

Allergic Rhinitis: an Overview

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Abstract Allergic rhinitis is an inflammatory disorder of the nasal mucosa induced by allergen exposure triggering IgE-mediated inflammation. Clinically, it is characterized by four major symptoms—rhinorrhea, sneezing, nasal itching, and nasal congestion. It can also be associated with co-morbid conditions as Asthma, Atopic Dermatitis & Nasal polyps. Around 20–30 % of the Indian population suffers from allergic rhinitis and that 15 % develop asthma. The diagnosis & treatment of allergic rhinitis should follow ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines while of asthma should follow the GINA (Global Initiative for Asthma) guidelines. The treatment of allergic rhinitis should combine allergen avoidance (whenever possible), pharmacotherapy, and allergen immunotherapy. Intranasal corticosteroids are the most effective modality for treating allergic rhinitis and their sensory attributes are important in patient compliance.

Keywords Allergic rhinitis · Asthma · Intranasal corticosteroid · Immunotherapy

Introduction [1]

Allergic Rhinitis is a symptomatic disorder of the nose induced after allergen exposure due to an IgE-mediated

inflammation of membranes lining the nose. It is clinically defined as a symptomatic condition with four major symptoms as anterior or posterior rhinorrhoea, sneezing, nasal itching & nasal congestion. Allergic Rhinitis symptoms result in sleep disturbance, fatigue, depressed mood and cognitive function compromise that impairs quality of life and productivity [2]. There may be associated conjunctivitis, postnasal drip, Eustachian tube dysfunction, otitis media, sinusitis & in children, dental malocclusions & facial deformities also. Triggers of Allergic rhinitis are domestic allergens as mites, domestic animals, insects or of plant origin; common outdoor allergens include pollens and moulds; occupational triggers as latex; tobacco smoke; automobile exhaust include ozone, oxides of nitrogen and sulphur dioxide; aspirin and other non-steroidal anti-inflammatory drugs.

It can also be associated with co-morbid conditions as Asthma, Atopic Dermatitis & Nasal polyps. AR is a global health problem also with considerable economic & societal burdens. About 40 % of the world's population is atopic, and allergic rhinitis is the commonest of preservation of this atopic tendency. The reported incidence of allergic rhinitis in the western countries is 1.4–39.7 %. The indirect costs resulting from Allergic Rhinitis associated absenteeism and presenteeism result in losses to employers that exceed those for other common conditions such as migraine, diabetes and asthma.

A number of pharmacologic interventions are prescribed to treat Allergic Rhinitis. Intranasal corticosteroids (INSs) are recommended in current guidelines as first-line therapy for patients with moderate to severe Allergic Rhinitis, particularly when nasal congestion is the prominent symptom [3]. INSs inhibit the onset of the inflammatory response and reduce nasal mucosa permeability, the number of inflammatory cells and the release of mediators.

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Patient perception of sensory attributes (e.g. odor, taste) is a key contributor to patient preference for currently marketed INS products [4]. Unpleasant sensory attributes may be related to decrease patient adherence to treatment.

Classification of Allergic Rhinitis

Allergic rhinitis was previously subdivided, based on time of exposure, into seasonal, perennial, and occupational. This subdivision is not entirely satisfactory. The recent classification of allergic rhinitis as suggested by ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines [5] is on the basis of:

- (1) Duration as “intermittent” or “persistent” disease,
- (2) Severity of symptoms and quality of life as “mild” or “moderate-severe” (Fig. 1).

Patients with intermittent AR have sneezing, eye symptoms and watery secretions; while patients with persistent AR have seromucous secretions, postnasal drip, smell disturbances, nasal obstruction and may be associated with asthma and chronic sinusitis. Rhinoconjunctivitis quality of life questionnaire can be used to assess the severity of symptoms.

Allergic Rhinitis & Asthma Coexistence

Asthma is a chronic inflammatory disorder of the airways that results in reversible airway obstruction and bronchial hyperresponsiveness to various stimuli; causing symptoms of wheezing, breathlessness, chest tightness, and coughing. In the unified airway model, the nose and paranasal sinuses through respiratory bronchi are considered as components of one functional unit; epidemiologically & pathophysiologically. A survey by All India Co-ordinated Project on

Aeroallergens and human health, New Delhi, 2000, showed that 20–30 % of the population suffers from allergic rhinitis and that 15 % develop asthma. According to one hypothesis, lack of microbial exposure in childhood may lead to modified immunity toward T helper 2 (Th₂) skewing causing increased risk for asthma & atopic diseases. This may explain the role of immunotherapy in AR patients in the prevention of asthma development.

Studies have shown that not treating allergic rhinitis leads to increased asthma costs and hospitalization. Early and aggressive management of Allergic Rhinitis can prevent the development of asthma. Hence physicians treating rhinosinusitis should know early signs of asthma and its management.

Epidemiology

- AR typically presents at a younger age and more common in boys. Seasonal rhinitis is more prevalent among children, but adults are more affected by perennial rhinitis.
- Around one fifth of individuals with rhinitis develop asthma in their later life. Individuals sensitized with perennial allergens (dust mite) are more prone to develop asthma than individuals having sensitization with seasonal allergens (pollen grains).
- Genetic predisposition to atopy may be a factor deciding susceptibility to develop allergic rhinitis or asthma.
- There is a significant geographic variation in prevalence of allergic rhinitis, asthma & other atopic diseases.
- Individuals having severe, persistent AR are more susceptible to develop asthma.
- Firstborn children; a serum total IgE higher than 100 IU/ml before the age of 6 years; higher socioeconomic class; air pollution; exposure to moisture damage among farmers; tobacco smoke; obesity; aspirin; RSV (respiratory syncytial virus) infection are some other risk factors for these atopic diseases.

Pathophysiology

Allergic rhinitis is characterized by an inflammatory infiltrate made up of different cells (Fig. 2). This cellular response includes:

- Chemotaxis, selective recruitment and trans-endothelial migration of cells,
- Release of cytokines and chemokines,
- Activation and differentiation of eosinophils, T-cells, mast cells and epithelial cells,

ARIA Classification

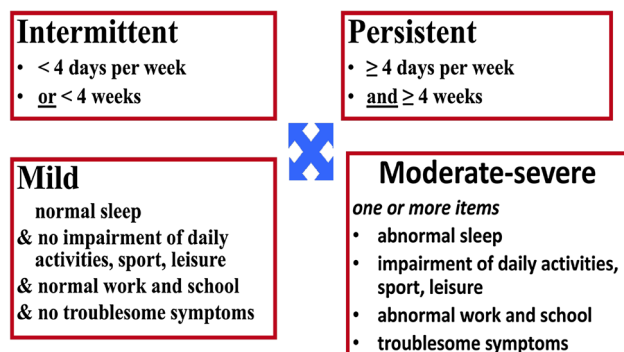


Fig. 1 ARIA classification

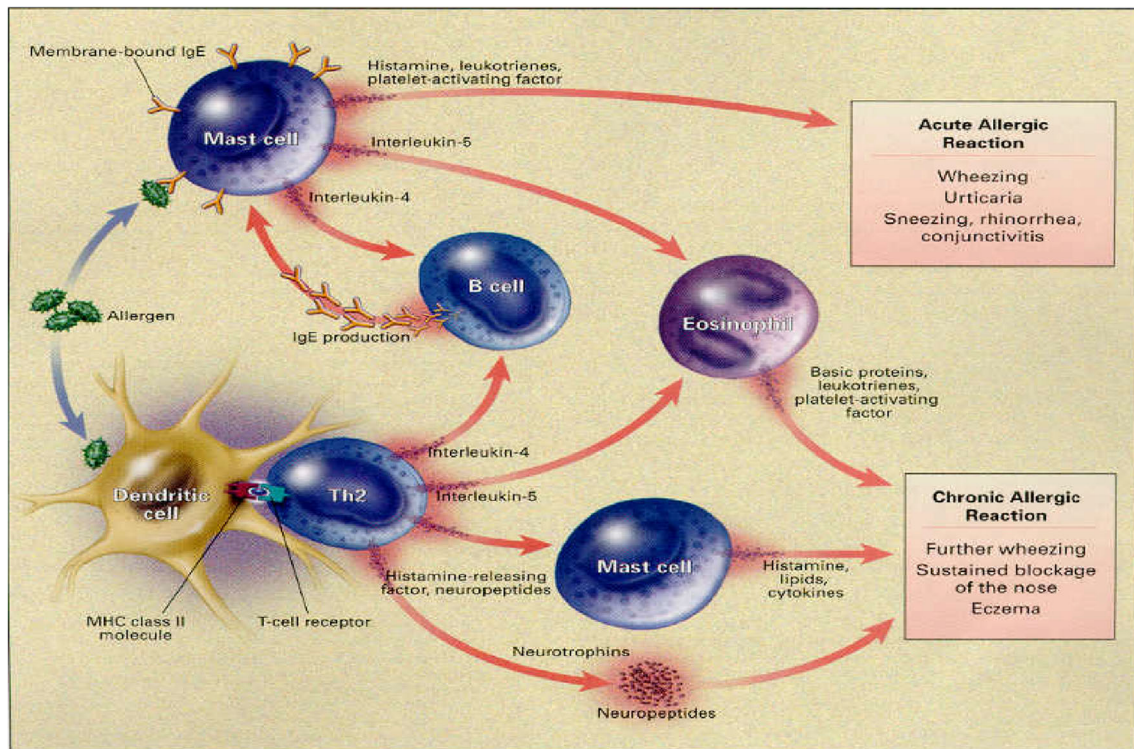


Fig. 2 Pathophysiology

- Prolongation of their survival,
- Release of mediators by these activated cells: among these, histamine and cysteinyl-leukotrienes (CystLT) are the major mediators,
- Communication with the immune system and the bone marrow.

In persistent allergic rhinitis patients, these inflammatory responses occur within the respiratory tract also. Neuronal stimulation in nose results into release of cholinergic neurotransmitters which contract bronchial smooth muscles. Vagal stimulation or para-sympathetic system activation also results in bronchoconstriction through substance-P and CGRP (calcitonin gene-related peptide). These mechanisms produce features of asthma.

Diagnosis

The Diagnosis of Allergic Rhinitis

It is based on:

- (1) typical history of allergic symptoms.
- (2) allergic symptoms are those of “sneezers and runners” (Table 1). All patients with persistent allergic rhinitis need a nasal examination (Anterior rhinoscopy, Nasal endoscopy). Functional tests (peak nasal

inspiratory flow, rhinomanometry, or acoustic rhinometry) can be used to measure nasal obstruction.

3. 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 an IgE-mediated allergic reaction. These represent a major diagnostic tool in the field of allergy. If properly performed, they yield useful confirmatory evidence for the diagnosis of a specific allergy. As there are many complexities for their performance and interpretation, they should be carried out by trained health professionals.
- The measurement of allergen-specific IgE (radioallergosorbent testing, RAST) in serum is of importance and is of similar value to skin tests. They are more useful in patients having dermatitis, dermographism, and in cases where antihistamines have to be continued during testing [6].
- Nasal challenge tests with allergens are commonly used in research. They may be useful, especially in the diagnosis of occupational rhinitis.

A computerized tomography (CT) scan is used to exclude chronic rhinosinusitis, tumors, or when a complication is suspected.

Table 1 Comparison of sneezers/runners with blockers

	Sneezers and Runners	Blockers
Sneezing	Especially paroxysmal	Little or none
Rhinorrhoea	Watery anterior and posterior	Thick mucus more posterior
Nasal 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	

– The diagnosis of asthma

Asthma and rhinitis are common co-morbidities, suggesting the concept of “one airway, one disease”. Due to the transient nature of the disease and the reversibility of the airflow obstruction (spontaneously or with treatment) the diagnosis of concomitant asthma may be difficult. Guidelines for recognizing and diagnosing asthma have been published by the Global Initiative for Asthma (GINA) and are recommended by ARIA. Measurement of lung function and confirmation of the reversibility of airflow obstruction are essential steps in the diagnosis of asthma.

Treatment

The rationale for treatment choice in developing countries is based upon:

- (1) Level of efficacy.
- (2) Low drug cost affordable for the majority of patients.
3. Inclusion in the WHO essential list of drugs (only chlorpheniramine and beclomethasone are listed). New drugs will shortly be included on this list.

The treatment of allergic rhinitis should combine allergen avoidance (whenever possible), pharmacotherapy, and immunotherapy. Environmental and social factors should be optimized to allow the patient to lead a normal life. Patients with persistent allergic rhinitis should be evaluated for asthma by history, chest examination, and if possible, by the assessment of airflow obstruction before and after a bronchodilator. Patients with asthma should be appropriately evaluated (history and physical examination) for rhinitis. A combined strategy should ideally be used to treat coexistent upper and lower airway diseases in terms of efficacy and safety. Follow-up is required in patients with persistent rhinitis and severe intermittent rhinitis.

Special Considerations

- (1) *Pregnancy*-Rhinitis is often a problem during pregnancy since nasal obstruction may be aggravated by the pregnancy itself. Caution must be taken when administering any medication during pregnancy, as

most medications cross the placenta. Intranasal Budesonide is preferred INS during pregnancy [1].

- (2) *Ageing*-With ageing, various physiological changes occur in the connective tissue and vasculature of the nose predisposing to chronic rhinitis.

Allergy is a less common cause of persistent rhinitis in subjects over 65 years. Atrophic rhinitis is common and difficult to control. Rhinorrhoea can be controlled with anticholinergics. Some drugs (reserpine, guanethidine, phentolamine, methyldopa, prazosin, chlorpromazine or ACE inhibitors) can cause rhinitis. Some drugs may induce specific side effects in elderly patients.

- decongestants and drugs with anticholinergic activity may cause urinary retention in patients with prostatic hypertrophy,
- sedative drugs may have greater side effects,
- dexamethasone isonicotinate is the only INS linked to increased risk of bone fractures & Cushing's syndrome [7].

3. *Paediatric Aspects*-Allergic rhinitis is part of the “allergic march” during childhood. Intermittent allergic rhinitis is unusual before two years of age. Allergic rhinitis is most prevalent during school age years. Allergy tests can be done at any age and may yield important information. The principles of treatment for children are the same as for adults, but special care has to be taken to avoid the side effects typical in this age group. Doses of medication have to be adjusted and special considerations followed. In children, symptoms of allergic rhinitis can impair cognitive functioning and school performance, which can be further impaired by the use of sedating oral H1-antihistamines. Disodium cromoglycate is commonly used to treat allergic rhinoconjunctivitis in children because of the safety of the drug.

Oral and intramuscular glucocorticosteroids should be avoided in the treatment of rhinitis in young children. Intranasal glucocorticosteroids (INC) are an effective treatment for allergic rhinitis. However, their possible effect on growth for some, but not all, INC is of concern. It has been shown that the recommended doses of intranasal Budesonide, Mometasone and Fluticasone did not affect growth in

children with allergic rhinoconjunctivitis. Mometasone [1] & Fluticasone furoate [8] are the only INS with indication down to age 2, so, preferred in pediatric patients.

The Treatment of Asthma Should Follow the GINA Guidelines. Some drugs are effective in the treatment of both rhinitis and asthma (e.g. glucocorticosteroids and anti-leukotrienes), others are only effective in the treatment of either rhinitis or asthma (e.g. α - and β -adrenergic agonists, respectively). H_1 -antihistamines are more effective in rhinitis than in asthma. Inhaled corticosteroids are the drug of choice in the treatment of both allergic rhinitis and asthma. Optimal management of rhinitis may improve coexisting asthma. Drugs giving by oral route, used only in severe refractory cases, may affect both nasal and bronchial symptoms.

Fexofenadine, loratadine & desloratadine have sedation profiles no different than placebo at recommended doses. Azelastine is the only intranasal antihistamine available commercially & it may be slightly superior to desloratadine, fexofenadine & cetirizine in reducing symptoms of AR [9]. Immunomodulator such as Omalizumab (monoclonal anti-IgE antibody) is effective in both allergic rhinitis and asthma but is very costly.

There are studies ongoing proving efficacy of osmotically-acting medical device (containing mannitol, etc.) to reduce nasal congestion in allergic rhinitis patients.

Treatment in a Stepwise Approach

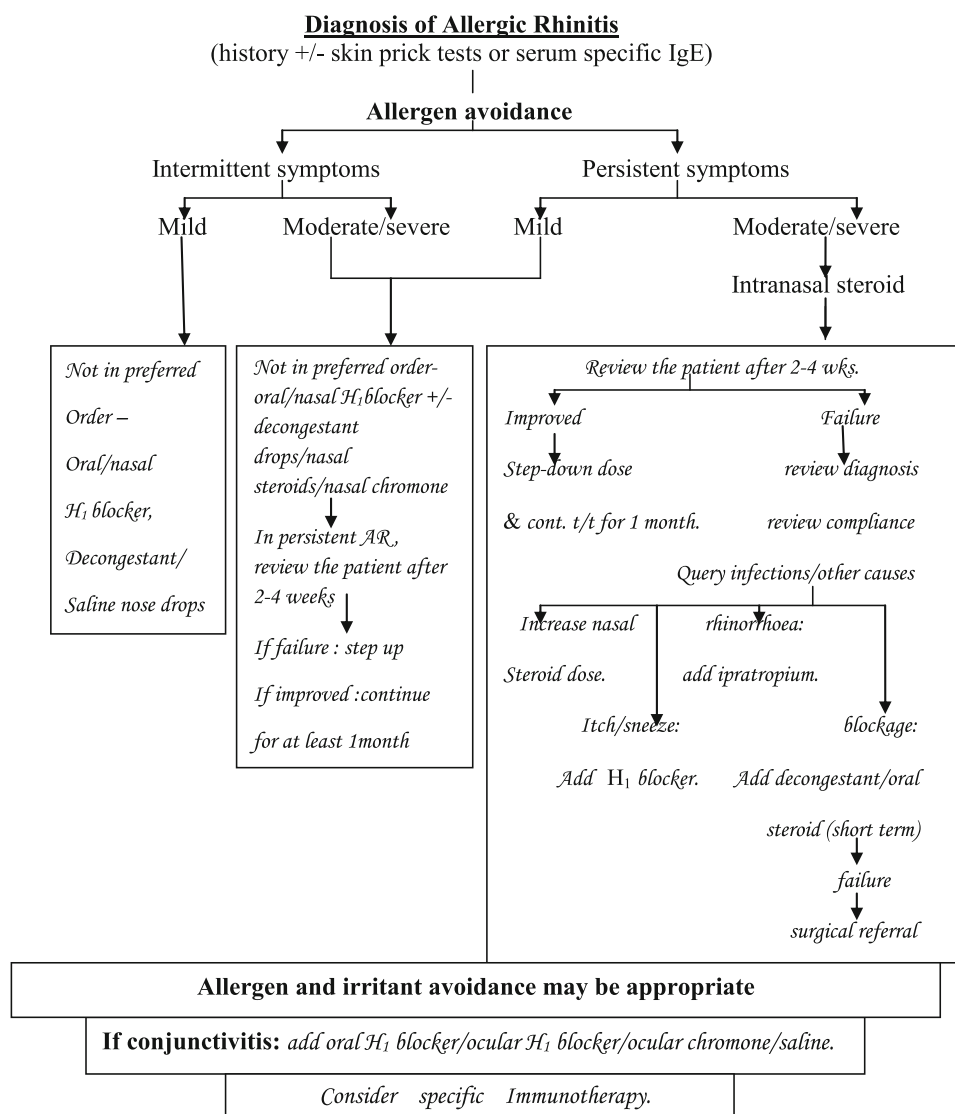


Table 2 Effect of drugs on symptoms of allergic rhinitis

	Sneezing	Rhinorrhea	Nasal obstruction	Nasal itching	Eye symptoms
H1-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
Anti-cholinergics	0	++	0	0	0
Anti-leukotrienes	0	+	++	0	++
Immunotherapy	+++	+++	+++	+++	+ to ++

Effect of drugs on symptoms of Allergic rhinitis: It is shown in Table 2.

Formulation Considerations of INC for the Treatment

Inhaled corticosteroids are the drug of choice in the treatment of both allergic rhinitis and asthma. Patient compliance is central to the successful use of INC which is largely influenced by the sensory attributes of the nasal spray, which depend on formulation factors. Preservatives in the INC formulation (benzalkonium chloride, BKC- 0.05 %) may produce nasal irritation; other excipients may impart unacceptable taste or odor to the formulation. Further, the relative osmotic pressure or tonicity of the formulation can modulate nasal retention and absorption, thereby potentially influencing clinical efficacy. In one study by Varshney et al. [10], although the immediate efficacy and tolerability were comparable, an overall patient preference was for Fluticasone propionate formulation rather than Ciclesonide. Here tolerability was based on the patient responses for seven sensory attributes rated on a 7-point Likert scale while immediate efficacy was assessed by TNSS scale. In this study, the fluticasone nasal spray, despite having 0.02 % benzalkonium chloride did not produce an appreciable nasal irritation in majority of the patients.

Allergen Immunotherapy [1]

Allergen immunotherapy is the repeated controlled administration of increasing doses of allergen extract to an allergic subject to ameliorate the symptoms associated with the

subsequent exposure to the causative allergen. It was first used by Noon and Freeman to treat hay fever in 1911.

Types of Immunotherapy

- (1) Subcutaneous immunotherapy (SIT).
- (2) Local nasal immunotherapy (LNIT) and sublingual immunotherapy (SLIT).

Subcutaneous immunotherapy alters the natural course of allergic diseases. Doses of 5–20 µg of the major allergen are optimal doses for most allergen vaccines. Subcutaneous immunotherapy should be performed by trained personnel and patients should be monitored for 20 min after injection. In children, specific immunotherapy is effective. However, it is not recommended to commence immunotherapy in children less than 5 years of age.

Mechanism of Action

- (1) Blunting of the usual seasonal rise in IgE antibodies,
- (2) Increase in serum IgE antibodies with change in subclasses (increased IgG 1 and IgG 2),
- (3) Down-regulation of the cellular and inflammatory mediators of allergic response,
- (4) Up-regulation of counter regulatory cytokines expressed by Th 1 response.

Indications

- Inadequate response to usual therapy in patients with IgE-mediated seasonal pollen-induced rhinitis and/or conjunctivitis.

- Persistent symptoms despite a trial of medical therapy.
- Systemic allergic reactions to stinging insect venom (wasp or bee).
- A history indicating that exposure to a particular allergen precipitates symptoms and contributes to illness.
- Documented sensitivity to the clinically relevant aeroallergen.
- Future exposure to the allergen is unavoidable or only partially reducible.
- Co-existing conditions such as sinusitis, asthma, or both.

Contraindications

- Unstable asthma symptoms.
- Concomitant illness such as severe pulmonary and cardiovascular disease.
- Patients with autoimmune disease or malignancy.
- Pregnancy.
- Patients taking β -blockers, or ACE inhibitors.

Surgery

It is indicated as an adjuvant therapy if there is nasal septal deviation causing obstruction, drug-resistant turbinate hypertrophy, chronic rhinosinusitis, or polyps.

Summary

Allergic rhinitis and asthma are highly prevalent worldwide. Understanding the pathophysiology would lead to an improved medical management of these disorders. The diagnosis & treatment should follow ARIA and GINA guidelines. Pharmacologic treatments should target

symptoms to improve quality of life for patients. Sensory attributes are potentially important considerations when evaluating intranasal products for allergic rhinitis and their formulary placement. Novel treatments are required for cheaper, early, better and more permanent symptoms resolution in these disorders.

Conflict of interest None.

References

1. CME Self study program on allergic rhinitis in adults and children, guidelines for clinical care from University of Michigan Medical School, USA (2009)
2. Meltzer EO (2001) Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol* 108(Suppl 1):S45–S53
3. Bousquet J, van Cauwenberge P, Ait Khaled N et al (2006) Pharmacologic and anti-IgE treatment of allergic rhinitis ARIA update (in collaboration with GA2LEN). *Allergy* 61:1086–1096 (for GA2LEN)
4. Stokes M, Amorosi SL, Thompson D et al (2004) Evaluation of patients' preferences for triamcinolone acetonide aqueous, fluticasone propionate, and mometasone furoate nasal spray in patients with allergic rhinitis. *Otolaryngol Head Neck Surg* 131:225–231
5. Bousquet J, Khaltayev N, Cruz AA et al (2008) Allergic rhinitis and its impact on asthma (ARIA). *Allergy* 63(s86):8–160
6. Greiner AN, Hellings PW, Rotiroti G (2012) Allergic rhinitis. *Lancet* 378(9809):2112–2122
7. Kimmerle R, Rolla AR (1985) Iatrogenic Cushing's syndrome due to dexamethasone nasal drops. *Am J Med* 79:535–537
8. Allergic Rhinitis, an update on treatment. *BMJ Learning* 2009
9. Corren J, Storms W, Bernstein J, Berger W, Nayak A, Sacks H, Azelastine Cetirizine Trial No. 1 (ACT 1) Study Group (2005) Effectiveness of azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. *Clin Ther* 27:543–553
10. Varshney J, Varshney H, Dutta SK, Hazra A (2012) Comparison of sensory attributes and immediate efficacy of intranasal ciclesonide and fluticasone propionate in allergic rhinitis: a randomized controlled trial. *Indian J Pharmacol* 44:550–554