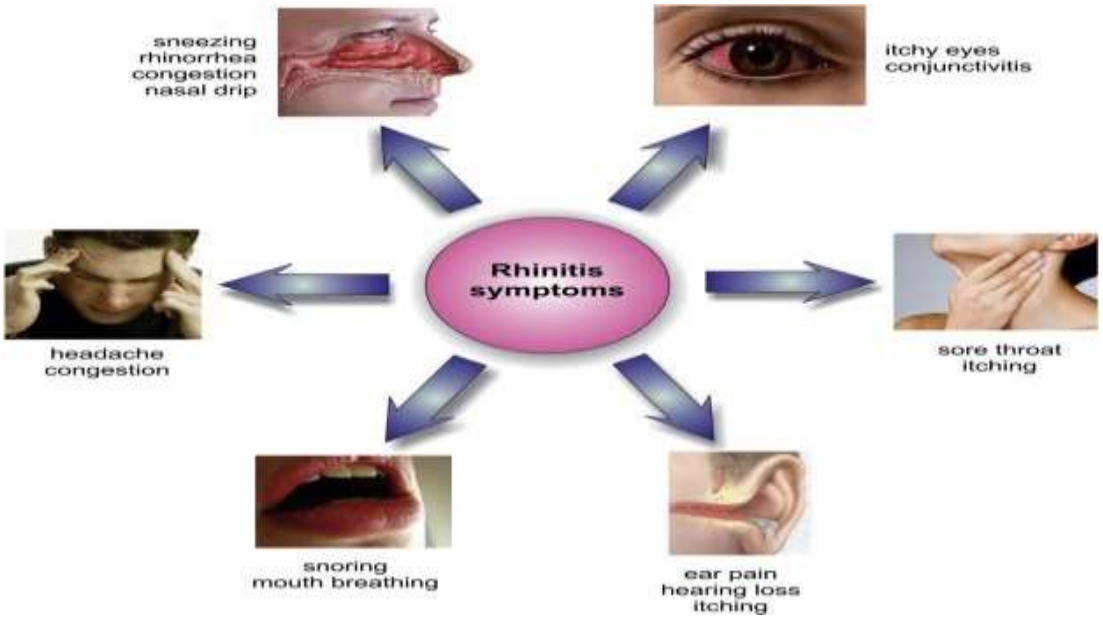
a chronic inflammatory disease of the upper airways that has a major impact on the quality of life of patients and is a socio-economic burden. Understanding the underlying immune mechanisms is central to developing better and more targeted therapies. The inflammatory response in the nasal mucosa includes an immediate IgE-mediated mast cell response as well as a latephase response characterized by recruitment

of eosinophils, basophils, and T cells expressing Th2 cytokines including interleukin (IL)-4, a switchfactor for IgE synthesis, and IL-5, an eosinophil growth factor and on-going allergic inflammation. Recent advances have suggested new pathways like local synthesis of IgE, the IgE-IgE receptor mast cell cascade in on-going allergic inflammation and the epithelial expression of cytokines that regulate Th2 cytokine responses (i.e., thymic stromal lymphopoietin, IL-25, and IL- 33). In this review, we briefly review the conventional pathways in the pathophysiology of allergic rhinitis and then elaborate on the recent advances in the pathophysiology of allergic rhinitis. An improved understanding of the immune mechanisms of allergic rhinitis
can provide abetter insight on novel therapeutic targets.

2-2 Symptoms of allergic rhinitis:

Common symptoms of allergic rhinitis include:

- sneezing
- a runny nose
- a stuffy nose
- an itchy nose
- coughing
- a sore or scratchy throat
- itchy eyes
- watery eyes
- dark circles under the eyes
- frequent headaches
- eczema-type symptoms, such as having extremely dry, itchy skin that can blister and weep
- hives
- excessive fatigue



(Fig. 2-1)

You'll usually feel one or more of these symptoms immediately after coming into contact with an allergen. Some symptoms, such as recurrent headaches and fatigue, may only happen after long-term exposure to allergens.
Fever isn't a symptom of hay fever.
Some people experience symptoms only rarely. This likely occurs when you're exposed to allergens in large quantities. Other people experience symptoms all year long. Talk to your doctor about possible allergies if your
symptoms last for more than a few weeks and don't seem
to be improving.

People might also find that cross-reactivity occurs.[13] For example, people allergic to birch pollen may also findthat they have an allergic reaction to the skin of apples orpotatoes.[14] A clear sign of this is the occurrence of an itchy throat after eating an apple or sneezing when peeling potatoes or apples. This occurs because of similarities in the proteins of the pollen and the food.[15]
There are many cross-reacting substances. Hay fever is nota true fever, meaning it does not cause a core body temperature in the fever over 37.5–38.3 °C (99.5–
100.9 °F).

2-3 Causes:

Allergic rhinitis triggered by the pollens of specific seasonal plants is commonly known as "hay fever", because it is most prevalent during haying season. However, it is possible to have allergic rhinitis throughout the year. The pollen that causes hay fever varies between individuals and from region to region; in general, the tiny, hardly visible pollens of wind-pollinated plants are the predominant cause. Pollens of insect-pollinated plants aretoo large to remain airborne and pose no risk. Examples ofplants commonly responsible for hay fever include:

- Trees: such as pine (Pinus), birch (Betula), alder (Alnus), cedar (Cedrus), hazel (Corylus), hornbeam (Carpinus), horse chestnut (Aesculus), willow (Salix), poplar (Populus), plane (Platanus), linden/lime (Tilia), and olive (Olea). In northern latitudes, birch is considered to be the most common allergenic tree pollen, with an estimated 15–20% of people with hay fever sensitive to birch pollen grains. A major antigen in these is a protein called Bet V I. Olive pollen is most predominant in Mediterranean regions. Hay fever in Japan is caused primarily by sugi (Cryptomeria japonica) and hinoki (Chamaecyparis obtusa) tree pollen.
- "Allergy friendly" trees include: ash (female only),red maple, yellow poplar, dogwood, magnolia, double- flowered cherry, fir, spruce, and flowering plum.[16]
- Grasses (Family Poaceae): especially ryegrass (Loliumsp.) and timothy (Phleum pratense). An estimated 90% of people with hay fever are allergic to grass pollen.
- Weeds: ragweed (Ambrosia), plantain (Plantago),nettle/parietaria

(Urticaceae), mugwort (Artemisia Vulgaris), Fat hen (Chenopodium), and sorrel/dock (Rumex)

Allergic rhinitis may also be caused by allergy to Balsam ofPeru, which is in various fragrances and other products.[17][18]
Predisposing factors to allergic rhinitis include eczema (atopic dermatitis) and asthma. These three conditions can often occur together which is referred to as the atopictriad.[19] Additionally, environmental exposures such as air pollution and maternal tobacco smoking can increase an individual's chances of developing allergies.[19]

2-4 Classification:

Etiological classification of rhinitis [20] Traditionally, allergic rhinitis has been categorized as seasonal (occurs during a specific season) or perennial (occurs throughout the year). However, not all patients fit into this classification scheme. For example, some allergic triggers, such as pollen, may be seasonal in cooler climates, but perennial in warmer climates, and patients with multiple "seasonal" allergies may have symptoms throughout mostof the year [21]. Therefore, allergic rhinitis is now classified according to symptom duration (intermittent or persistent) and severity (mild, moderate or severe)

(see Fig. 2-2) [20].

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines have classified "intermittent" allergic rhinitis assymptoms that are present less than 4 days per week or for less than 4 consecutive weeks, and "persistent" allergic rhinitis as symptoms that are present more than 4 days/week and for more than 4 consecutive weeks [22].Symptoms are classified as mild when patients have no impairment in sleep and are able to perform normal activities (including work or school). Symptoms are categorized as moderate/severe if they significantly affectsleep or activities of daily living, and/or if they are considered bothersome. It is important to classify the severity and duration of symptoms as this will guide the management approach for individual patients [20].

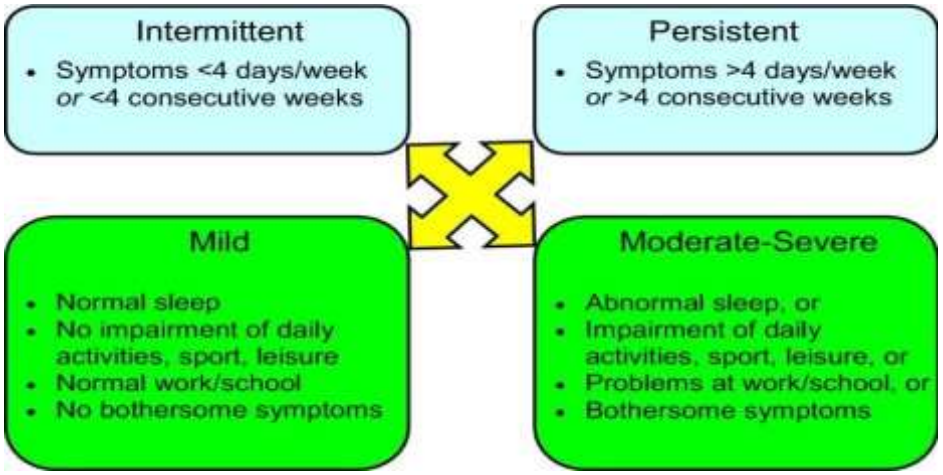


Fig. 2-2 Classification of allergic rhinitis according to. symptom duration and severity.

2-5 Early and late phase allergic reactions:

After deposition and elution of allergens into the mucuslayer, the allergens are taken up by antigen presenting cells and processed and presented to helper T lymphocytes. Activated helper T lymphocytes release cytokines like IL-4and IL-13 and interact with B lymphocytes to induce the synthesis of allergen specific IgE. Thereafter, the allergen-specific IgE binds to the high affinity receptor for IgE on the surface of mast cells.

2-5-1 Early phase response

The early or immediate phase response occurs in sensitized individuals within min of exposure to the allergen and lasts for about 2-3 h. One of the cardinal components of the early phase response is the degranulation of mast cells. In the sensitized individual mast cells are abundant in the epithelial compartment ofthe nasal mucosa and can be easily activated upon re exposure to the allergens. Upon crosslinking of the allergen specific IgE bound to the surface of mast cells by the specific allergen, mast cells degranulate and release a variety of pre-formed and newly formed mediators leading to what is known as the early phase response.
Histamine, which is the major mediator of allergic rhinitis,stimulates the sensory nerve endings of the Vth nerve (trigeminal) and induces sneezing. Histamine also stimulates the mucous glands causing the secretion of mucous (rhinorrhea) and histamine, leukotrienes and prostaglandins acts on the blood vessels causing nasal congestion [23].

2-5-2 Late phase response

The early phase response is usually followed by the late phase response which occurs 4-6 h after antigen stimulation. The late phase response is characterized by a prolongation of symptoms - sneezing, rhinorrhea but mostpredominantly a sustained nasal congestion which lasts for about 18-24 h. The late phase response is

predominantly inflammatory in nature and is characterized by a inflammatory cellular influx comprisingof predominantly T lymphocytes, basophils and eosinophils [23]. A variety of mediators are released by
these cells including leukotrienes, kinins, histamine which result in the continuation of the symptoms and the development of the late phase. The key to the orchestration of the late phase response lies in the production and release of a variety of cytokines and chemokines like IL-4, IL-13 from mast cells [24-25] as these cytokines can upregulate the expression of 'adhesion molecules' like vascular cell adhesion molecule 1 (VCAM- 1) on the endothelial cells facilitating the infiltration of eosinophils, T lymphocytes and basophils into the nasal mucosa. In addition, chemokines like RANTES, eotaxin, MCP-4 and Thymus-and activation Regulated chemokine (TARC) released from epithelial cells serve as chemoattractants for eosinophils, basophils and T lymphocytes [26-27] (Fig. 2). Other cytokines like granulocytemacrophage colony stimulating factor (GM- CSF) released largely by epithelial cells and IL-5 from mast cells and T lymphocytes prolong the survival of the infiltrated eosinophils in the nasal mucosa [25].

More recently, mast cells have been found to further contribute to the late phase response through the histamine/tryptase-induced upregulation of GM-CSF and RANTES in nasal epithelial cells and the synergetic actionof IL-4/IL-13 and TNF-α-inducing the upregulation of eotaxin and TARC production in nasal epithelial cells [28](Fig. 2-3). In addition, a variety of other mediators released like eosinophil cationic protein (ECP),
platelet activating factor, major basic protein (MBP) arealso implicated in the late phase response.

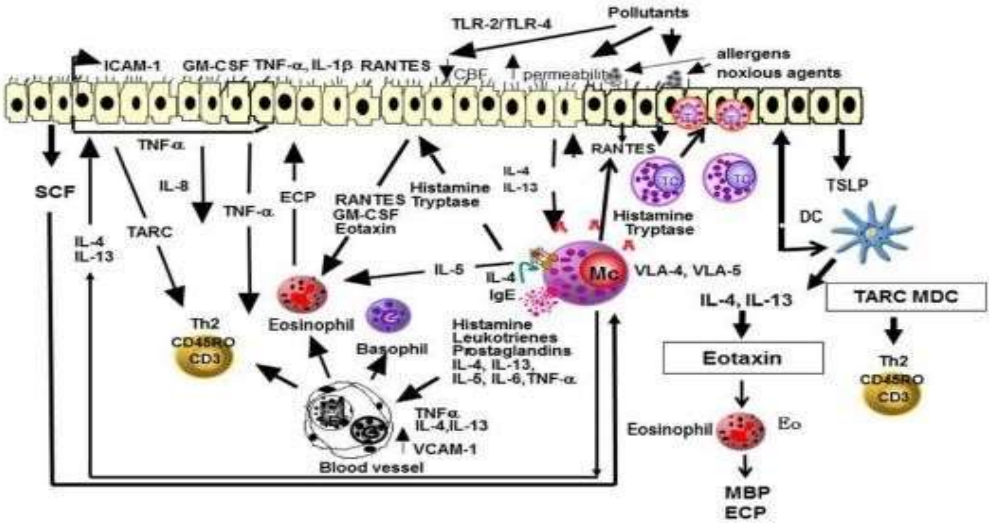


Fig. 2-3 Ongoing inflammation in allergic rhinitis. Adapted from Pawankar R et al. Curr Opin Allergy ClinImmunol 2002;2:1-5.

2-6 Pathophysiology:

In allergic rhinitis, numerous inflammatory cells, including mast cells, CD4-positive T cells, B cells, macrophages, and eosinophils, infiltrate the nasal lining upon exposure to aninciting allergen (most commonly airborne dust mite fecal particles, cockroach residues, animal dander, moulds, and pollens). In allergic individuals, the T cells infiltrating the nasal mucosa are predominantly T helper 2 (Th2) in natureand release cytokines (e.g., interleukin [IL]-3, IL-4, IL-5, and IL-13) that promote immunoglobulin E (IgE) production by plasma cells.

Crosslinking of IgE bound to mast cells by allergens, in turn, triggers the release of mediators, such as histamineand leukotrienes, that are responsible for arteriolar dilation, increased vascular permeability, itching, rhinorrhea, mucous secretion,

and smooth muscle contraction in the lung [20]. The mediators and cytokines released during the early phase of an immune response to an inciting allergen trigger a further cellular inflammatory response over the next 4–8 h (late-phase inflammatory response) which results in recurrent symptoms (usually nasal congestion) that often persist [20,21].

2-7 Diagnostic tests:

Although a thorough history and physical examination are required to establish the clinical diagnosis of rhinitis, further diagnostic testing is necessary to confirm that underlying allergies cause the rhinitis. Skin-prick testing is considered the primary method for identifying specific allergic triggers of rhinitis. Skin prick testing involves placing a drop of a commercial extract of a specific allergen on the skin of the forearms or back, then pricking the skin through the drop to introduce the extract into the epidermis. Within 15–20 min, a wheal-and-flare response (an irregular blanched wheal surrounded by an area of redness) will occur if the test is positive. Testing is typicallyperformed using the allergens relevant to the patient's environment (e.g., pollen, animal dander, moulds and house dust mites). A reasonable alternative to skin prick testing is the use of allergen-specific IgE tests (e.g., performed by immunosorbent assay—previously performed by radioallergosorbent tests [RASTs]) that provide an in vitro measure of a patient's specific IgE levels against particular allergens. These in vitro tests can be performed when eczema is extensive, or if the patient cannot stop antihistamine therapy to allow for testing
However, skin prick tests are generally considered to be more sensitive and cost effective than allergen-specific serum IgE tests, and have the further advantage of providing physicians and patients with immediate results[20].

2-8 Treatment:

The goal of rhinitis treatment is to prevent or reduce the symptoms caused by the inflammation of affected tissues.Measures that are effective include avoiding the allergen.[21] Intranasal corticosteroids are the preferred medical treatment for persistent symptoms, with other options if this is not effective.[21] Second line therapies include antihistamines, decongestants, cromolyn, leukotriene receptor antagonists, and nasal irrigation.[21] Antihistamines by mouth are suitable for occasional use with mild intermittent symptoms.[21] Mite-proof covers, air filters, and withholding certain foods in childhood do not have evidence supporting their effectiveness.[21]

2-8-1 Antihistamines

Antihistamine drugs can be taken orally and nasally to control symptoms such as sneezing, rhinorrhea, itching,and conjunctivitis.

It is best to take oral antihistamine medication before exposure, especially for seasonal allergic rhinitis. In the case of nasal antihistamines like azelastine antihistamine nasal spray, relief from symptoms is experienced within 15minutes allowing for a more immediate 'as-needed' approach to dosage. There is not enough evidence of antihistamine efficacy as an add-on therapy with nasal steroids in the management of intermittent or persistentallergic rhinitis in children, so its adverse effects and additional costs must be considered.[22]

Ophthalmic antihistamines (such as azelastine in eye dropform and ketotifen) are used for conjunctivitis, while intranasal forms are used mainly for sneezing, rhinorrhea,and nasal pruritus.[23]
Antihistamine drugs can have undesirable side-effects, themost notable one being drowsiness in the case of oral antihistamine tablets. First-generation antihistamine drugs such as diphenhydramine cause drowsiness, while second- and third-generation antihistamines such as cetirizine and loratadine are less likely to.[23]
Pseudoephedrine is also indicated for vasomotor rhinitis.
It is used only when nasal congestion is present and can beused with antihistamines. In the United States, oral decongestants containing pseudoephedrine must be purchased behind the pharmacy counter in an effort to prevent the manufacturing of methamphetamine.[23] Desloratadine/pseudoephedrine can also be used for this condition[citation needed]

2-8-2 Steroids

Intranasal corticosteroids are used to control symptoms associated with sneezing, rhinorrhea, itching, and nasal congestion. Steroid nasal sprays are effective and safe, and may be effective without oral antihistamines. They take several days to act and so must be taken continuallyfor several weeks, as their therapeutic effect builds up with time.

In 2013, a study compared the efficacy of mometasone furoate nasal spray to betamethasone oral tablets for thetreatment of people with seasonal allergic rhinitis and found that the two have virtually equivalent effects on nasal symptoms in people.[24]

Systemic steroids such as prednisone tablets and intramuscular triamcinolone acetonide or glucocorticoid(such as betamethasone) injection are effective at reducing nasal inflammation,[citation needed] but theiruse is limited by their short duration of effect and the side-effects of prolonged steroid therapy.[25]

2-8-3 Other

Other measures that may be used second line include: decongestants, cromolyn, leukotriene receptor antagonists, and nonpharmacologic therapies such as nasal irrigation.[21]

Topical decongestants may also be helpful in reducing symptoms such as nasal congestion, but should not be used for long periods, as stopping them after protracted use can lead to a rebound nasal congestion called rhinitis medicamentosa.

For nocturnal symptoms, intranasal corticosteroids can becombined with nightly oxymetazoline, an adrenergic alpha-agonist, or an antihistamine nasal spray without risk of rhinitis medicamentosa.[26]

Nasal saline irrigation (a practice where salt water is poured into the nostrils), may have benefits in both adultsand children in relieving the symptoms of allergic rhinitis and it is unlikely to be associated with adverse effects.[27]

2-8-4 Allergen immunotherapy

Allergen immunotherapy (AIT, also termed desensitization) treatment involves administering doses ofallergens to accustom the body to substances that are generally harmless (pollen, house dust mites), thereby inducing specific long-term tolerance.[28]

Allergen immunotherapy is the only treatment that alters the disease mechanism.[29] Immunotherapy can be administered orally (as sublingual tablets or sublingual drops), or by injections under the skin (subcutaneous).

Subcutaneous immunotherapy is the most common formand has the largest body of evidence supporting its effectiveness.[30]

2-8-5 Alternative medicine

There are no forms of complementary or alternative medicine that are evidence-based for allergic rhinitis. Therapeutic efficacy of alternative treatments such as acupuncture and homeopathy is not supported by available evidence.[31] While some evidence shows that acupuncture is effective for rhinitis, specifically targeting the sphenopalatine ganglion acupoint, these trials are stilllimited.[32] Overall, the quality of evidence for complementary-alternative medicine is not strong enoughto be recommended by the American Academy of Allergy,Asthma and Immunology.[33]

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