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Management of allergic rhinitis

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Based on the ARIA guidelines[1] and the EAACI Consensus Statement on the Treatment of Allergic Rhinitis[2]

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Abstract. Due to its high and increasing prevalence, its impact on quality of life, the association with multiple comorbidities and the considerable socio-economic burden, allergic rhinitis is a major respiratory disorder and represents a global health concern.
The ARIA working group has proposed a new classification for allergic rhinitis into intermittent or persistent, based on the duration of symptoms.
The severity of allergic rhinitis is graded according to the impact of the disease on the quality of life.
The diagnosis of allergic rhinitis involves a thorough history and clinical examination. In patients suspected of having persistent AR a complete and systematic nasal examination is an absolute requirement. Anterior rhinoscopy provides limited information. Nasal endoscopy is more useful, not to confirm AR but in particular to exclude other conditions, such as polyps, foreign bodies, tumours and septal deformations.
To confirm the allergic origin of rhinitis symptoms, allergy tests must be performed. The first choice test is the skin prick test.
Patients with allergic rhinitis should be evaluated for asthma and patients with asthma should be evaluated for rhinitis.
A stepwise therapeutic approach is recommended based on the duration and severity of disease.
The treatment of allergic rhinitis consists of allergen avoidance, pharmacotherapy and immunotherapy.

1. Definition and epidemiology of allergic rhinitis

Definition of rhinitis and allergic rhinitis

Table 1

Causes of rhinitis[3]

Allergic rhinitis
Infectious rhinitis: viruses, bacteria, fungi
Occupational rhinitis: allergic and non-allergic
Drug-induced rhinitis: e.g. aspirin
Hormonal rhinitis: puberty, pregnancy, menstruation, endocrine disorders
Emotional rhinitis
Atrophic rhinitis
Irritants-induced rhinitis
Food-induced rhinitis e.g. red pepper
NARES: non-allergic rhinitis with eosinophilic syndrome
Rhinitis associated with gastrooesophageal reflux
Idiopathic rhinitis

Rhinitis is a heterogeneous disorder, characterised by one or more symptoms of sneezing, itching, rhinorrhoea, and/or nasal congestion and frequently accompanied by symptoms involving the eyes, ears and throat, including postnasal drainage. As shown in Table 1, there are various causes of rhinitis.

In about 50% of cases, rhinitis has an allergic aetiology and is called ‘allergic rhinitis’.

Allergic rhinitis (AR) is defined as a nasal disease with the presence of immunologically mediated nasal hypersensitivity symptoms such as itching, sneezing, increased secretion and blockage. The vast majority of cases of AR are IgE-antibody-mediated.[4]

Classification of allergic rhinitis

Before the development of the ARIA report, AR was subdivided into seasonal and perennial AR, and by extension occupational AR, based on the time of exposure to the offending allergen(s). Seasonal AR is linked to a wide variety of outdoor allergens such as pollens and moulds. Perennial AR is most frequently caused by indoor allergens such as house dust mite, moulds, cockroaches and animal dander. Occupational AR occurs in response to aeroallergens in the workplace; common causes are laboratory animals, wood dust (particularly hard woods), chemicals and solvents.
The distinction between seasonal and perennial AR, however, is not applicable in all patients and in all countries as:

– symptoms of perennial rhinitis may not be present all year around;
– pollens and moulds are perennial allergens in some parts of the world;
– many patients are sensitised to multiple allergens and present

symptoms at several periods of the year or even throughout the year;
– symptoms of seasonal AR do not always occur strictly within the defined allergen season due to the 'priming effect' and the phenomenon of 'minimal persistent inflammation' in the nasal mucosa.

As a consequence, this classification was no longer satisfactory and the ARIA Working Group reviewed and changed the classification of AR. ARIA classifies AR as 'intermittent' and 'persistent', based on the duration of symptoms. Depending on the impact of symptoms on the patient's quality of life, the severity of disease is graded as 'mild' or 'moderate-severe' (Table 2).

Table 2

ARIA classification of allergic rhinitis[1]

'Intermittent' means that symptoms are present for:
- ≤ 4 days/week
- Or ≤ 4 consecutive weeks

'Persistent' means that symptoms are present for:
- > 4 days/week
- And > 4 consecutive weeks

'Mild' means that none of following items are present:
- Sleep disturbance
- Impairment of daily activities, leisure and/or sport
- Impairment of school or work
- Troublesome symptoms

'Moderate-severe' means that one or more of the following items are present:
- Sleep disturbance
- Impairment of daily activities, leisure and/or sport
- Impairment of school or work
- Troublesome symptoms

Epidemiology of allergic rhinitis

Before giving an overview of the epidemiology of AR, it is important to point out that different epidemiological studies have used different definitions and diagnostic criteria for AR, which makes it difficult to interpret and compare figures on the prevalence and incidence of this disorder. In addition, most data are obtained from studies where AR is still classified as 'seasonal' or 'perennial'.

The majority of monocentric studies have reported a prevalence of seasonal AR ranging from 1 up to 40 % and a prevalence of perennial rhinitis of 1 to 18 %. Several large-scale epidemiological surveys have confirmed this large variation in the prevalence of AR symptoms among adults and children throughout the world and found the highest prevalence rates in countries with a Western lifestyle. The European Community Respiratory Health Survey (ECRHS) investigated approximately 130,000 adults aged 20-44 years from 22 countries, and found that the prevalence of nasal allergies ranged from 9.5% to 40.9%. The highest prevalences of nasal allergies were found in Western Europe, Australia, New Zealand and the USA.[5] Similarly, the International Study of Asthma and Allergies in Childhood (ISAAC) investigated over 500,000 children from two age groups (6-7 years from 91 centres in 38 countries and 13–14 years from 155 centres in 56 countries) and demonstrated that the prevalence of rhinoconjunctivitis in the past year varied across centres from 0.8% to 14.9% in the 6-7-year-old group and from 1.4% to 39.7% in the 13-14-year-old group. The lowest prevalence rates for rhinoconjunctivitis were found in parts of Eastern Europe, and in Southern and Central Asia.[6]

Recently, a cross-sectional population-based survey was undertaken to measure the prevalence of AR among European adults in Belgium, France, Italy, Spain and the UK. The overall prevalence of AR was estimated at 23%, ranging from 17% in Italy to 29% in Belgium, and the proportion of undiagnosed AR was estimated to be 45%. Furthermore, 51% were classified as perennial AR (on the basis of sensitisation to house dust mite) and 49% as seasonal AR (on the basis of sensitisation to grass/tree/weed pollens). According to the ARIA classification, however, one third of these patients were classified as persistent rhinitics and two thirds as intermittent rhinitics.[7] This indicates that breaking down AR into intermittent and persistent is independent from, and not equivalent to, the traditional breakdown into seasonal and perennial AR respectively.

The prevalence of AR not only varies between regions and populations but has also shown to vary over time, with a progressive increase in prevalence over the last decades. Strachan reviewed the results of successive epidemiological studies of allergic conditions and found that a two- to threefold increase in the prevalence of hay fever among adolescents was found in population surveys in Britain, Sweden and Finland when they were repeated after 10 or more years.[8]

Furthermore, prospective and retrospective epidemiological studies have indicated that AR is not an isolated disorder but that it is associated with multiple comorbidities:
– Up to 80% of the patients with asthma have symptoms of rhinitis, while approximately 20-40% of the patients with AR have clinical asthma. Furthermore, rhinitis often precedes the onset of clinical asthma and independently increases the risk

for developing asthma by up to three times.[9,10]
– It is estimated that 42% of the patients with AR experience symptoms of allergic conjunctivitis and that 33–56% of the cases of allergic conjunctivitis occur in association with AR.[11]
– Up to 54% of adults with chronic rhinosinusitis have symptoms of AR and, conversely, abnormal sinus radiographs are found in over 50% of adults and children with perennial AR.[12,13]

2. Pathophysiology of allergic rhinitis

Symptoms of AR result from the inhalation of allergens by individuals previously exposed to such allergens and against which they have made IgE antibodies, leading to a specific IgE-mediated immune response and associated with nasal inflammation of variable intensity.

The pathophysiological process of AR can be subdivided into two phases. During the initial sensitisation phase, allergen exposure results in primary allergen-specific IgE antibody formation by B-lymphocytes. During the clinical disease phase, symptoms become manifest, in response to subsequent allergen re-exposure.

Sensitisation phase

Sensitisation to an allergen requires IgE antibody production directed at the epitope. After allergen exposure, antigen-presenting cells present the allergens to CD4+ cells. A subset of these CD4+ cells, the Th2 lymphocytes, generate Th2 cytokines, including IL-4 and IL-13. These cytokines, in combination with B-T cell ligand-receptor interactions, drive B-cell isotype switching towards IgE synthesis. As a result, allergen-specific IgE antibodies are produced and these sensitise mast cells and other IgE-receptor-bearing cells.[14]

Clinical disease phase

The clinical disease phase can be subdivided further into two distinct phases: an early phase, largely mediated through mast cells, and a late phase which involves cellular infiltration and mediator release.

During the *early phase*, allergen re-exposure in sensitised patients mediates cross-linkage of adjacent IgE molecules bound to mast cell surfaces. Mast cells, activated by IgE cross-linking, release preformed granule products including histamine, tryptase, chymase and cytokines such as IL-4, IL-5, IL-8, IL-13 and TNF-a into the extracellular environment. Furthermore, activated mast cells also generate arachidonic acid products including cysteinyl-leukotrienes (LTC4, LTD4, LTE4) and prostaglandin D2 (PGD2) from the phospholipid cell membrane. Nasal challenge with allergens results in the local release of histamine, tryptase, PGD2, LTB4 and LTC4 within 10 to 15 minutes.

These mediators have multiple activities. They cause the characteristic watery rhinorrhoea by stimulating gland and globet cell secretion, vasodilation and blood vessel leakage. Vessel dilation and the pooling of blood in the cavernous sinusoids already produce a certain degree of nasal congestion during this early phase. Sensory nerve stimulation leads to itching sensations and sneezing reflexes. Histamine is the most important mediator in AR and causes symptoms of nasal itching, sneezing, nasal discharge and transient nasal blockage, whereas leukotrienes appear to be relatively more important than histamine in inducing nasal blockage.[14]

Through the release of pro-inflammatory and chemo-attractant cytokines, activated mast cells also contribute to the cellular-driven ‘late phase’.

The *late phase* follows 4-8 hours after allergen exposure. Clinically, it can be similar to the early phase but, in general, nasal congestion is more prominent. The late response involves inflammatory cell accumulation. The increased expression of adhesion molecules (intercellular adhesion molecule-1: ICAM-1 and vascular cell adhesion molecule-1: VCAM-1) and the cytokines IL-3, IL-4, IL-5, IL-8, GM-CSF and TNF-enhance the recruitment, trans-endothelial migration and infiltration of activated T-cells, eosinophils, basophils, neutrophils and macrophages into the nasal mucosa.

Eosinophils are the predominant cell type in this late phase. They generate vasoactive mediators and cytotoxic proteins (including major basic protein, eosinophil peroxidase, eosinophil-derived neurotoxin and eosinophil cationic protein). During the late phase, activated basophils are responsible for histamine release. In the course of the inflammatory process, activated inflammatory cells are an important source of cytokine, chemokine and inflammatory mediator release. This leads to an increased expression of adhesion molecules, an enhanced priming of inflammatory cells to respond to chemotactic stimuli and an up-regulation of the activa-

tion and survival of the inflammatory leukocytes within the nasal mucosa. All these events amplify the allergic inflammatory response, leading to a real cascade of reactions.[15]

Although the inflammatory reaction in AR is triggered by allergen exposure, it has been demonstrated that, even in cases of subliminal exposure to the allergen(s) and in the absence of symptoms, a certain degree of inflammatory infiltration at the mucosal level persists: the 'minimal persistent inflammation'.[16]

The priming effect

The 'priming effect' refers to the phenomenon that the amount of allergens necessary to evoke an immediate response decreases with repeated allergen challenges or exposures. Nasal challenge induces an immediate clinical response in allergic subjects and the concomitant appearance of an inflammatory infiltrate. This mucosal inflammation may persist some time after allergen exposure. If the subjects are re-challenged within this period the response is more pronounced: this is the 'priming effect'. This effect is hypothesised to be a result of the influx and subsiding activity of inflammatory cells during the late-phase allergic response.[14] Clinically this explains the observation that decreasing allergen quantities are required to elicit symptoms as the pollen season progresses. In patients allergic to tree and grass pollen, the tree pollen season has a priming effect on the subsequent grass pollen season and these patients often develop severe symptoms early in the grass pollen season when pollen counts are still very low.

Table 3
Clinical difference between rhinitis patients[3]

	"sneezers and runners"	"blockers"
Sneezing	mainly paroxysmal	little or none
Rhinorrhoea	watery, anterior and posterior	thick mucus, more posterior
Itching	yes	no
Nasal blockage	variable	often severe
Diurnal rhythm	worse during day, improving at night	constant day and night, may be worse at night
Conjunctivitis	often present	

Systemic component in the allergic rhinitis response

Next to the local events in the nose, there is also a systemic participation in the inflammatory process of AR. A variety of mechanisms has been proposed to explain the pathophysiological link between the upper and the lower airways, including the loss of nasal protective function, altered breathing pattern, postnasal drip causing pulmonary aspiration of nasal contents, the presence of a nasal-bronchial reflex and the progression of systemic inflammation. Recent data suggest that bi-directional systemic inflammation involving the bone marrow is likely to be important. Local allergen provocation (in the nose or bronchi) leads to up-regulation and release from the bone marrow of haemopoietic eosinophil/basophil progenitor cells, which migrate to both nose and lungs and can undergo differentiation and activation *in situ.*[17-19]

3. Diagnostic management of allergic rhinitis

Clinical history

Rhinitis symptoms include rhinorrhoea, nasal obstruction, nasal itch and sneezing. On the basis of on the main symptomatology, patients with rhinitis can be subdivided into 'sneezers and runners' and 'blockers' (Table 3).

These nasal symptoms, however, do not necessarily have an allergic origin. In the differential diagnosis, AR must be differentiated from several types of non-allergic rhinitis and other nasal inflammatory conditions. (Table 1, Table 4)

Table 4
Differential diagnosis of rhinitis[3]

- Polyps
- Mechanical factors
  - Deviated septum
  - Adenoidal hypertrophy
  - Hypertrophic turbinates
  - Foreign bodies
  - Choanal atresia
- Tumours
  - Benign
  - Malignant
- Granulomas
  - Wegener's Granulomatosis
  - Sarcoid
  - Infectious (Tuberculosis, Leprosy)
  - Malign – midline destructive granuloma
- Ciliary defects
- Cerebrospinal rhinorrhoea

Other symptoms commonly associated with rhinitis include loss of smell, snoring, sleep disturbance, postnasal drip, cough, sedation, conjunctivitis and lower respiratory symptoms.

In addition to an assessment of the symptomatology, the history also includes an evaluation of the severity and duration of the problem, the impact on the quality of life and response to treatment. A thorough history should also document allergic and non-allergic

triggers and must include a family and occupational history.[1]

Clinical examination

Clinical examination starts with a general inspection of nose, ears and throat. In patients suspected of having mild intermittent AR, a nasal examination is optimal; in patients suspected of having persistent AR a complete and systematic nasal examination is absolutely required. Anterior rhinoscopy produces limited information. Nasal endoscopy, usually performed by specialists, is more useful, not to confirm AR, but in particular to exclude other conditions such as polyps, foreign bodies, tumours and septal deformations. During allergen exposure, the nasal mucosa of patients with AR can demonstrate a bilateral, but not always symmetrical, swelling. Often, mucosal changes in colour are seen, ranging from a purplish to a more common pale coloration. An increase in vascularity is also common. In the absence of allergen exposure, the nasal mucosa may appear completely normal, but in patients who have suffered from rhinitis for several years, irreversible mucosal hyperplasia and/or viscous secretions may also occur.[1]

Allergy testing

To confirm the allergic origin of rhinitis symptoms, allergy tests must be performed. *In vivo* and *in vitro* allergy tests are directed towards the detection of free or cell-bound IgE. When possible, only standardised allergen extracts should be used.

If properly performed, immediate hypersensitivity skin tests are the best available method for detecting the presence of allergen-specific IgE. The first-choice test is the skin prick test; sensitivity and specificity are good. To ensure that skin tests are performed carefully and that they are interpreted correctly, they should be carried out by trained health-care professionals. The skin reaction can be affected by the quality of the allergen extract, the patient's age, the use of some pharmacological agents (e.g. oral antihistamines and topical skin corticosteroids) and can also demonstrate some seasonal variations.[1,20] In addition, the possibility of false positive and false negative tests must be considered (Table 5). The measurement of total serum IgE lacks specificity and is of little predictive value in allergy screening in rhinitis. Serum-specific IgE, by contrast, has similar value to skin testing. Skin tests, however, are less expensive, have a greater sensitivity, allow for a broad allergen selection and results are available in less than half an hour. Serum-specific IgE, on the other hand, is indicated when the patient has dermographism or widespread dermatitis, in young children, when the patient is non-compliant for skin testing or did not discontinue antihistamine treatment (short-acting antihistamines for 36-48 hours, long-acting anti-histamines for 4 to 6 weeks), as this can result in false negative skin test results. Serum-specific IgE measurement is also a safer option when the patient is very allergic and anaphylactic reaction to skin testing is a possible risk.[21]

Table 5

Causes of false positive and false negative skin tests[1]

Causes of false positive skin tests
• Dermographism
• Irritant reactions
• Non-specific enhancement of a nearby strong reaction
• Improper technique/material
Causes of false negative skin tests
• Poor initial potency or loss of potency of extracts
• Use of drugs modulating allergic reaction
• Diseases attenuating skin response
• Decreased activity of the skin (infants and elderly patients)
• Improper technique/material

Nasal challenge tests are used particularly for research purposes and are important in the diagnosis of occupational rhinitis. The "International Committee on the Objective Assessment of Nasal Airways" has set up guidelines for the indications, techniques and evaluation of nasal challenge tests.[22] Alongside allergen provocations, nasal challenge tests with aspirin, non-specific agents (histamine, metacholine) and occupational agents can be performed.

Other diagnostic tests

An overview of the value of different methods for diagnosis of allergic rhinitis is given in Table 6. Imaging (sinus RX, CT, MRI) is not indicated for the diagnosis of AR, but may be necessary to exclude other conditions or complications. Diagnostic tests to assess the nasal airways, including nasal peak flow, rhinomanometry and acoustic rhinometry are rarely used in the diagnosis of AR. Objective testing of a patient's ability to smell can be performed by olfactory testing and mucociliary function can be measured by nasomucociliary clearance, ciliary beat frequency or electron microscopy, but these tests are of little relevance in the diagnosis of AR.[1]

Diagnosis of asthma

In the course of the diagnostic assessment, not only AR must be

Table 6
Value of different methods for diagnosis of allergic rhinitis

	Sensitivity	Specificity	Cost	Time	Skills
Medical history	+++	+++	++++	20-30 minutes	Allergology training
Total serum IgE	+	-	++	several days	Clinical chemistry
Specific serum IgE	+++	+++	+	several days	Clinical chemistry
Skin prick test	++++	+++	+++	15 minutes	Trained paramedic
Intracutaneous test	++++	+++	+++	15 minutes	Trained paramedic
Blood eosinophilia	+	-	+++	2 hours	Haematology
Nasal eosinophilia	++	-	+++	2 hours	Haematology
Nasal provocation	++++	+++	+	1 hour	Medical professional

considered; the physician must also be aware of the possible comorbidities of AR (asthma, conjunctivitis, sinusitis, otitis media...).

Due to the transient nature of asthma and the reversibility of airway obstruction, the diagnosis of concomitant asthma may be difficult. The Global Initiative for Asthma (GINA) has published international guidelines for the recognition and diagnosis of asthma.[23] Patients with AR, especially those with persistent rhinitis, should be evaluated for asthma by history, chest examination and – if possible and when necessary – by measuring lung function and confirming the reversibility of airflow obstruction.[1]

4. Therapeutic management of allergic rhinitis

The treatment of AR includes allergen avoidance, pharmacotherapy, immunotherapy and education. Surgery may be indicated as an adjunctive intervention in small numbers of selected patients. In 2001, the ARIA Working group published evidence-based guidelines for the treatment of AR based on the evidence from the literature available until December 1999.

The following treatment recommendations are based on the information available at the time of the development of the ARIA guidelines and on new evidence obtained since then. With respect to the recommendations directly based on the ARIA guidelines, we refer to the ARIA report[1] for further information on the literature and evidence underlying these recommendations.

The levels of evidence and grades of recommendations follow the Belgian definitions from the Consensus Committee of the INAMI-RIZIV (c.f. foreword).

Allergen avoidance

There is a paucity of data relating to the effectiveness of allergen avoidance in the treatment of AR. A systematic review of the efficacy of house dust mite avoidance in the management of perennial AR using the Cochrane approach indicated that, when compared to controls, significant reduction of allergen load can be achieved by physical and chemical means, but that there is little evidence at present that these reductions also translate into sustained improvements in clinical outcome.[24]

The only effective way to avoid pet allergen is to remove the pet and to carefully vacuum all carpets, mattresses and upholstered furniture. Although frequent washing of cats reduces allergen load, clinical studies have not been able to show a clear clinical benefit. There has been only one controlled trial looking at the effects of domestic pet removal/allergen avoidance in rhinitis, and it found no significant effect on rhinitis symptoms as a result of the use of a HEPA air cleaner.[25]

Although some methods have been developed to reduce exposure to outdoor allergens (including filters and ventilation systems), avoidance of pollen and fungal spores is often impossible and impractical due to their ubiquitous nature.

Despite the lack of evidence, allergen avoidance is still recommended as the first step in the management of patients allergic to house dust mite and/or indoor pets. For house dust mite, allergen-reducing measures include:

- regular washing of bedding (every 1 or 2 weeks) at 55-60°C;
- regular washing of pillows and duvets at 55–60°C;
- encasing pillows and mattresses with documented protective coverings;
- reducing indoor humidity to below 50%;
- removing/reducing carpets, curtains and soft furnishings, especially in the bedroom;
- removing soft toys from the bedroom, washing them at 55-

60°C or freezing them to kill house dust mites.[26]

The only effective way to avoid animal dander allergens in the home is to remove the pet and to carefully vacuum all carpets, mattresses and upholstered furniture.[2] If this is impossible, the pet(s) should be kept outside or at least outside the bedroom. A change of clothes is also recommended after contacts with a pet to which one is allergic.[26]

Pharmacological treatment

If allergen avoidance does not result in sufficient improvement, pharmacological treatment is the next step. An overview of the medications used in the treatment of AR, their mechanism of action and side-effects is provided in Table 7. The effect of the different pharmacological agents on the symptoms of AR is represented in Table 8.

Oral antihistamines

Oral antihistamines are effective in the rapid relief of sneezing, rhinorrhoea and itching associated with the early phase reactions, but have less effect on nasal congestion. In addition, antihistamines administered orally have the additional advantage of reducing non-nasal symptoms such as conjunctivitis, which is often associated with AR. First-generation antihistamines are effective in the treatment of AR, but their use is considerably limited by their sedative and anticholinergic side-effects. Because of their better risk/benefit ratio and enhanced pharmacokinetics (most of new H1 antihistamines have an onset of action after 1-2 hours and their activity lasts for up to 24 hours), new-generation H1 antihistamines should be considered as the first-choice treatment.[1]

Decongestants

Topical decongestants are very effective in the treatment of nasal congestion, but their use is limited because of the risk of developing rhinitis medicamentosa. Oral decongestants generally have a weaker effect on nasal obstruction than topical decongestants, and they do not cause rebound vasodilatation, but they are associated with a higher risk of sympathicomimetic side effects.[1]

Combination of oral antihistamines and oral decongestants

Although the available studies of this combination (usually with pseudo-ephedrine as the decongestant) generally found more reduction of nasal symptoms as compared to an antihistamine alone, combination treatment causes more side-effects, including insomnia and nervousness, and should be used cautiously (c.f. section on oral decongestants).[1,27,28]

Topical antihistamines

Topical (intranasal or intraocular) H1 antihistamines have the major advantage that drugs are delivered directly to the target organ. They have a rapid onset of action at low dosages, but they only act on the treated organ. To maintain a satisfactory clinical effect, they usually require twice-daily administration.[1]

Intranasal corticosteroids

Regular prophylactic use of intranasal glucocorticosteroids has proven to be effective in the treatment of nasal blockage, sneezing, rhinorrhoea and nasal itch in both adults and children. In comparative trials they were more effective in controlling symptoms of AR than oral H1 antihistamines,[29] intranasal H1 antihistamines,[30] intranasal cromoglycate[31,32] and oral antileukotrienes.[33] The potent effect of intranasal GCSs on nasal blockage and the extensive anti-inflammatory properties make them preferable to other treatments, especially when nasal obstruction is a major symptom and when the disease is long-lasting.[2] In terms of efficacy in relieving conjunctivitis, which is often part of the clinical picture of AR, a meta-analysis comparing intranasal GCSs and oral H1 receptor antagonists surprisingly found no significant differences between these two treatments, but there were significant variances between studies.[29]

A recent meta-analysis of randomised controlled trials, comparing at least two different intranasal steroid sprays, indicates that there is currently no clear evidence to support the suggestion that one steroid spray is more effective than another. All nasal corticosteroid sprays have a similar side-effect profile, the most common being epistaxis, with an incidence between 17 and 23%, compared to 10–15% with placebo sprays. The authors concluded that variations in costs, palatability and frequency of administrations may be the biggest factor in prescribing practice, with beclomethasone and budesonide being the most cost-effective sprays.[34]

Despite low systemic bioavailability, systemic absorption may still occur following intranasal administration of GCSs and the risk of systemic side-effects of nasal steroids has been evaluated in many studies. For patients receiving only intranasal GCS at recommended doses, however, the

risk of hypothalamic-pituitary-adrenal axis suppression or disturbed bone metabolism appears to be very low.[35] There has been some concern about skeletal growth restriction since Skoner *et al.*[36] recorded an average reduction of 0.9 cm of growth in a year in children using intranasal beclomethasone. This study, however, is flawed because it did not have age- or height-matched controls. No growth retardation, however, has been observed in one-year follow-up studies of children treated with fluticasone proprionate[37] or mometasone furoate.[38] Furthermore, there is increasing and reassuring evidence that the observed small effect (approximately 1 cm) of inhaled and intranasal GCSs on the one-year growth of children with asthma and AR that has been reported in studies is transient and not long-lasting. In addition, impaired health can also lead to growth suppression, and it is clinically impossible to determine whether an effect on growth is due to the underlying disease or to the treatment with inhaled or intranasal GCSs.[39]

Special caution, however, should still be taken with children treated with both inhaled and intranasal corticosteroids.[1]

Combination of nasal corticosteroids and antihistamines

Although there is currently no proof of the additional beneficial effects of the combination of an antihistamine and an intranasal corticosteroid compared to an intranasal corticosteroid alone,[40] many experts feel that these effects do exist.[2]

Chromones

Chromones have been found to be more effective than placebos for the treatment of allergic rhinitis and conjunctivitis. They have an excellent safety profile, but are less effective than H1 antihistamines and intranasal glucocorticosteroids.[1]

Anticholinergics

Studies performed in perennial AR have demonstrated that this treatment only improves nasal hypersecretion. No data are available for seasonal AR. Topical side-effects, of which nasal dryness, irritation and burning are the most common, are rare and usually dose-dependent.[1]

Systemic glucocorticosteroids

Because of the major risk of systemic side-effects, systemic corticosteroids are never the first-line treatment for AR. They have been shown to be effective for most rhinitis symptoms, especially nasal obstruction and loss of smell. By contrast with intranasal treatment, systemic corticosteroids have the advantage that they can reach all parts of the nose and the paranasal sinuses. Only one double-blind study has compared oral and injected GCSs in AR. Laursen *et al.* gave 36 birch pollen allergic patients either an injection of betamethasone diproprionate 5 mg plus betamethasone phosphate 2 mg, or oral prednisolone 7.5 mg daily for three weeks. The two treatments did not differ with regard to effect on nose or eye symptoms, but significantly reduced plasma cortisol levels were measured in the prednisolone group after three weeks of treatment and not in the intramuscular (IM) treated group.[41] The selection of either oral and IM GCSs, however, cannot be based on one study. Furthermore, intramuscular corticosteroid administration can cause local tissue atrophy, whereas oral GCSs are usually cheaper and have the benefit that treatment dose can be adjusted to the changing needs of treatment.[1]

Anti-leukotrienes

While sneezing and nasal itch correlate best with histamine levels in experimental AR, nasal congestion correlates with LTC4 levels. A combined analysis of three multicentre, randomised, double-blind, parallel-group studies indicated that montelukast significantly improved daytime nasal symptom scores in patients with seasonal AR, and the effect was greater in patients exposed to higher pollen levels.[42] No data are available for perennial AR.

A number of direct comparative studies found that leukotriene modifier therapy may be less effective than intranasal steroids in seasonal AR.[43,44] In a 2004 systemic review and meta-analysis that evaluated 11 studies of seasonal AR, leukotriene receptor antagonists were found to be slightly better than a placebo, as effective as antihistamines, but less effective than nasal corticosteroids in improving the symptoms and quality of life in patients with seasonal allergic rhinitis.[45]

In seasonal AR, the combination of a leukotriene receptor antagonist and an antihistamine may provide additional benefits. A multicentre, double-blind, randomised, parallel-group, placebo-controlled, two-week trial demonstrated that symptoms of rhinitis and conjunctivitis were more effectively treated with a combination of montelukast and loratadine than with each agent alone or with placebo.[46]

Turning to the comparison of intranasal glucocorticosteroids

Table 7

Overview of pharmacological agents for the treatment of allergic rhinitis[1]

Generic name	Mechanism of action	Side-effects	Comments
Oral H1 antihistamines			
Second generation	- Blockage of H1 receptor - Some anti-allergic activity - New-generation drugs can be used once daily - No development of tachyphylaxis	***Second generation*** - Most drugs: no sedation - No anti-cholinergic effect - No cardiotoxicity - Acrivastine: sedative - Azelastine: may induce sedation and bitter taste	- New generation oral H1 antihistamines are preferred for their favourable efficacy/safety ratio and pharmacokinetics - 2nd-generation medications may be used once daily - Rapid effect (< 1 hour) on nasal and ocular symptoms - Poor effect on nasal congestion - Cardiotoxic drugs should be avoided
Cetirizine Ebastine Fexofenadine Loratadine Mizolastine Acrivastine Azelastine Desloratadine Levocetirizine Emedastine Rupatadine			
First generation		***First generation***	
Chlorpheniramine Clemastine Hydroxyzine Ketotifen Mequitazine Oxatomide		- Sedation is common - and/or anti-cholinergic effect	
Cardiotoxic Astemizole* Terfenadine * * banned in Belgium			
Local H1 antihistamines (intranasal, intraocular)			
Azelastine Levocabastine Olopatadine	- Blockage of H1 receptor - Some anti-allergic activity for azelastine	- Minor local side effects - Azelastine: bitter taste in some patients	Rapid effect (<30 min) on nasal or ocular symptoms
Intranasal corticoids			
Beclomethasone Budesonide Flunisolide Fluticasone Mometasone Triamcinolone Ciclesonide	- Reduce nasal hyperreactivity - Potently reduce nasal inflammation	- Minor local side-effects - Low risk of systemic side-effects - Growth concerns with some molecules (budesonide diproprionate) - In young children: consider combination of inhaled and intranasal drugs	- Most effective medication for AR - Effective on nasal congestion - Effect on smell - Effect observed after 7-8 h, maximum after up to 2 weeks
Oral/IM corticosteroids			
Dexamethasone Hydrocortisone Methylprednisolone Prednisolone Prednisone Triamcinolone Betamethasone Deflazacort	- Potently reduce nasal inflammation - Reduce nasal hyperreactivity	- Systemic side-effects: common, in particular for IM drugs - Depot injections may cause local tissue atrophy	- When possible, intranasal corticosteroids should replace oral or IM drugs - A short course of oral corticosteroids may be indicated with severe symptoms

Table 7 (continuation)

Generic name	Mechanism of action	Side-effects	Comments
Topical chromones (intranasal, intraocular)			
Cromoglycate Nedocromil	Mechanism of action poorly known	- Minor local side-effects - Overall excellent safety	- Intraocular chromones are effective - Intranasal chromones are less effective than other therapies, their effect is short-lasting
Oral decongestants			
Ephedrine Phenylephrine Phenylpropanolamine Pseudo-ephedrine	- Sympathicomimetic drug - Relieve symptoms of nasal congestion	Hypertension, palpitations, restlessness, agitation, tremor, insomnia, headache, dry mucous membranes, urinary retention, exacerbation of glaucoma or thyrotoxicosis	- Use oral decongestants with caution in patients with underlying diseases - Oral H1 antihistamine-decongestant combination may be more effective than either product alone, but side-effects are combined
Intranasal decongestants			
Epinephrine Naphazoline Oxymethazoline Phenylephrine Tetrahydrozaline Xylometazoline	- Sympathicomimetic drug - Relieve symptoms of nasal congestion	- Same side-effects as oral decongestants but less intense - Rhinitis medicamentosa (rebound phenomenon occurring with prolonged use > 10 days)	- Act more rapidly and more effectively than oral decongestants - Limit duration of treatment to < 10 days to avoid rhinitis medicamentosa
Intranasal anticholinergics			
Ipratropium	Block almost exclusively anterior watery rhinorrhoea	- Minor local side-effects - Almost no systemic anticholinergic activity	Effective in allergic and non-allergic patients with rhinorrhoea
Antileukotrienes			
Montelukast Pranlukast Zafirlukast	Block CysLT receptor	Well tolerated	Effective treatment for AR, alone or in combination with H1 antihistamines

and combined leukotriene-antihistamine treatment, there is a lack of large and well-designed controlled trials. The scarce data, however, suggest that intranasal corticosteroids are superior to a combination of an antileukotriene and an antihistamine.[47,48]

Allergen-specific immunotherapy

For more detailed information, we refer to the WHO position paper on allergen immunotherapy.[49]

Allergen-specific subcutaneous immunotherapy (SCIT)

The efficacy of allergen-specific SCIT for AR in carefully selected patients has been extensively evaluated in numerous double-blind placebo-controlled studies. Efficacy has been documented when SCIT is used for AR induced by:

- birch and betulaceae pollen;
- grass pollen;
- ragweed pollen;
- Parietaria pollen;
- house dust mite.

In the case of mould allergy, the evidence is limited to only one study investigating Alternaria[50]; there has been no study for Cladosporium immunotherapy for rhinitis. Cat-specific SCIT has proven effective for asthma. For AR, however, the effect on nasal symptoms has not yet been thoroughly evaluated.[1]

A meta-analysis published in 2000 evaluated sixteen prospective, single- or double-blind, placebo-controlled studies on the effectiveness of SCIT in the treatment of AR published between 1966 and 1996. In the combined analysis of 759 patients, SCIT was associated with a significant clinical improvement compared to control groups.[51]

The long-term efficacy (of at least 3 years) of subcutaneous SCIT after the cessation of treatment has been demonstrated with grass, ragweed and Dermatophagoides pteronyssinus allergen extract.[1] In a retrospective study of mite-sensitive children, SCIT was associated with a more prolonged

Table 8

Effect of pharmacological treatments on symptoms of allergic rhinitis[2]

	sneezing	rhinorrhoea	nasal obstruction	nasal itch	eye symptoms
H1 antihistamines					
oral	++	++	0 to +	+++	++
intranasal	++	++	+	++	0
intraocular	0	0	0	0	+++
Corticosteroids					
intranasal	+++	+++	++	++	+
Chromones					
intranasal	+	+	+	+	0
intraocular	0	0	0	0	++
Decongestants					
intranasal	0	0	+++	0	0
oral	0	0	+	0	0
Anti-cholinergics	0	+++	0	0	0
Anti-leukotrienes	0	+	++	0	++

(+: marginal effect, +++: substantial effect)

remission of symptoms, when continued for more than 3 years, compared to children who had received SCIT for less than 3 years.[52]

Allergen-specific SCIT, when administered early in the disease process, has also been shown to modify the long-term progress of the allergic inflammation and disease. A prospective non-randomised study was carried out in a population of asthmatic children aged under 6 years whose only allergic sensitivity was to house dust mite. Approximately 45% of the children receiving SCIT did not develop new sensitivities compared to none in the control group.[53] Another retrospective study compared monosensitised patients with respiratory symptoms that were treated with specific immunotherapy (and anti-allergic drugs when needed) for four years, followed by medication for at least three years, with patients treated with drugs only for at least seven years. After four and seven years, the number of polysensitised patients was significantly lower in the SCIT group compared to the medication group, and asthmatic subjects were more prone to develop polysensitisation compared to subjects suffering only from rhinitis.[54] In addition, the Preventive Allergy Treatment (PAT) study demonstrated that the administration of SCIT for three years in children with seasonal allergic rhinitis (grass and/or birch pollen allergy) significantly reduced the risk of the development of asthma after three years.[55]

As SCIT is not free of risks, including systemic reactions (severe asthma attacks and anaphylaxis in particular), it should only be considered in patients with severe symptoms of AR, when allergen avoidance and pharmacotherapy have failed to reduce symptoms or when pharmacotherapy has been associated with unacceptable side-effects. Because of the potentially serious side-effects, it can only be carried out by, or under the supervision of, trained specialists with direct access to the necessary rescue medication. Because of these risks, patients must also be closely observed for 20 to 30 minutes after injection. Table 9 has been adapted from the WHO Position Paper and it lists some considerations before initiating immunotherapy.

Table 9

Considerations for initiating immunotherapy. WHO Position Paper on Allergen Vaccines[39]

1. Presence of demonstrated IgE-mediated disease:
   - Positive skin tests and/or serum specific IgE
2. Documentation indicating that specific sensitivity is involved in symptoms:
   - Exposure to the allergen(s) determined by allergy testing, related to appearance of symptoms
   - If required, allergen challenge with the relevant allergen(s)
3. Characterisation of other triggers that may be involved in symptoms
4. Severity and duration of symptoms:
   - Subjective symptoms
   - Objective parameters e.g. work loss, school absenteeism
   - Pulmonary function (essential): exclude patients with severe asthma
   - Monitoring of pulmonary function by peak flow
5. Response of symptoms to non-immunological treatment:
   - Response to allergen avoidance
   - Response to pharmacotherapy
6. Availability of standardised or high-quality vaccines
7. Relative contra-indications:
   - Treatment with beta-blocker
   - Other immunological disease
   - Inability of patients to comply
8. Sociological factors:
   - Cost
   - Occupation of candidate
   - Impaired quality of life despite adequate pharmacological treatment
9. Objective evidence of efficacy of immunotherapy for the selected patient (availability of controlled clinical studies)

Allergen-specific nasal and sublingual-swallow immunotherapy

In recent years, increasing attention has been paid to the use of nasal and sublingual-swallow immunotherapy.

The efficacy of high-allergen-dose *allergen-specific intranasal immunotherapy* has been docu-

Table 10
Level of evidence of different interventions in allergic rhinitis: grades of recommendations

Intervention	Seasonal AR		Perennial AR	
	Adults	Children	Adults	Children
Anti-H1				
- Oral	A	A	A	A
- Intranasal	A	A	A	A
Glucocorticosteroids				
- Intranasal	A	A	A	A
- Oral	A			
- IM	A			
Chromones				
- Intranasal	A	A	A	
- Intra-ocular	A	A	A	
Anti-leukotrienes	A			
Subcutaneous SIT	A	A	A	A
Sublingual/nasal SIT	A			A
Allergen avoidance				
- house dust mite		C		C
- cats, dogs	C	C		
- outdoor allergens	C	C		

mented in most double-blind, placebo-controlled studies carried out in AR (and often conjunctivitis as well) when induced by:

- birch and alder pollen[1]
- grass pollen[1,56]
- ragweed pollen[1]
- Parietaria pollen[1]
- house dust mite[1]

Lower doses are not effective.

In general, intranasal immunotherapy has been found to have a very good safety profile; the only reported systemic effect is asthma (probably caused by an incorrect administration of allergen vaccine).[1]

The efficacy of high-dose *allergen-specific sublingual-swallow immunotherapy* (SLIT) has also been documented in most double-blind, placebo-controlled studies carried out in AR for:

- ragweed[157]
- birch pollen[1]
- grass pollen[1,58,59]
- Parietaria pollen[1]
- house dust mite[1,60]
- Cupressus[61]

Lower doses are not effective.

A recent meta-analysis of the Cochrane Collaboration evaluated the efficacy of SLIT in AR compared to a placebo. Twenty-two double-blind placebo-controlled trials involving 979 patients were included. There were six trials of SLIT for house dust mite allergy, five for grass pollen, five for Parietaria, two for olive, and one each for ragweed, cat, tree and Cupressus. Eight studies involved treatment lasting less than six months, ten involved treatment lasting 6-12 months and four studies looked at periods of treatment in excess of twelve months. Five studies looked exclusively at children. Overall, there was a significant reduction in both symptoms and medication requirements following immunotherapy. Although there was significant heterogeneity overall, there was a significant reduction in both symptoms and medication requirements. Increasing duration of treatment did not clearly increase efficacy. In those studies involving only children, however, there were no significant reductions in symptoms or medication scores. But total numbers of participants were small, casting doubt on the validity of the conclusion.[62]

Furthermore, in a very recent open randomised study in 113 children with hay fever limited to grass pollen and no other clinically important allergies (none reported seasonal asthma with more than three episodes per season), short-term co-seasonal sublingual immunotherapy (SLIT) for three years was found to reduce the development of asthma. Development of asthma after three years was 3.8 times more frequent in children receiving standard symptomatic therapy compared to those receiving SLIT.[63]

At present, however, there is still a shortage of studies of the long-term administration of SLIT and there also is a lack of evidence about the long-term benefits of locally administered immunotherapy.

In general, sublingual-swallow immunotherapy has shown to be a safe treatment.[1,62] In one study, however, some serious systemic side-effects were observed in children.[64] Only mild reactions were observed in other studies. A post-marketing surveillance of SLIT showed that this treatment is well tolerated in children.[65]

Level of evidence of different interventions in allergic rhinitis: strength of recommendation

Based on the evidence available from the literature, the strength of recommendation underlying the different interventions for AR is graded from A to C in accordance with the classification scheme defined in Belgium by the Con-

sensus Committee of the INAMI-RIZIV (Table 10).

Role of surgery in the management of allergic rhinitis

Surgery does not relieve allergic inflammation and should only be used in cases where turbinate hypertrophy or cartilaginous or bony obstructions contribute to or aggravate rhinitis symptoms. In these cases, conchotomy and/or septo(rhino)plasty is recommended. In secondary or independent sinus disease, functional endoscopic sinus surgery can be performed.

4. Decisional algorithms

Definition of terms

AR is classified as persistent or intermittent in accordance with ARIA because this classification has been validated and has shown to be more useful than the previous classification of AR into seasonal or perennial (see Table 2). However, AR severity has not been classified in accordance with ARIA; it has been broken down into 3 subgroups to allow a more gradual stepwise treatment approach and to make the algorithms applicable to the management of the AR patient in general practice as well as in specialist practice.
Mild means that the patient has only few symptoms that do not interfere with daily activities and sleep (in untreated patients).
Moderate means that the symptoms are important enough to disturb the patient during daily activities or sleep (in untreated patients).
Severe means that the symptoms are so pronounced that the patient cannot function properly during the day and suffers from impaired sleep (in untreated patients).

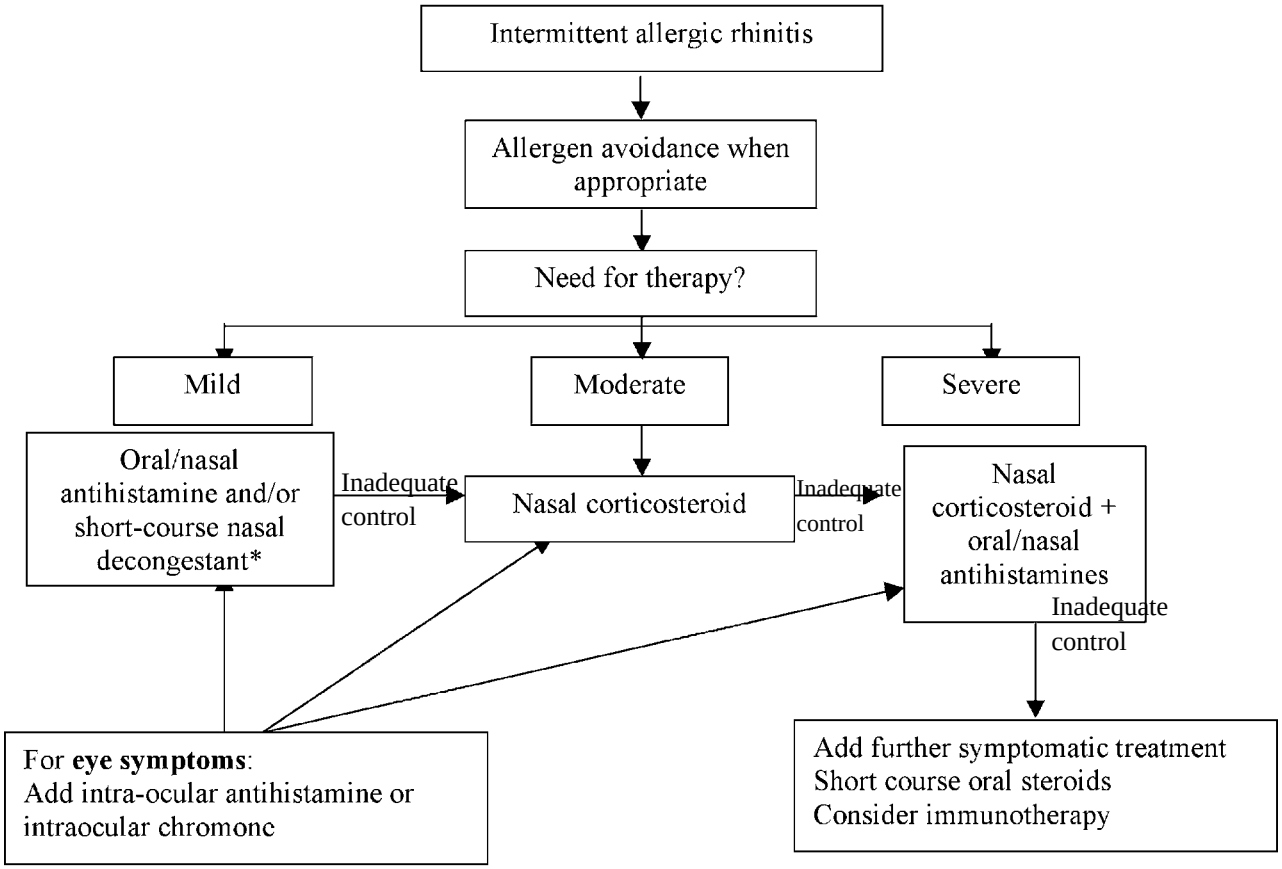
Patient information

What is allergy?

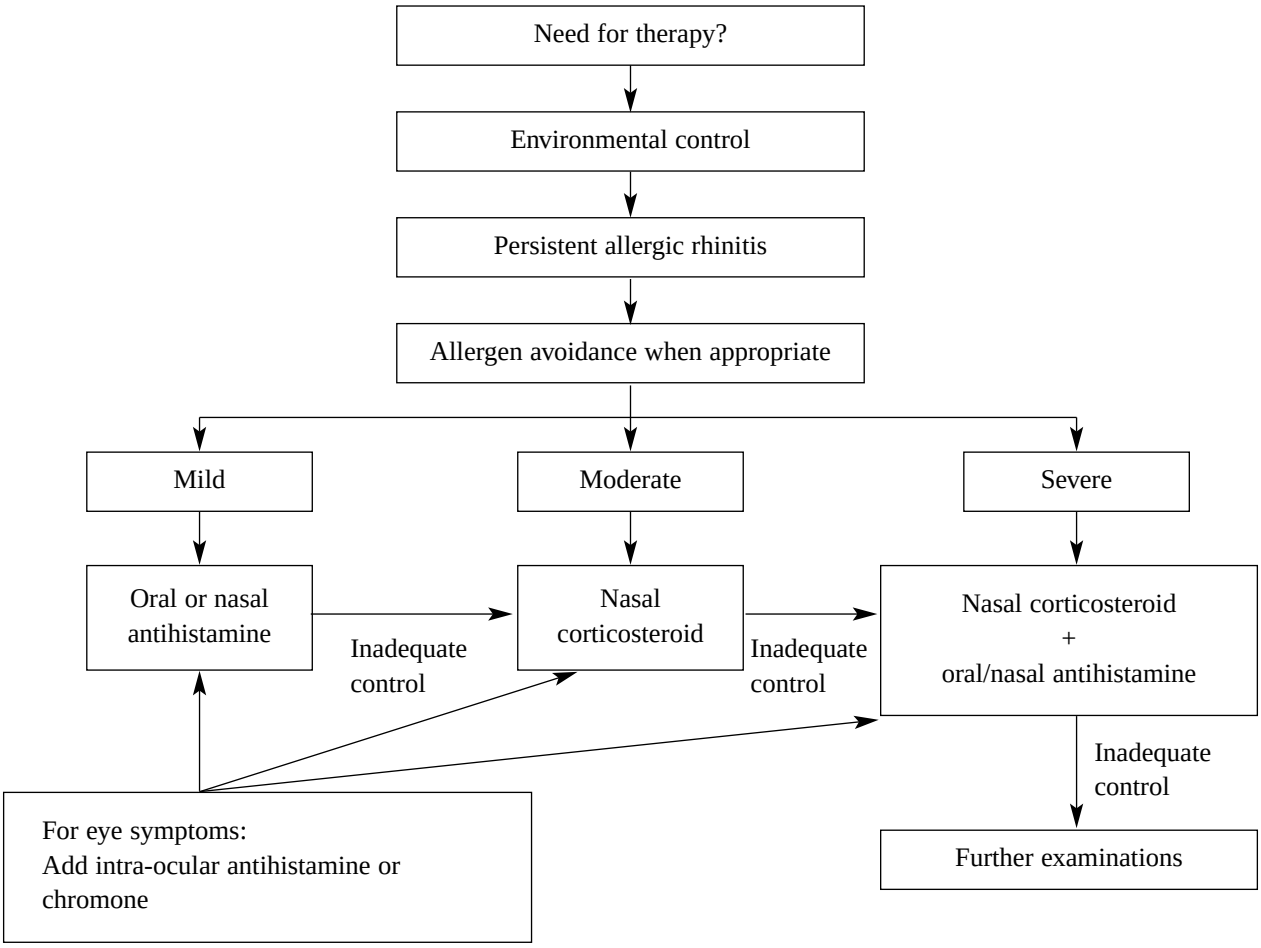
Allergy is an inappropriate response of the immune system to agents that are usually not harmful for the body: allergens. The response of the immune system to these allergens leads to an allergic inflammation, which in turn results in symptoms of nose, eyes, skin or lungs.

What are the symptoms of allergic rhinitis?

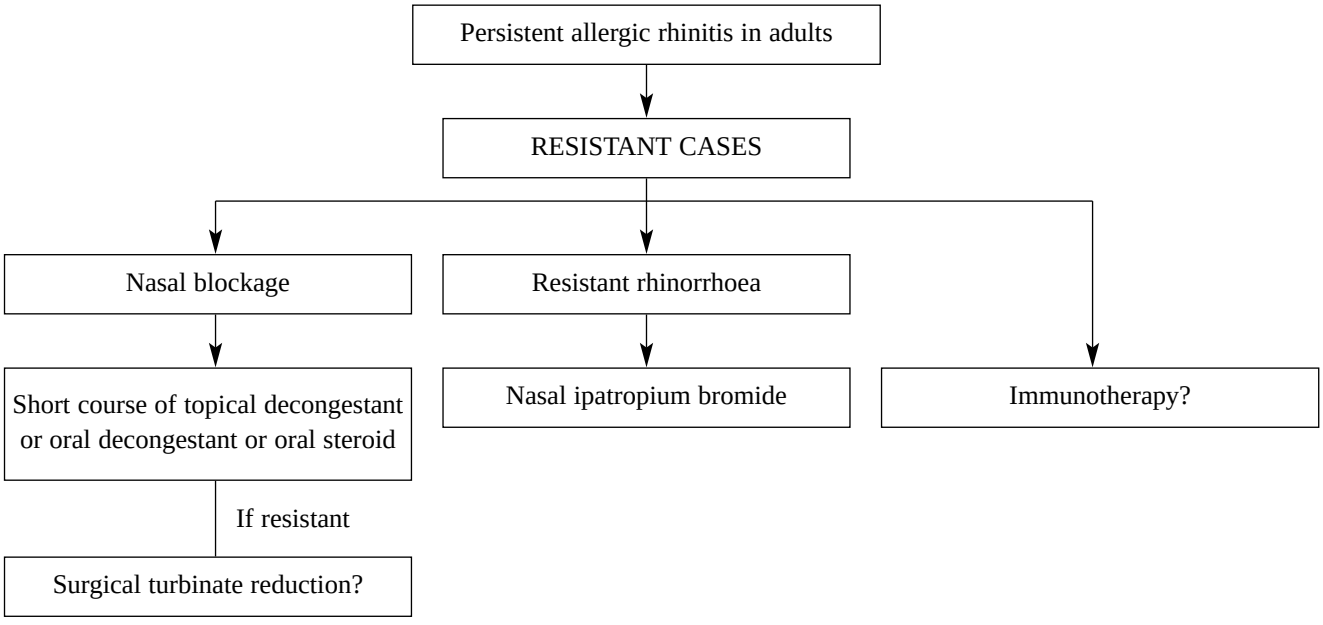
Allergic inflammation of the nose causes one or more of following



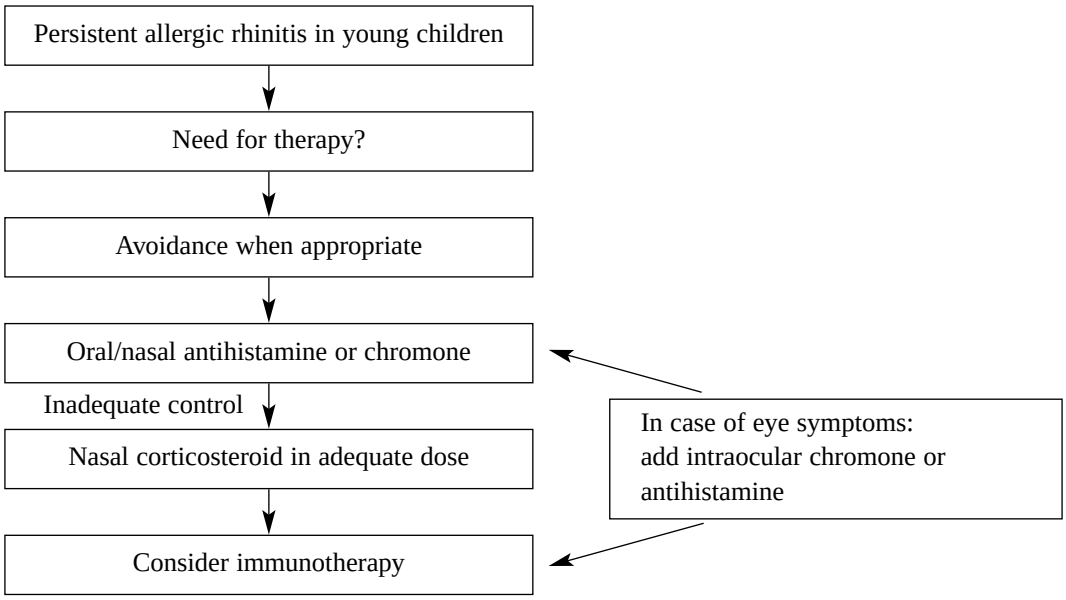
Algorithm 1
Stepwise therapeutic approach for intermittent allergic rhinitis in adults



Algorithm 2
Stepwise therapeutic approach for persistent allergic rhinitis in adults



Algorithm 3
Stepwise therapeutic approach in resistant cases of persistent allergic rhinitis in adults



Algorithm 4
Stepwise therapeutic approach for allergic rhinitis in young children

symptoms: runny nose, nasal stuffiness, nasal itch and sneezing. Allergic rhinitis may also be associated with loss of smell, cough, snoring, headache, tiredness, red, weeping or itchy eyes, sinusitis and asthma.

Why should you consult your physician?

If you have these symptoms it is essential that you consult your physician for a correct diagnosis of your condition. Symptoms of rhinitis (runny nose, nasal stuffiness, nasal itch and sneezing) are often, but not always, caused by allergy. Your physician can distinguish between the different causes of rhinitis, is aware of the complications of rhinitis (such as asthma and sinusitis) and is able to initiate an appropriate treatment strategy.

How is allergic rhinitis diagnosed?

A complete and structured description of your symptoms provides the most essential clues for a diagnosis. Some specific questions about your family history, occupation and potential allergic exposures are necessary to get more information. A clinical ear, nose and throat examination is particularly important, but the rest of body should not be overlooked. To confirm the allergic origin of rhinitis symptoms, and to identify possible allergens that may cause your symptoms, allergy tests are performed. A ‘skin prick test’ is often performed: small drops of allergen solution are placed on the forearm and pricked through with a small needle; a positive reaction is seen as a “wheal and flare” at the site of pricking. Alternatively, a blood sample can be taken to perform a RAST test to determine the presence of antibodies for a series of allergens.

How should allergic rhinitis be treated?

The treatment of rhinitis is a stepwise process, depending on the duration and the severity of your symptoms. Environmental measures are recommended to prevent or reduce exposure to the responsible allergens. If you are allergic to house dust mite, allergen-reducing measures include: regular washing of bedding, pillow and duvets at 55–60°C, encasing pillows and mattresses with documented protective coverings, reducing indoor humidity to less than 50%, removing/reducing carpets, curtains, soft toys and soft furnishings (especially in the bedroom). If you are allergic to your pet, the only effective way to avoid allergens is to remove the pet. If this is impossible, the pet should be kept outside (or at least outside the bedroom). In the case of allergy to outdoor allergens (pollens of grasses/trees/weeds, moulds) allergen avoidance is often impractical or impossible.

If allergen avoidance provides insufficient relief, medical treatment is advised. Several safe and efficient anti-allergic medications are currently available to relieve

symptoms. Antihistamines and nasal corticosteroids are the most commonly prescribed medications.

If you have severe symptoms and inadequate response to anti-allergic medication, a specific allergy vaccine (immunotherapy) may be an option. Immunotherapy is a long-term treatment (up to three or five years) involving the administration of gradually increasing doses of the allergen to which a patient is allergic. The aim of this treatment is to make the patient less sensitive to this allergen and therefore to reduce the symptoms of allergy. Immunotherapy is not indicated for all patients and for all types of allergy and is not free of side-effects (usually mild, but severe and even life-threatening in rare cases). The choice of this treatment option should therefore always be considered with care and must be discussed clearly by you and your physician.

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CME questions

1. Allergic rhinitis is classified as :
   A - Seasonal or perennial
   B - Periodic or non-periodic
   C - Acute, recurrent or chronic
   D - Intermittent or persistent
   E - Occupational or non-occupational

2. Which cell has a key role in the early clinical disease phase of allergic rhinitis ?

   A - Mast cell
   B - Eosinophil
   C - Neutrophil
   D - Basophil
   E - Macrophage

3. Which cell has a key role in the late clinical disease phase of allergic rhinitis ?

   A - Mast cell
   B - Eosinophil
   C - Neutrophil
   D - Basophil
   E - Macrophage

4. Which proportion of patients with allergic rhinitis also have clinical asthma ?

   A - 5–10%
   B - 10–20%
   C - 20–40%
   D - 40–60%
   E - 60–80%

5. Which statement about the diagnosis of allergic rhinitis is <u>incorrect</u> ?

   A - By contrast to the measurement of total serum IgE, the measurement of serum-specific IgE is a very valuable test with a high predictive value in the diagnosis of allergic rhinitis.
   B - Allergen provocation is indicated in case of occupational allergic rhinitis.
   C - In patients suspected for allergic rhinitis presenting in ENT practice, imaging (RX or CT) is strongly recommended, not to confirm allergy, but to exclude other disorders of the nose or paranasal sinuses.
   D - In the case of specific IgE measurements, skin test results may be affected by the quality of the allergen extract, and the use of standardised allergens is therefore recommended.
   E - Skin testing involves a positive control solution to detect suppression by medications or disease, to detect exceptional patients who are poorly reactive to histamine and to determine variations in technician performance.

6. Which statement about allergen avoidance is <u>incorrect</u> ?

   A - Although there is at present little evidence that allergen avoidance effectively results in sustained improvements in clinical outcome, allergen avoidance is still recommended as a first step in the management of allergic rhinitis.

B - For patients allergic to their pet, frequent washing of the pet and careful vacuum-cleaning of all carpets, mattresses and upholstered furniture is as effective as removal of the pet.
C - Frequent washing of bedding, pillows and duvets at 55–60° significantly reduces house dust mite load.
D - As high levels of humidity in the home are essential for mite population growth, reducing indoor humidity is recommended to reduce house dust mite levels.
E - Cat allergen can be found in homes up to months after removal of the cat from the home.

7. What is incorrect ? Second-generation oral H1 antihistamines

A - Are first-line treatment options for children and adults presenting with mild symptoms of allergic rhinitis.
B - Have a favourable efficacy/safety ratio and pharmacokinetics compared to first-generation H1 antihistamines.
C - Are less effective than intranasal glucocorticosteroids in reducing nasal symptoms of allergic rhinitis, nasal obstruction in particular.
D - Have an anti-allergic action beyond the H1 receptor blocking effect.
E - Are as effective as intraocular H1 antihistamines in reducing symptoms of allergic conjunctivitis.

8. What is incorrect ? High doses of oral decongestants can cause

A - rhinitis medicamentosa
B - tachycardia
C - insomnia
D - hypertension
E - dizziness

9. Which statement about intranasal glucocorticosteroids is correct ?

A - They should not be prescribed in children younger than 6 years old.
B - The effect of intranasal glucocorticosteroids is observed after 7–8 hours and reaches a maximum up to 2 weeks after administration.
C - They are indicated for the treatment of allergic rhinitis, but not for non-allergic rhinitis.
D - They only exert a local effect in the nose and no systemic absorption occurs.
E - Because of the risk of local side-effects such as crusting, dryness and epistaxis, they should not be used for longer than 3 months.

10. Which statement about allergen-specific immunotherapy is correct ?

A - Allergen-specific immunotherapy is indicated for the treatment of asthma when symptoms are severe.
B - Allergen-specific immunotherapy is completely free of side-effects when administered locally.
C - Allergen-specific immunotherapy may alter the natural course of allergic disease and may prevent the development of asthma.
D - Allergen-specific immunotherapy should not be performed in children.
E - Similar doses are used when allergen-specific immunotherapy is administered subcutaneously or locally.

Answers: 1D; 2A; 3B; 4C; 5C; 6B; 7E; 8A; 9D; 10D