

Allergic Rhinitis and its Impact on Asthma (ARIA)

In collaboration with the World Health Organization

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Recommendations

- (1) Classification of allergic rhinitis is a major chronic respiratory disease due to its:
 - prevalence

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- impact on quality of life
 - impact on work/school performance and productivity
 - economic burden
 - links with asthma
 - association with sinusitis and other comorbidities such as conjunctivitis.
- (2) Along with other known risk factors allergic rhinitis should be considered as a risk factor for asthma.
 - (3) A new subdivision of allergic rhinitis has been proposed, into:
 - intermittent
 - persistent.
 - (4) The severity of allergic rhinitis is classified as “mild” and “moderate/severe” depending on the severity of symptoms and on quality of life outcomes.
 - (5) Depending on the subdivision and severity of allergic rhinitis, a stepwise therapeutic approach has been proposed.
 - (6) The treatment of allergic rhinitis should combine:
 - allergen avoidance (when possible)
 - pharmacotherapy
 - immunotherapy.
 - (7) Environmental and social factors should be optimized to allow the patient to lead a normal life.
 - (8) Patients with persistent allergic rhinitis should be evaluated for asthma by history, by chest examination and, if possible and when necessary, by the assessment of airflow obstruction before and after a bronchodilator.

Table 1. Classification of rhinitis

Infectious
viral
bacterial
other infectious agents
Allergic
intermittent
persistent
Occupational (allergic, nonallergic)
intermittent
persistent
Drug-induced
aspirin
other medications
Hormonal
Other causes
atrophic
emotional
food
gastroesophageal reflux
irritants
NARES
Idiopathic

NARES: Non allergic rhinitis with eosinophilic syndrome.

- (9) Patients with asthma should be appropriately evaluated (history and physical examination) for rhinitis.
- (10) A combined strategy should ideally be used to treat the upper and lower airway diseases in terms of efficacy and safety.
- (11) In developing countries, a specific strategy may be needed, depending on available treatments and interventions as well as their cost.

Preface

Allergic rhinitis is clinically defined as a symptomatic disorder of the nose, induced by an IgE-mediated inflammation of the nasal membranes (Tables 1 and 2).

Allergic rhinitis represents a global health problem. It is a common disease worldwide affecting at least 10–25% of the population (1) and its prevalence is increasing. Although allergic rhinitis is not usually a severe disease, it alters the social life of patients (2), and affects school performance (3) and work productivity (4). Moreover, the costs incurred by rhinitis are substantial (5).

Asthma and rhinitis are common comorbidities suggesting the concept of “one airway, one disease” (6–8).

New knowledge about the mechanisms underlying allergic inflammation of the airways has resulted in better therapeutic strategies. New routes of drug administration, dosages and schedules have also been studied and validated.

Guidelines for the diagnosis and treatment of allergic rhinitis have already been published. However some of these were not based on evidence-based medicine, and only a few, if any, consider the patient globally in terms of comorbidities. The Allergic Rhinitis and its Impact on Asthma (ARIA) initiative has been developed in collaboration with the World Health Organization WHO. This document is intended to be a state-of-the-art reference for the specialist as well as for the general practitioner. It aims:

Table 2. Differential diagnosis of rhinitis

Polyps
Mechanical factors
deviated septum
adenoidal hypertrophy
foreign bodies
choanal atresia
Tumors
benign
malignant
Granulomas
Wegener's granulomatosis
sarcoid
infectious
malignant (midline destructive granuloma)
Ciliary defects
Cerebrospinal rhinorrhea

(1) to update clinicians' knowledge of allergic rhinitis
 (2) to highlight the impact of allergic rhinitis on asthma

(3) to provide an evidence-based documented revision of diagnosis methods

(4) to provide an evidence-based revision of the treatments available

(5) to propose a stepwise approach to the management of the disease.

The present paper is the Executive Summary of the full-length document prepared from a workshop held in collaboration with WHO in December 1999. The full-length document has been published as a supplement to the Journal of Allergy and Clinical Immunology (9).

Classification

Symptoms of rhinitis include: rhinorrhea, nasal obstruction, nasal itching and sneezing which are reversible spontaneously or with treatment. The severity of allergic rhinitis can be classified as "mild" or "moderate-severe" (Fig. 1) based on symptoms and quality of life parameters.

Previously, allergic rhinitis has been subdivided, based on the time of exposure, into seasonal, perennial and occupational disease (10–12). Perennial allergic rhinitis is most frequently caused by indoor allergens such as dust mites, moulds, insects (cockroaches) and animal dander. Seasonal allergic rhinitis is related to a wide variety of outdoor allergens such as pollens or moulds. However, this subdivision is not entirely satisfactory since:

- (1) it is often difficult to differentiate between seasonal and perennial symptoms
- (2) the exposure to some pollen allergens is long-standing
- (3) the exposure to some perennial allergens is not consistent over the year
- (4) the majority of patients are now sensitized to pollen and perennial allergens.

Thus, a major change in the subdivision of allergic rhinitis has been proposed in this document using the terms "intermittent" and "persistent" (Fig. 1). However, in the present document, the terms "seasonal" and "perennial" are still used for the description of published studies.

Epidemiology and genetics

Despite recognizing that allergic rhinitis is a global health problem, there are insufficient epidemiological data with regards to its distribution, etiological risk factors and natural history. However, new national or multinational studies are rapidly improving our knowledge about the prevalence of rhinitis and its possible risk factors. These include:

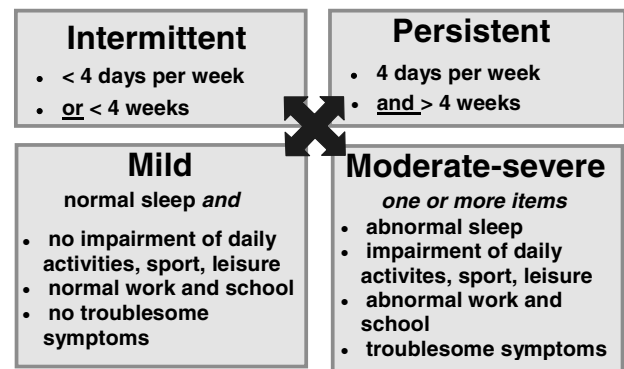


Figure 1. Classification of allergic rhinitis.

- (1) the second National Health and Nutrition Examination Survey (NHANES II) (13, 14)
- (2) European Community Respiratory Health Survey (ECRHS) (15)
- (3) International Study on Asthma and Allergy in Childhood (ISAAC): in the worldwide ISAAC study, the prevalence of seasonal allergic rhinitis varied in different parts of the world from 0.8% to 14.9% in 6–7-year-olds and from 1.4% to 39.7% in 13–14-year-olds (1)
- (4) Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) (16)
- (5) Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen (SCARPOL) (17).

Overall, it is estimated that allergic rhinitis is present in 3–35 or 40% of the population, depending on the area and the age of the patients.

An increase in the prevalence of allergic rhinitis has been observed over the past 40 years (18–20).

A genetic component in allergic rhinitis as well as in other allergic diseases has been shown (21). For the past decade, various antigens of the human leukocyte antigen (HLA) system have been identified as being responsible for allergen reactivity (21). Some genes have also become candidates to explain the genetic component of allergic rhinitis, but problems with the definition of the studied phenotypes still exist. There are apparently no genes clearly predisposing individuals to asthma or rhinitis. In addition, the recent increase in prevalence of allergic rhinitis cannot be due to a change in the gene pool.

Allergens and trigger factors

Allergens

Aeroallergens are often involved in allergic rhinitis (22). The increase in domestic allergens is partly responsible for the increase in the prevalence of rhinitis, asthma and allergic respiratory diseases (23). The allergens present in the home are principally mites, domestic animals, and insects, or are of from plant origin (e.g. *Ficus*). Common outdoor allergens include pollens and moulds.

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Occupational rhinitis is less well documented than occupational asthma, but nasal and bronchial symptoms often coexist in the same patient (24). Rhinitis often appears before the onset of occupational asthma (24, 25).

Latex allergy has become of increasing concern to patients and health professionals (26). Health professionals should therefore be aware of this problem and develop strategies for treatment and prevention.

Pollutants

Epidemiological evidence suggests that pollutants exacerbate rhinitis. The mechanisms by which pollutants cause or exacerbate rhinitis are now better understood (27).

Indoor air pollution is of great importance since subjects in industrialized countries spend over 80% of their time indoors. Indoor pollution includes domestic allergens and indoor gas pollutants (28, 29), of which tobacco smoke is the major source.

In many countries, urban-type pollution is primarily of automobile origin, and the principal atmospheric oxidant pollutants include ozone, oxides of nitrogen, and sulfur dioxide. These may be involved in the aggravation of nasal symptoms either in patients with allergic rhinitis (30, 31) or in nonallergic subjects (32). Moreover, diesel exhaust may enhance the formation of IgE (33) and allergic inflammation (34, 35).

Aspirin intolerance

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) commonly induce rhinitis and asthma (36).

Mechanisms involved in allergic rhinitis

Classically, allergy is considered to result from an IgE-mediated response associated with nasal inflammation of variable intensity. Pollen-induced rhinitis is the most characteristic IgE-mediated allergic disease and is triggered by the interaction of mediators released by cells, which are implicated in both allergic inflammation and nonspecific hyperreactivity (37). However, it is now also appreciated that allergens may directly activate cells, on account of their enzymatic proteolytic activity (38). The relative importance of non-IgE and IgE-mediated mechanisms is undetermined.

Allergic rhinitis is characterized by an inflammatory infiltrate made up of different cells (39). This cellular response includes:

- (1) chemotaxis, selective recruitment and transendothelial migration of cells
- (2) release of cytokines and chemokines (40, 41)
- (3) localization of cells within the different compartments of the nasal mucosa
- (4) activation and differentiation of various cell types

including eosinophils, T cells (34, 42), mast cells (43), and epithelial cells (44), as well as a prolongation of their survival

- (5) release of mediators by these activated cells; among these, histamine and cysteinyl-leukotrienes are the major vasoactive mediators
- (6) regulation of local and systemic IgE synthesis
- (7) communication with the immune system and bone marrow.

Nonspecific nasal hyperreactivity is an important feature of allergic and nonallergic rhinitis (45). It is defined as an increased nasal response to normal stimuli resulting in sneezing, nasal congestion and/or secretion.

Intermittent rhinitis can be mimicked by nasal challenge with pollen allergens and it has been shown that an inflammatory reaction occurs during the late-phase reaction.

In persistent allergic rhinitis, allergic triggers interact with an ongoing inflammatory reaction. Symptoms are due to this complex interaction.

“Minimal persistent inflammation” is a new and important concept (46). It has been confirmed in perennial (46, 47) and seasonal rhinitis (48). In patients with persistent allergic rhinitis, the allergen exposure varies throughout the year and there are periods during which there is little exposure. Even though symptom-free, these patients still present with inflammation of the nose.

Understanding the mechanisms of disease generation helps to provide a framework for rational therapy in this disorder, based on the complex inflammatory reaction rather than the symptoms alone.

Comorbidity and complications

Allergic inflammation is not necessarily limited to the nasal airway. Multiple comorbidities have been associated with rhinitis.

Asthma

The nasal and bronchial mucosa share many similarities (7, 49). Epidemiological studies have shown consistently that asthma and rhinitis often coexist in patients (18, 50–52). Most patients with allergic and nonallergic asthma have rhinitis. Allergic rhinitis is associated with, and also constitutes a risk factor for, asthma (19). Many patients with allergic rhinitis have increased nonspecific bronchial hyperreactivity (53, 54).

There is a temporal relationship between the onset of allergic rhinitis and asthma, with rhinitis frequently preceding the development of asthma.

In normal subjects, the structure of the airway mucosa presents similarities between the nose and the bronchi. There are also differences. In the nose, there is a large blood supply and changes in the vasculature can lead to severe nasal obstruction (55). On the other hand, it is the

Table 3. Diagnostic tests for allergic rhinitis

Routine tests
History
General ENT examination
Allergy tests
skin tests
serum specific IgE
Endoscopy
rigid
flexible
Nasal secretions
cytology
Nasal challenge
allergen
lysine aspirin
Radiology
CT scan
Optional tests
Nasal biopsy
Nasal swab
bacteriology
Radiology, CT scans
MRI
Mucociliary function
nasal mucociliary clearance (NMCC)
ciliary beat frequency (CBF)
ciliary beat frequency (CBF)
electron microscopy
Nasal airway assessment
nasal inspiratory peak flow (NIPF)
rhinomanometry (anterior and posterior)
acoustic rhinometry
Olfaction
Nitric oxide measurement

smooth muscle present from the trachea to the bronchioles that accounts for the bronchoconstriction of asthma.

Pathophysiological studies suggest that a strong relationship exists between rhinitis and asthma. Recent progress in the cellular and molecular biology of airway diseases has shown that inflammation of nasal and bronchial mucosa plays a critical role in the pathogenesis of asthma and rhinitis. A similar inflammatory cell infiltrate (56, 57), the same pro-inflammatory mediators (histamine, Cys LT), Th2 cytokines (58–60), chemokines (61, 62), and adhesion molecules (44, 63, 64) appear to be involved in both nasal and bronchial inflammation. However, very few studies have compared nasal and bronchial mucosa in the same patients. In these cases, there are differences in the extent of the inflammatory indices, and epithelial shedding is more pronounced in the bronchi than in the nose of the same patient (65). Airway remodelling exists microscopically in most, if not all, asthmatics (57) but may not be so obvious in rhinitis.

Endobronchial allergen challenge in patients with allergic rhinitis leads to an asthmatic response with recruitment of inflammatory cells and pro-inflammatory mediators (66).

Several mechanisms have been postulated to link uncontrolled allergic rhinitis and the occurrence or

worsening of asthma (67). Although a nasal challenge with allergen does not induce airflow limitation of the lower airways, it may cause nonspecific bronchial responsiveness (68, 69). These data have led to the concept that upper and lower airways may be considered as a unique entity, influenced by a common, evolving inflammatory process which may be sustained and amplified by interconnected mechanisms.

Therefore, when considering a diagnosis of rhinitis or asthma, an evaluation of both the lower and upper airways should be made.

Other comorbidities

These include sinusitis, nasal polyposis, and conjunctivitis. The association between allergic rhinitis, nasal polyposis and otitis media are less well understood.

Diagnosis and assessment of severity

The tests and procedures listed in Table 3 represent the spectrum of investigations that may be used in the diagnosis of allergic rhinitis. However, only a number of these are routinely available or applicable to an individual patient.

History and general ear, nose and throat (ENT) examination

A clinical history is essential in making an accurate diagnosis of rhinitis, assessing its severity and its likely response to treatment.

In patients with mild intermittent allergic rhinitis, a nasal examination is optimal. All patients with persistent allergic rhinitis require a nasal examination. Anterior rhinoscopy using a speculum and mirror gives limited information. Nasal endoscopy is usually performed by specialists and is more useful.

Diagnosis of allergy

The diagnosis of allergic rhinitis should be based on the history of allergic symptoms and diagnostic tests. *In vivo* and *in vitro* tests used to diagnose allergic diseases are directed towards the detection of free or cell-bound IgE. The diagnosis of allergy has been improved by allergen standardization, providing satisfactory diagnostic vaccines for most inhalant allergens.

Immediate hypersensitivity skin tests are widely used to demonstrate IgE-mediated allergic reactions. These represent a major diagnostic tool in the field of allergy. If properly performed they yield useful confirmatory evidence for the diagnosis of specific allergies. However, as these tests are complex to perform and interpret, it is recommended that they are carried out by trained health professionals (70).

The measurement of total serum IgE is of little predictive value in allergy screening for rhinitis, and

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should be used rarely as a diagnostic tool (11). However, the measurement of allergen-specific IgE in serum is of importance and is of similar value to skin tests (71, 72).

Some *in vitro* specific IgE methods either use a combination of several allergens in a single assay (73), or test several different allergens during a single assay. These tests can therefore be used by specialized doctors and nonallergists as screening tests for the diagnosis of allergic diseases.

Nasal challenge tests with allergens are used in research and, to a lesser extent, in clinical practice. They are important, however, in the diagnosis of occupational rhinitis. A subcommittee of the International Committee on Objective Assessment of the Nasal Airways (ICOANA) has proposed guidelines for nasal provocation tests concerning indications, techniques and evaluation of the tests (74). The recommendations of this committee have been accepted in this document.

Diagnosis of asthma

Due to the transient nature of the disease and the reversibility of airflow obstruction (spontaneously or with treatment), the diagnosis of asthma may be difficult. Guidelines for recognizing and diagnosing asthma have been published by the Global Initiative for Asthma (GINA) and have been recommended in the WHO document (75). As already identified by GINA, measuring lung function and confirming the reversibility of airflow obstruction are essential steps in the diagnosis of asthma. An update of the 1995 document is being prepared and will represent state-of-the-art management of asthma.

Assessment of severity of rhinitis

For asthma there are objective measures of severity, such as pulmonary function tests, and well-defined criteria for symptom severity (75). For atopic dermatitis there are clinical scores of severity, such as SCORAD (76). However, for rhinitis there is no accepted objective measure of nasal obstruction. The nasal inspiratory peak flow (NIPF) has been extensively studied, but the results of these studies are not consistent (77–79). Moreover, the correlation between objective measurement of nasal resistance and subjective report of nasal airflow sensation is usually poor. Therefore, this document proposes a clinical assessment of rhinitis (Fig. 2).

Management

The management of allergic rhinitis includes allergen avoidance, medication (pharmacological treatment),

Clinical classification of rhinitis

International Consensus on Rhinitis 1994 (84)

	sneezers and runners	blockers
sneezing	especially paroxysmal	little or none
rhinorrhea	watery	thick mucus
	anterior and posterior	more posterior
itching	yes	no
nasal blockage	variable	often severe
diurnal rhythm	worse during day	constant, day and night, may be worse at night
conjunctivitis	often present	

Rhinitis

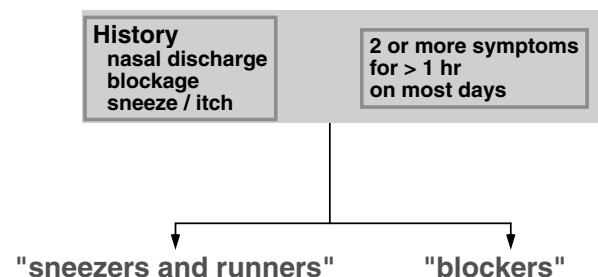


Figure 2. Clinical assessment of rhinitis.

immunotherapy, and education. Surgery may be used as an adjunctive intervention in a few highly selected patients.

These recommendations propose a strategy combining treatment of both the upper and lower airway disease in terms of efficacy and safety.

Allergen avoidance

Many allergens have been associated with allergic rhinitis, of which house-dust mite is the most important and the most investigated (80). Most allergen avoidance studies have dealt with asthma symptoms, and very few have studied rhinitis symptoms. Unfortunately the majority of interventions have failed to achieve a sufficient reduction in allergen load to lead to a clinical improvement. A meta-analysis of house-mite avoidance trials indicated that this approach was unlikely to succeed in the treatment of asthma (81). The authors suggested that a single intervention may be insufficient. However, this metanalysis raised certain issues (82, 83).

All the current asthma and rhinitis guidelines (10, 75) now suggest that allergen avoidance, including house mites, should be an integral part of a management strategy, but more data are needed to fully appreciate the value of allergen avoidance.

Medications

Medications have no long-lasting effect when stopped,

Table 4. Glossary of medications used in allergic rhinitis

Group name/Generic name	Mechanism of action	Side-effects	Comments
Oral H₁-antihistamines 2nd generation: acrivastine azelastine; cetirizine; ebastine; fexofenadine; loratadine; mizolastine; New products; desloratadine; levocetirizine 1st generation: chlorpheniramine/chlorphenamine; clemastine; hydroxyzine; ketotifen; mequitazine; oxatomide; others. Cardiotoxic products: astemizole; terfenadine	Blockage of H ₁ receptor Some anti-allergic activity New generation drugs can be used once daily No development of tachyphylaxis	2nd generation: No sedation for most drugs No anticholinergic effect Acrivastine has sedative effects Oral azelastine may induce sedation and bitter taste 1st generation: Sedation is common and/or anticholinergic effect Mequitazine has anticholinergic effects	2nd generation oral H ₁ -antihistamines should be preferred for their No cardiotoxicity favorable efficacy/safety ratio and pharmacokinetics Rapidly effective (less than 1 h) on nasal and ocular symptoms Poorly effective on nasal congestion Cardiotoxic drugs should be avoided
Local (intranasal/intraocular) H₁-antihistamines azelastine; levocabastine	Blockage of H ₁ receptor Azelastine has some anti-allergic activity	Minor local side-effects Azelastine has a bitter taste	Rapidly effective (<30 mins) on nasal or ocular symptoms
Intranasal corticosteroids beclometasone; budesonide; flunisolide; fluticasone; mometasone; triamcinolone	Potently reduce nasal inflammation Reduce nasal hyperreactivity	Minor local side-effects Wide margin for systemic side-effects. Growth concerns with some molecules only In young children consider the combination of intranasal and inhaled drugs	The most effective pharmacological treatment of allergic rhinitis Effective on nasal congestion Effective on smell Effect observed after 12 h but maximal after a few days
Oral/intramuscular corticosteroids betamethasone; deflazacort; dexamethasone; hydrocortisone; methylprednisolone; prednisolone; prednisone; triamcinolone	Potently reduce nasal inflammation Reduce nasal hyperreactivity	Systemic side-effects common particularly for intramuscular drugs Depot injections may cause local tissue atrophy	When possible, intranasal corticosteroids should replace oral or intramuscular drugs However, a short course of oral corticosteroids may be needed with severe symptoms
Local (intranasal/intraocular) chromones cromoglicate; nedocromil	Mechanism of action poorly known	Minor local side-effects	Intraocular chromones are very effective. Intranasal chromones are less effective and their effect is short-lasting. Overall excellent safety
Oral decongestants ephedrine; phenylephrine; phenylpropanolamine; pseudoephedrine	Sympathomimetic drug Relieve symptoms of nasal congestion	Hypertension, palpitations restlessness, agitation tremor, insomnia, headache, dry mucous membranes, urinary retention, exacerbation of glaucoma, thyrotoxicosis	Use oral decongestants with caution in patients with heart disease Oral H ₁ -antihistamine/decongestant combination products may be more effective than either product alone but side-effects are combined
Intranasal decongestants epinephrine/adrenaline; naphthazoline ; oxymetazoline; phenylephrine; propylphenrine; tetrahydrozoline; xylometazoline	Sympathomimetic drug Relieve symptoms of nasal congestion	Same side-effects as oral decongestants but less intense Rhinitis medicamentosa (a rebound phenomenon from prolonged use > 10 days)	Act more rapidly and more effectively than oral decongestants Limit duration of treatment to less than 10 days to avoid rhinitis medicamentosa
Intranasal anticholinergics ipratropium	Anticholinergic block of rhinorrhea almost exclusively	Minor local side-effects Almost no systemic	Effective in allergic and nonallergic patients with rhinorrhea anticholinergic activity
Cysteinyl leukotriene antagonists montelukast; pranlukast; zafirlukast	Block cysteinyl leukotriene receptor	Well tolerated	Promising drugs used alone or in combination with oral H ₁ -antihistamines but more data needed to position these drugs

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Table 5. Symptomatic effects of pharmacologic treatments (Adapted from Van Cauwenberge et al. (11))

	Sneezing	Rhinorrhea	Nasal obstruction	Nasal itch	Eye symptoms
H ₁ -antihistamines					
oral	++	++	+	+++	++
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
Anticholinergics	0	++	0	0	0
Antileukotrienes	0	+	++	0	++

so maintenance treatment is required for persistent disease. Tachyphylaxis does not usually occur with prolonged treatment.

Medications used for rhinitis are most commonly administered intranasally or orally (Table 4). There are several advantages of intranasal medication. High concentrations can be delivered directly into the nose, thus avoiding or minimizing systemic effects. However, there are problems with intranasal dosing as many patients with allergic rhinitis also have conjunctivitis and/or asthma, and medications need to be administered to various target organs. In a number of patients, the intranasal distribution of this medication is not optimal.

Medications for treatment of allergic rhinitis include oral and topical (intranasal/intraocular) H₁-antihistamines (H₁-receptor antagonist/blockers) (85), intranasal corticosteroids (86), oral corticosteroids, intranasal and intraocular chromones, oral and intranasal decongestants, oral decongestants combined with H₁-receptor antagonists, intranasal anticholinergics, and leukotriene receptor antagonists (87) (Table 4). The efficacy and safety of each of these is reported in the full-length document. Some studies have compared the relative efficacy of these medications. Intranasal corticosteroid is the most effective treatment (86). However, the choice of a treatment also depends on many other criteria.

The different pharmacologic treatments have varying effects on symptoms (Table 5).

The use of alternative care for the treatment of rhinitis is increasing. There is an urgent need for large, randomized, controlled clinical trials of alternative therapies for allergic diseases and rhinitis. Scientific and clinical evidence is lacking for these therapies (88).

Allergen-specific immunotherapy: therapeutic vaccines for allergic diseases

A number of guidelines for specific immunotherapy with inhalant allergens have been published. The WHO

document endorsed the conclusions of their previous guidelines (88), and the European Academy of Allergy and Clinical Immunology (EAACI) (88) update used newly published randomized, double-blind and placebo-controlled trials.

The WHO document highlighted the fact that subcutaneous immunotherapy alters the natural course of allergic diseases (91, 92).

Subcutaneous immunotherapy raises contrasting issues about efficacy and safety. Thus the use of optimal doses of vaccines, labeled in either biological units or in mass of major allergens, has been proposed. Doses of 5–20 µg of the major allergen are optimal for most allergen vaccines (89). The indications for this form of immunotherapy are similar to those published in 1998 (89).

New studies have been published for high-dose, sublingual-swallow immunotherapy. The current WHO document updates the previous recommendations on allergen immunotherapy. It has been confirmed that the only effective doses are those that are at least 10 times greater than those used for subcutaneous immunotherapy.

Local nasal and high-dose, sublingual-swallow specific immunotherapy may be indicated in:

- (1) carefully selected patients with rhinitis, conjunctivitis and/or asthma caused by pollen and mite allergy
- (2) patients insufficiently controlled by conventional pharmacotherapy
- (3) patients who have presented with systemic reactions during injection specific immunotherapy
- (4) patients showing poor compliance with, or refusing, injections.

The safety of sublingual-swallow immunotherapy has been demonstrated in several papers and pharmacosurveillance data. In this ARIA Position Paper, it is proposed that sublingual specific immunotherapy can be administered to children and adults.

Table 6. Strength of evidence for the treatment of rhinitis

Intervention	Seasonal		Perennial	
	adults	children	adults	children
Allergen avoidance				
house dust mites			D	D
cats, dogs			D	D
cockroaches			D	D
outdoor allergens	D	D		
latex			D	
H ₁ -antihistamines				
oral	A	A	A	A
intranasal	A	A	A	A
intraocular	A	A		
Glucocorticosteroid				
intranasal	A	A	A	A
oral	A			
intramuscular	A			
Chromones				
intranasal	A	A	A	
intraocular	A	A	A	
NAAGA				
intranasal*	A			
Decongestant				
intranasal				
oral				
Oral decongestant + H ₁ -antihistamine	A	A	A	
Anti-cholinergic				
intranasal			A	A
Cysteinyl leukotriene antagonist	A			
Cysteinyl leukotriene antagonist + H ₁ -antihistamine	A			
Anti-allergic drugs†	A			
Homeopathy†	A*			
Acupuncture				
chiropractic medicine				
other alternative medicine				
Antibiotics				
Specific immunotherapy				
subcutaneous				
asthma	A	A	A	A
subcutaneous				
rhinitis + conjunctivitis	A	A	A	A
intranasal‡				
rhinitis + conjunctivitis	A	A	A	
sublingual‡				
rhinitis + conjunctivitis	A	A	A	

NAAGA, N-acetyl-aspartyl-glutamic acid.

A: level of evidence 1b with double-blind, placebo-controlled studies.

* Level of evidence 1b with double-blind studies.

† Based on a single study ;more data are needed.

‡ Recommendation applied only to high-dose vaccine.

Future potential treatment modalities

Several novel approaches are currently under consideration for the treatment or prevention of allergic inflammation. Studies in this area are driven by a search for disease-modifying therapies for asthma.

Novel therapies for the treatment of asthma include a humanized monoclonal antibody against IgE, which is in the latest phase of its development (93).

Many novel treatments for asthma are based on inhibition of eosinophil development or tissue recruitment, on inhibition of allergic inflammation (mast cells, T cells), and on new forms of immunotherapy.

Practical guidelines for the treatment of allergic rhinitis and comorbidities

Development of guidelines for rhinitis. The 1994 International Consensus for Rhinitis guidelines (10) followed a stepwise approach to the treatment of allergic and nonallergic rhinitis. This seemed the most practical approach for both general practitioners and specialists.

In 1999, the EAACI proposed new guidelines (12). Unlike the 1994 guidelines (10) which only considered mild and moderate cases, the new guidelines make recommendations for severe disease.

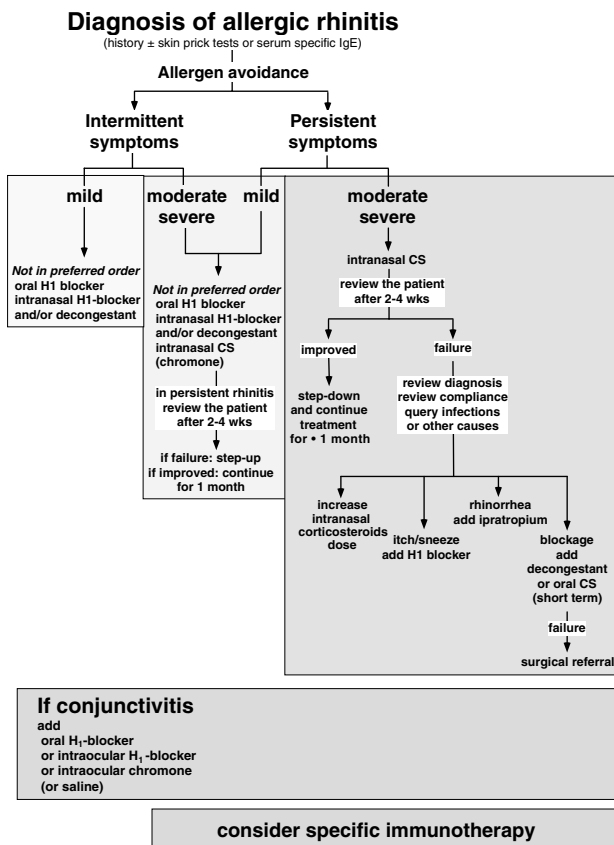


Figure 3. Stepwise treatment approach in adolescents and adults.

In the present guidelines, suggestions were made by a panel of experts. These were based on an extensive review of available literature up to December 1999. Papers for review were extracted from MEDLINE using PubMed and EMBASE. A consensus was reached on all of the material presented in the position paper. The panel recognized that the suggestions it put forward are valid for the majority of patients within a particular classification, but that individual patient responses to a particular treatment may differ.

It is assumed that a correct diagnosis is made before treatment commences.

The statement of evidence for the development of these guidelines has followed WHO rules, and is based on Shekelle et al. (94).

The statements of evidence for the different treatment options of allergic rhinitis have been examined by the report panel (Table 6).

Availability of the treatment. The guidelines do not take into account the cost of the treatment. They are made with the presumption that all treatments are readily available to and financially affordable by the patients (on health insurance). A list of essential drugs is published by WHO (95). It is important that all the major drugs recommended for treatment of rhinitis should be available worldwide.

Recommendations for the management of allergic rhinitis

Pharmacologic management of rhinitis. In adults and adolescents, the pharmacologic management of allergic rhinitis follows a stepwise approach (Fig. 3).

Pharmacologic management of conjunctivitis. If the patient suffers from conjunctivitis, the options are (not in order of preference):

- (1) ocular H₁-antihistamines
- (2) ocular chromones
- (3) oral H₁-antihistamines
- (4) saline.

Ocular glucocorticosteroids have been associated with serious short-term and long-term complications. Their administration is not recommended unless eye examinations have been carried out.

Avoidance of allergens and trigger factors. Although there is no definite evidence that allergen-avoidance measures are effective in the treatment of rhinitis, they are indicated when possible.

Allergen-specific immunotherapy. Specific immunotherapy may be used in patients with demonstrable IgE-mediated diseases who have had a long duration of symptoms, or in whom pharmacotherapy has been partially or totally ineffective or induced side-effects.

Treatment of rhinitis and asthma

The treatment of asthma should follow the GINA guidelines (75).

Allergen avoidance is always indicated in the treatment of allergic rhinitis (10) and asthma (75).

The indications for specific immunotherapy in allergic asthma and rhinitis have been separated in some guidelines (89). This artificial separation has led to some unresolved issues (96, 97) possibly because the allergen-induced IgE-mediated reaction has not been considered as a multiorgan disease. It is therefore important to consider specific immunotherapy based on the allergen sensitization, rather than on the disease itself, as most patients with allergic asthma also present rhinitis or rhinoconjunctivitis.

Some drugs are effective in treating both rhinitis and asthma (e.g. glucocorticosteroids and antileukotrienes). However, others are only effective in the treatment of either rhinitis or asthma (e.g. α - and β -adrenergic agonists, respectively). Moreover, some drugs are more effective in rhinitis than in asthma (e.g. H₁-antihistamines).

Finally, optimal management of rhinitis may partly improve coexisting asthma. In a few studies, intranasal glucocorticosteroids have been associated with moderately improved asthma in some (98, 99), but not all, patients (100). Less is known about the beneficial effects

on nasal disease by inhaled (intrabronchial) glucocorticosteroids (101). Drugs administered orally may effect both nasal and bronchial symptoms.

The safety of intranasal glucocorticosteroids has been established (102). However, large doses of inhaled (intrabronchial) glucocorticosteroids can induce side-effects (103). One of the problems with dual administration is the possibility of creating additive side-effects. In one study it was found that the addition of intranasal formulations to inhaled formulations did not produce any further significant suppression of mean values, but there were more individual abnormal cortisol values associated with the dual therapy (104). However, more data are needed.

It has been proposed that the prevention or early treatment of allergic rhinitis may help to prevent the occurrence of asthma or the severity of bronchial symptoms, but again more data are needed.

Pediatric aspects

Allergic rhinitis is part of the “allergic march” during childhood (80, 105) but occurrence of intermittent allergic rhinitis is unusual in children under two years of age. Allergic rhinitis is most prevalent during the school-age years.

The principles of treatment for children are the same as for adults, but special care must be taken to avoid the typical side-effects in this age group (12, 106). Doses should be adjusted and special consideration given. Few medications have been tested in children under the age of two years.

Oral and intramuscular glucocorticosteroids should be avoided when treating rhinitis in young children. Intranasal glucocorticosteroids are an effective treatment for allergic rhinoconjunctivitis. However the possible effect on body growth by some, but not all, intranasal glucocorticosteroids is of concern (107). Recommended doses of intranasal mometasone (108) and fluticasone were shown not to affect growth in children with allergic rhinoconjunctivitis.

Disodium cromoglicate is commonly used to treat allergic rhinoconjunctivitis in children because of its safety.

Special considerations

Rhinitis is often a problem during pregnancy since nasal obstruction may be aggravated by the pregnancy itself (109). Caution must be taken when administering any medication during pregnancy, as most medications cross the placenta. For most drugs limited studies have been completed, and only on small groups, with no long-term analysis performed (110, 111). Moreover, there are different regulations in different countries.

With the ageing process, various physiological changes occur in the connective tissue and vasculature

of the nose which may predispose or contribute to chronic rhinitis (112). Some drugs may induce specific side-effects in elderly patients.

Education

It is essential to educate the patient and/or the caregiver about the management of rhinitis. Such education is likely to maximize compliance, with the possibility of optimizing treatment outcome (113). However, in allergic rhinitis the benefit of education has never been tested in terms of treatment efficacy, compliance or effectiveness.

Prevention of rhinitis

There is a general misconception that the factors involved in the induction of allergy are also likely to incite disease once established. However, this is not necessarily the case. Thus, strategies for primary prevention or prophylaxis may be very different to those required for the management of established disease. These include:

- (1) primary prophylaxis, employed in situations where there is no evidence of allergic sensitization focused on populations at a high risk of becoming sensitized (114);
- (2) secondary prophylaxis, for individuals who show evidence of sensitization to allergens but not yet any evidence of disease in the upper respiratory tract;
- (3) tertiary prophylaxis, preventive strategies for the management of established allergic rhinitis (most publications are concerned with tertiary prophylaxis).

A more complete description of preventive measures is reported in the WHO initiative “Prevention of allergy and asthma” (115).

Quality of life

In the last decade, the socioeconomic burden of rhinitis has been demonstrated in terms of effects on health-related quality of life (HRQL) in day-to-day life at home, at work and in school (2, 116). Treatments for allergic rhinitis improve quality of life.

The socioeconomic impact of asthma and rhinitis

Asthma and rhinitis are chronic conditions that have a substantial economic impact on the affected subjects, their families, the healthcare system, and society as a whole. This includes direct and indirect costs associated with a loss of economic productivity.

The world literature on the economic burden of asthma and rhinitis has only recently emerged and, to date, has focused primarily on asthma. However, the few

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studies which examine the economic impact of rhinitis also provide compelling evidence of its substantial impact (5, 117). It has also been shown that rhinitis increases the costs for asthma (52).

ARIA in developing countries

In developing countries, the management of *rhinitis* is based on medication affordability and availability (118), and on cultural differences (119). The rationale for treatment choice in developing countries is based upon:

- (1) level of efficacy
- (2) low drug costs, affordable for the majority of patients
- (3) inclusion in the WHO essential list of drugs (only chlorpheniramine and beclometasone are listed)
- (4) it is hoped that new drugs will shortly be included on this list.

Immunotherapy is not usually recommended in developing countries for the following reasons:

- (1) many allergens in developing countries are not well identified
- (2) specialists must prescribe
- (3) desensitization immunotherapy must be administered by doctors because of possible side-effects.

A stepwise approach to treatment is proposed:

- **Mild intermittent rhinitis:** oral H₁-antihistamines.
- **Moderate-severe intermittent rhinitis:** intranasal beclometasone (300–400 µg daily). If needed, after a week of treatment, oral H₁-antihistamines and/or oral corticosteroids will be added.
- **Mild persistent rhinitis:** treatment with oral H₁-antihistamines or a low dose (100–200 µg) of intranasal beclometasone will be sufficient.

- **Moderate-severe persistent rhinitis:** A high dose of nasal beclometasone (300–400 µg). If symptoms are severe, add oral H₁-antihistamines and/or steroids at the beginning of the treatment.

Asthma management for developing countries is included in the IUATLD Asthma Guide (120). The ability to afford inhaled steroids is uncommon in developing countries. If the patient can afford to receive treatment for both manifestations of the disease, it is recommended to add the treatment of allergic rhinitis to the asthma management plan.

Further needs and research

Several unmet needs have been identified that require additional research:

- (1) Epidemiological studies are needed to better assess the prevalence of intermittent and persistent rhinitis, and to increase understanding of the relationship between asthma and rhinitis.
- (2) The natural history of asthma and rhinitis needs further study.
- (3) Common and differential pathophysiologic mechanisms in upper and lower airways need to be identified.
- (4) Does remodelling of the nose occur in rhinitis?
- (5) Can rhinitis predict asthma exacerbations?
- (6) Does the treatment of rhinitis influence the severity of established asthma?
- (7) Does the treatment of rhinitis in childhood prevent the development of asthma? (see the WHO “Prevention of allergy and asthma” initiative (115)).

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