Review Article

Allergic Rhinitis: epidemiological aspects, diagnosis and treatment*

Rinite alérgica: aspectos epidemiológicos, diagnósticos e terapêuticos

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Abstract

This study was a review of the literature on the epidemiological, clinical, diagnostic and therapeutic aspects of allergic rhinitis. Bibliographic searches were based on the information contained within the Medline, Latin American and Caribbean Health Sciences Literature and HighWire databases, covering the last thirty years and using the following search terms: 'allergic rhinitis', 'epidemiology', 'diagnosis' and 'treatment'. Sixty articles were selected. This study describes the increase in the prevalence of allergic rhinitis, its relationship with asthma, the diagnostic criteria and the treatment. The classification of allergic rhinitis and strategies for its treatment are presented. Therapeutic modalities presented and discussed include the administration of antihistamines, corticosteroids, immunotherapy, anti-leukotrienes, sodium cromoglycate and anti-IgE antibodies, as well as minimizing exposure to inhaled allergens. Finally, the importance of the management of allergic rhinitis in public health is emphasized.

Keywords: Rhinitis/therapy; Hypersensitivity; Epidemiology; Diagnosis.

Resumo

Este estudo tem como objetivo revisar a literatura a respeito da rinite alérgica quanto aos aspectos epidemiológicos, clínicos, diagnósticos e terapêuticos. A revisão da bibliografia foi realizada utilizando-se as bases de dados Medline, Literatura Latino-Americana e do Caribe em Ciências da Saúde e HighWire, nos últimos trinta anos, utilizando-se os descritores *allergic rhinitis*, *epidemiology*, *diagnosis*, e *treatment*. Foram selecionados 60 artigos. Este estudo destaca o aumento na prevalência da rinite alérgica, sua associação com a asma, os critérios diagnósticos e seu tratamento. A classificação da rinite alérgica é apresentada, bem como as estratégias de tratamento. As modalidades terapêuticas apresentadas e discutidas são anti-histamínicos, corticóides, imunoterapia, antileucotrienos, cromoglicato dissódico e anticorpos anti-IgE, bem como a redução da exposição aos alérgenos. Finalmente, ressalta-se a importância da abordagem da rinite alérgica em saúde pública.

Descritores: Rinite/terapia; Hipersensibilidade; Epidemiologia; Diagnóstico.

Introduction

Allergic rhinitis is defined as inflammation of the nasal mucosa, induced by exposure to allergens that, after sensitization, trigger an immunoglobulin E (IgE)-mediated inflammatory response that can result in chronic or recurrent symptoms. The principal symptoms include aqueous rhinorrhea, nasal obstruction/pruritus and sneezing, as well as ocular symptoms such as pruritus and conjunctival hyperemia, which resolve spontaneously or through treatment.[1]

In view of its high prevalence in urban populations, some authors call it the disease of modern civilization.[2] The objective of this review article is to present the most important clinical and epidemiological aspects of allergic rhinitis and their therapeutic implications, based on data presented in studies published within the last thirty years and available from Medline, the Latin American and Caribbean Health Sciences Literature database and HighWire.

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Epidemiological aspects

The collaborative study known as the International Study on Asthma and Allergies in Childhood (ISAAC) has shown that there is wide variation in the prevalence of allergic rhinitis. In addition, an increase in prevalence was observed in the various regions where the study was conducted two or more times using the same methodology. Worldwide, the prevalence of symptoms associated with allergic rhinoconjunctivitis, during the 12 months prior to the application of the standard questionnaire, ranged from 2.2 to 14.6% among children aged 6-7 years, and from 4.5 to 45.5% among adolescents aged 13-14 years.[3]

For the adult population, the questionnaire European Community Respiratory Health Survey was conceived in order to standardize the epidemiological investigation of asthma-related respiratory symptoms and the presence of allergies, as well as the use of treatment in adults aged 20-44 years. Through the use of this questionnaire, the prevalence of rhinitis symptoms in Europe was determined to be 21%.[4]

The ISAAC results for Brazil showed that the mean prevalence of allergic rhinitis-related symptoms was 29.6% among adolescents and 25.7% among school children. Regarding active asthma-related symptoms, the mean prevalence was 19% and 24.3% among adolescents and school children, respectively.[5] Brazil belongs to a group of countries that present the highest prevalence rates of asthma and allergic rhinitis in the world.[3]

Allergic rhinitis can be considered the most prevalent of chronic respiratory diseases, and, although it is not among the most severe diseases, it is a worldwide public health problem, since it affects the quality of life of the patients and makes asthma control difficult. Its prevalence has increased over the years and is probably underestimated, since many individuals do not recognize it as a disease and do not seek medical attention. However, health professionals also frequently ignore rhinitis. Nevertheless, allergic rhinitis is one of the ten leading reasons for seeking primary health care.[6]

Association with asthma

Allergic rhinitis presents a direct relationship with asthma, and the ISAAC study showed that approximately 80% of pediatric patients with asthma have allergic rhinitis. Allergic rhinitis is not only more difficult to control than asthma but also interferes with the control of asthma itself.[7] It might be said that asthma and allergic rhinitis are different manifestations of the same disease, since they share epidemiological and pathophysiological aspects, as well as similar treatment, which reinforces the concept of 'one airway, one disease'.[8]

Based on evidence that asthma and rhinitis are manifestations of the same disease, specialists from various countries, with the support of the World Health Organization, prepared an extensive review entitled Allergic Rhinitis and Its Impact on Asthma (ARIA). The objectives of the publication were to update the knowledge of health professionals on allergic rhinitis, to emphasize the impact that allergic rhinitis has on asthma, to provide evidence-based data on the available diagnostic and therapeutic methods, to assess the magnitude of the problem in developing countries and to implement lines of treatment, as well as to suggest that patients with persistent allergic rhinitis be tested for asthma and vice-versa.[1]

In a recently published editorial, Cruz[9] stated that the approach to allergic rhinitis and asthma has gone through three phases: dissociation, in which they were approached in a dissociated way, confirming Togias[10] and his analysis that the respiratory system was the victim of the fragmentation of medicine into medical specializations; causality, in which it was believed that allergic rhinitis could be related to asthma; and identity, in which it was understood that it was a single systemic disease, and that diagnosis and control should be integrated.

The symptoms of allergic rhinitis, regardless of the presence of asthma, worsen the quality of life of the patients, since they can lead to fatigue, headache, attention deficit and learning difficulties, as well as to other systemic disturbances such as sleep apnea. In the pediatric population, allergic rhinitis can lead to attention deficit and hyperactivity. Juniper et al. developed and assessed quality of life questionnaires to be applied in patients with allergic rhinoconjunctivitis, with the aim of evaluating the problems experienced by adults in their daily routine, and found that the use of these questionnaires, with separate versions for children and adolescents, can be useful in epidemiological and clinical studies, as well as in patient monitoring.[11-13] In addition, it is important to emphasize that allergic rhinitis is one of the causes of the mouth breathing

syndrome, which can have additional postural and cardiac repercussions.

Diagnostic aspects

Clinical diagnosis

An appropriate clinical examination can easily identify the signs of rhinitis (hypertrophy/pallor of the inferior turbinates and hyaline secretion), which are associated with epithelial dysfunction, as well as dysfunction of the vessels, glands and nerves. In addition, infiltration by inflammatory cells, inflammatory mediators and cytokines impairs the heating, humidification and filtration of inspired air.[14]

Symptoms can include paroxysmal sneezing, nasal pruritus/obstruction, rhinorrhea, oropharyngeal pruritus, hyperemia and ocular pruritus. It is of note that there can be comorbidities, recurrent serous otitis media and chronic rhinosinusitis.

Concomitant wheezing can suggest an association with asthma and, in such situations, the performance of pulmonary function tests with a bronchodilator test is indispensable to assessing subclinical asthma.[15]

Classically, allergic rhinitis was classified as seasonal or perennial. However, these categories do not correspond to the situation in Brazil, nor do they make it easier to treat the patient.

The ARIA initiative classifies allergic rhinitis as either intermittent or persistent and as either mild or moderate/severe (Chart 1), based on the frequency and intensity of the symptoms and their impact on the quality of life of the patient.[1] A study conducted in France,[16] involving over 2600 doctors and 6500 patients with allergic rhinitis, demonstrated that 43.7% of the patients diagnosed by their doctors as having seasonal rhinitis presented persistent symptoms, that is, for over four days in the week and over four consecutive weeks in the year, whereas 44.6% of the patients previously diagnosed with perennial rhinitis actually presented intermittent symptoms. It was concluded that the classification of the ARIA initiative is of great importance in clinical practice, since it correlates with the treatment option.

The use of clinical scores can be useful in the physician routine for the diagnosis and follow-up treatment of patients with allergic rhinitis. Wilson et al.,[17] for example, described a scoring system in which scores from 0 to 3 were attributed to each of six signs/symptoms (nasal obstruction, rhinorrhea, sneezing, nasal pruritus, oropharyngeal pruritus and ocular pruritus) according to their intensity. Therefore, a score of 0 indicates the absence of a certain sign/symptom, a score of 1 indicates that the sign/symptom is mild, well tolerated, and does not interfere with the sleep or daily activities of the individual, a score of 2 indicates that the sign/symptom assessed causes discomfort and interferes only with those activities that demand high concentration, and a score of 3 indicates that the sign/symptom assessed is of strong intensity and causes discomfort to the point of preventing sleep and interfering with the performance of daily activities. Points are totaled, and the total can vary from 0 to 18. A total score of 1-6 indicates mild allergic rhinitis, a total score of 7-12 indicates moderate rhinitis, and a total score of 13-18 indicates severe allergic rhinitis.

Chart 1 - Classification of allergic rhinitis according to the Allergic Rhinitis and its Impact on Asthma initiative.[1]

Intermittent
Duration of the symptoms:
<4 days a week
<4 weeks
Mild
All of the criteria below:
Normal sleep
Normal daily activities, sports and recreation
Normal activities at school and work
Normal activities at school and work
No relevant symptoms
Persistent
Duration of the symptoms:
≥4 days a week
≥4 weeks
Moderate to severe
One or more of the criteria below:
Disturbed sleep
Interference with daily activities, sports and recreation
Difficulties in school and at work
Relevant symptoms

Complementary tests

In mild intermittent rhinitis, when the clinical chart is unequivocal and response to treatment is

good, complementary tests are not necessary. When a patient has moderate/severe allergic rhinitis, skin tests for immediate hypersensitivity to allergens are indicated in order to investigate allergy. If there is no good response to treatment, rhinoscopy or an otorhinolaryngological examination should be performed whenever possible.

Immediate skin tests

Immediate skin tests adequately standardized and well performed are used in the investigation of atopy. They are widely used due to their simplicity and are typically available in most specialized clinics, although they are not available in basic health care clinics. It is important to bear in mind that responsiveness to the test varies considerably among individuals. Tests should always include a negative control that is typically saline solution and a positive control, which is histamine (1 mg/mL). Immediate skin tests indicate whether or not there is sensitization, in accordance to what is suspected from the clinical history, and have great educational value to the patient when they are well conducted. The aeroallergens that present the greatest prevalence of positivity in Brazil are those related to mites (*Blomia tropicalis* and *Dermatophagoides pteronyssinus*), cockroaches (*Blatella germanica* and *Periplaneta americana*) and fungi (*Alternaria* spp. and others).[18]

Factors related to the patient, extraction and technique can interfere with the performance of the test. Special attention should be given to the standardization of allergens and to maintaining an appropriate distance between antigens in terms of placement. The performance of the test should be postponed if severe systemic reactions develop or if there is a consumption of specific IgE for a certain antigen. False-negative results can occur.[18]

Nasal cytology

Nasal cytology, using the adequate technique, can, in exceptional cases, contribute to the differential diagnosis of the most common causes of persistent rhinitis: allergic rhinosinusitis; non-allergic rhinosinusitis with eosinophilia; and viral infectious or bacterial rhinosinusitis.

Nasal cytology can be useful in the differential diagnosis between allergic rhinitis and other clinical forms of chronic rhinitis, such as vasomotor and infectious rhinitis. It should be noted that it is a non-invasive affordable method. The difficulty encountered is the lack of standardization of nasal cytology techniques available in clinical practice (swab smears, sneeze material or curettage), and even cytology of nasal lavage presents techniques from several collections, which are often used as research instruments only. The simplified technique of quantitative nasal cytology described by Cruz et al. begins with nasal lavage, after which the cells are counted, and cytocentrifugation slides are used for differential counting. It is a low-cost technique and can help in differential diagnosis and even in the evaluation of the response to the treatment of vasomotor rhinitis. Due to the lack of technique standardization, this procedure is limited to the field of research.[7,19]

Total IgE and specific IgE

Levels of IgE and eosinophilia in peripheral blood and nasal secretion are indirect indicators of atopy and have low sensitivity and specificity. The presence of intestinal helminthiases, which still exist in Brazil, further limits the diagnostic value of elevated levels of total IgE in peripheral blood. For appropriate interpretation, determination of total IgE levels should accompany that of specific IgE levels.

Total serum IgE levels have been used in various conditions. As a means of screening for atopic conditions, it is one of the tests typically performed. However, an increase in total serum IgE is not specific of atopy and can represent other conditions, such as parasite infection. In addition, it is important to mention that 35 to 50% of patients with allergic rhinitis present normal total IgE levels, whereas 20% of non-atopic individuals present high total IgE levels.[7,20]

The determination of specific IgE provides quantitative data and complements the results of skin tests when necessary. The advantage of determining specific IgE is that it can be performed through blood collection and does not result in any risk to the patient. In addition, with 1 mL of blood, the levels of up to 16 allergens can be determined, with much less patient discomfort. In addition, antihistamines do not affect the results, and determination of specific IgE can be the test of choice for suckling infants. However, specific IgE levels can be affected by increased polyclonal total IgE, similar to what

occurs with helminthiases, and the test for specific IgE is much more expensive than are immediate skin tests.

Rhinoscopy

For patients presenting persistent allergic rhinitis that is refractory to treatment, video-assisted nasopharyngoscopy should be requested in order to investigate structural alterations as the cause of upper airway obstruction, as in the cases of adenoid tissue growing toward choanae, which cause significant nasal obstruction children whose cavum X-rays do not show alterations consistent with the diagnosis. In addition, it is useful in the evaluation and diagnosis of alterations confirmed on X-rays, such as isolated polyps or nasal polyposis. This test provides a clear view of the upper airways, detailing the middle and upper meatus, sphenoidal recess and posterior nasopharynx, as well as oropharyngeal and laryngeal structures. Rhinoscopy can be performed outside the hospital. Santos et al. conducted this test in 368 children aged 6-13 in the school, without the need for restraints or sedation of any kind.[7,21]

Acoustic rhinometry, rhinomanometry and peak nasal inspiratory flow

The evaluation of patients with allergic rhinitis is typically performed through anamnesis and clinical examination, with the objective of identifying the signs and symptoms already described. Although this will suffice in most cases, objective measures should, whenever possible, be added to the diagnosis and evaluation of the therapeutic response. The use of objective measures is even more important in clinical research, in which the comparison of quantitative variables is desirable. Nasal obstruction is one of the symptoms that cause the greatest patient discomfort and can be quantified in the laboratory through acoustic rhinometry or rhinomanometry, as well as in physician offices and even in the home of the patient through the use of the peak nasal inspiratory flow (PNIF) meter (Figure 1).

Acoustic rhinometry analyzes ultrasound waves reflected in the nasal cavity in order to calculate cross-sectional areas at any point of this cavity, as well as determine the nasal volume, and it is an objective method of measuring nasal obstruction in a painless, easily-performed and reproducible manner.[22] However, rhinomanometry consists of a dynamic test that allows evaluation of nasal patency through objective measurement of the nasal airway performed through the transnasal pressure-flow relationship. However, these tests are difficult to access and have to be performed and analyzed by otorhinolaryngologists. In addition, they are restricted to research.[23]

Figure 1 - Peak nasal inspiratory flow meter.

The measure of the PNIF is an efficacious, simple, economical and portable alternative to rhinomanometry. Response to treatment in patients with allergic rhinitis assessed through the measurement of PNIF at home was studied in 38 patients without asthma, with a mean age of 30 years.[24] Patients were divided into three groups, which received different treatments for allergic rhinitis (cetirizine+placebo, or cetirizine+mometasone, or cetirizine+montelukast) for four weeks. The PNIF was measured twice daily, in the morning and at night. In addition, patients filled out clinical score tables daily, reporting the occurrence of symptoms and their impact on their daily activities. Nasal symptoms correlated significantly ($p < 0.01$) with daily PNIF measurements in the morning ($r = -0.51$) and at night ($r = -0.56$), as did the impact of the symptoms on daily activities with PNIF in the morning ($r = -0.42$) and at night ($r = -0.48$). In the study, it was concluded that PNIF is an objective and useful measurement for short-term evaluation of response to allergic rhinitis treatment.

Some studies have demonstrated a good correlation between PNIF and rhinomanometry.[25] One study that compared rhinomanometry to PNIF reported a good, statistically significant, correlation between the two methods ($p < 0.01$), and the authors concluded that PNIF is an affordable technique, easily performed and presenting a good correlation with rhinomanometry.[26]

It should be noted that PNIF results depend on the cooperation of the patient and on the impression of the examiner who determines whether the patient performed a given maneuver appropriately. In addition, another limitation is the fact that it evaluates only one of the symptoms of allergic rhinitis, which is nasal obstruction. However, since it is easy to use, it can be very useful in the daily routine of clinicians and pediatricians, since the remaining symptoms can be objectively assessed using clinical scores and quality of life questionnaires.[27]

Nasal nitric oxide

Nitric oxide is a normal component of the air exhaled in human breathing and its biological functions consist of the participation in the immune system and in neurotransmission, as well as in vasodilation and bronchodilation. Since it is a marker of eosinophilic inflammation, it is increased in patients with allergic rhinitis. The inclusion of nitric oxide testing in the diagnosis and follow-up evaluation of various pulmonary diseases, especially asthma, has been described. The use of this method is currently limited to the field of research and, unfortunately, is not available at most Brazilian referral centers.[28-31]

Therapeutic aspects

General measures

The inclusion of general measures is an important phase in the management of patients with allergic rhinitis. Cigarette smoke, the principal domestic pollutant, can have harmful effects on the respiratory epithelium and is a risk factor for respiratory disease, especially allergic rhinitis and asthma.[32,33]

Pollution in large cities, global warming and the apparent relationship between air pollution and respiratory diseases (despite the methodological difficulties in confirming such a relationship) are relevant facts that have drawn the attention of health authorities in recent years. The high prevalence of allergic rhinitis in large centers illustrates the damage that pollution can cause to the nasal mucosa.[34]

Regarding compliance to environmental control measures, the literature demonstrates a variation from 17 to 42% in Brazilian and international studies. These findings confirm that environmental control measures are not always carried out, socioeconomic and cultural factors being implicated in this noncompliance. It is noteworthy that, despite the low compliance and conflicting results on the efficacy of individual measures, preventing contact with allergens that irritate the respiratory system should be recommended.[35,36]

Studies demonstrate that exposure to allergens in the first years of life results in decreased pulmonary function, increased bronchial hyperresponsiveness and increased exhaled nitric oxide, accompanied by persistent influx of eosinophils and T lymphocytes into the small airways. Recent studies have tried to associate environmental exposure, genetic predisposition and allergic diseases. In contrast to studies involving adults, most studies involving children suggest that environmental control measures are somewhat beneficial. In occupational asthma, the removal of the allergen is clearly associated with improved prognosis.[37,38]

The use of nasal isotonic or hypertonic saline solution in allergic rhinitis is controversial. Some recent studies suggest that the use of hypertonic saline solution (3%) can constitute an additional therapeutic option in patients with allergic rhinitis. Garavelo et al. conducted a randomized study involving 20 patients aged 6-12 years, in which 10 received hypertonic saline solution (3%) three times a day for six weeks, and 10 did not receive any nasal topical treatment.[39,40] Symptom scores were registered daily, and the use of oral antihistamines was allowed for symptom relief. Patients allocated to the group that used the hypertonic solution presented lower use of antihistamines and lower mean symptom scores. Other studies have not found favorable results for hypertonic saline solution. It is possible that nasal irrigation with hypertonic saline solution is more useful in nasal surgery. Adam et al. found no improvement in symptoms or duration of rhinitis.[41] In clinical practice, some children complain that nasal irrigation with hypertonic saline solution causes local burning. However, in the literature reviewed, we did not find any data related to the limitation of its use in any age bracket.

Nasal hygiene can be performed through nasal instillation of saline solution, using silicone syringes molded to the nasal cavity. In children who resist this administration, the presentation in spray can be an viable alternative. It is a simple and affordable adjuvant form of treatment, and it reduces the use of other medications, including antibiotics.

Therefore, it should always be recommended.[42,43] There is no data in the literature to suggest that nebulization with saline solution only or the use of vaporizers is efficacious, and it should be noted that cold saline solution can cause nasal or bronchial hyperreactivity.

Some studies confirm that certain preservatives used in nasal solutions, such as benzalkonium chloride, can cause mucosa irritation, thus aggravating rhinosinusitis. However, confirmation of presumed hazardous effects of these products in clinical practice calls for further studies.[43]

Drug therapy

The objective of drug therapy in allergic rhinitis is to promote effective prevention or symptom relief as safely and effectively as possible. Removal or prevention of contact with allergens is always recommended. However, drug therapy is often necessary. The use of simple measures such as nasal lavage with saline solution or the addition of topical or oral antihistamine, together with a low dose of intranasal corticosteroid, can help control allergic rhinitis and chronic rhinosinusitis.[44,45]

Antihistamines

Allergic rhinitis, like all allergic reactions, can present two phases. The first phase, known as the immediate phase, occurs within minutes after the antigenic stimulus, and the second phase, known as the late, or inflammatory, phase, occurs within four to eight hours after the stimulus. They both present release of chemical mediators, and, in the immediate phase, histamine is the principal mediator released, through the degranulation of mastocytes and basophils.[46]

Histamine is the principal mediator responsible for the appearance of characteristic symptoms of allergic rhinitis, such as sequential sneezing, rhinorrhea and nasal pruritus/obstruction. It was first identified in the laboratory by Windaus and Vogt in 1907, and, since then, studies have been initiated in search of drugs to prevent its effects.[46,47]

Histamine receptors can be classified into four groups (H1, H2, H3 and H4), which differ from one another by their expression, transduction of signal and function, the last being less important. All histamine receptors belong to the super family of G protein-coupled receptors. The G-protein receptor at position H1, encoded by chromosome 3, is responsible for various symptoms of allergic diseases, such as rhinorrhea, bronchoconstriction and contraction of gastrointestinal muscles.[46,47]

With the advances in molecular pharmacology, H1 antihistamines have been reclassified as reverse agonists rather than H1-receptor antagonists. They are G protein-coupled H1 receptors, in which active and inactive conformations coexist in balance. The activation degree of the receptor in the absence of histamine is a constitutive activity, and histamine acts as an agonist by combination and stabilization of the activated conformation of H1 receptor, with preponderance of the active state. The reverse agonist has greater affinity for the inactive state, which leads to the stabilization of the receptor and, consequently, to the induction of the inactive state.[46,47]

Antihistamines have been synthesized and introduced in the treatment of allergic rhinitis for over 50 years, the so-called first generation, whose principal adverse effect is drowsiness. They are available on the market, and among those provided by the Unified Health System are hydroxyzine, derived from piperazines, and dextrochloropheniramine, derived from alkylamines.

From the 1970s onward, research has led to the discovery of new antihistamines with fewer side effects, such as loratadine, cetirizine, levocabastine, azelastine, epinastine, ebastine and fexofenadine.[47,48]

Therefore, H1 antihistamines can be categorized as classical (first generation or sedating) or nonclassical (second generation or little sedating). The difference among them lies in the fact that classical H1 antihistamines have a simpler chemical structure, are liposoluble and cross the blood-brain barrier, causing drowsiness, fatigue, learning difficulties, mental confusion and appetite alterations.

Such effects are less intense with second generation H1 antihistamines, which have a more complex chemical structure and do not cross the blood-brain barrier as much, thus causing less drowsiness.[48] Second generation H1 antihistamines are preferable due to their more favorable efficacy/safety profile.

Intranasal corticosteroids

Intranasal corticosteroids have constituted the treatment of choice for persistent forms of allergic rhinitis since the early 1990s. Systemic side effects

are undetectable when used in the recommended dose. In addition, the use of a daily morning dose has minimized the potential impact on the hypothalamic-pituitary-adrenal (HPA) axis.[48]

The effect of intranasal corticosteroids is directed toward the reduction of the inflammation of the nasal mucosa, leading to improvement of nasal obstruction, pruritus and sneezing, as well as of rhinorrhea. It should be noted that the ease of administration contributes to greater compliance to treatment.[45,48]

The prolonged use of intranasal corticosteroids and the need to combine intranasal corticosteroids with steroids using other routes of administration increase the possibility of suppression of the HPA axis and of stunted growth in children. In particular, in patients with allergic rhinitis and asthma who receive topical nasal and pulmonary corticosteroids, it would be advisable to combine the corticosteroids with another group of drugs, aiming at reducing the total topical respiratory corticosteroid load. It is important to note that growth surveillance efforts should be redoubled in these patients. Regarding local side effects, local irritation, bleeding and septal perforation are rarely seen.[45]

Due to its good anti-inflammatory effect, low absorption and first pass metabolism, second generation topical corticosteroids are the treatment of choice in persistent allergic rhinitis.

From the 1970s onward, with the introduction of beclomethasone dipropionate, intranasal corticosteroids have been successfully used in patients with allergic rhinitis.[49-51] Corticosteroids available for nasal use, in Brazil, include beclomethasone, triamcinolone, budesonide, fluticasone and mometasone, the last two being efficacious in a daily single-dose regimen. The aqueous solution is better tolerated, since it causes less irritation in the mucosa, as well as since it fixes better and contains no propellants.

It should be noted that first generation corticosteroids such as dexamethasone and betamethasone present systemic effects when administered intranasally and are therefore contra-indicated.

Other therapeutic options

Disodium cromoglycate

Disodium cromoglycate, which stabilizes mastocytes, can be used in the treatment of allergic rhinitis and presents minimum side effects. However, its efficacy is modest. In a study that evaluated the efficacy of this medication, it was observed that cromoglycate relieved rhinorrhea and nasal pruritus when compared to a placebo, although the difference between the group that received the medication and the group that received the placebo was not statistically significant. However, wheezing and nasal obstruction were significantly relieved after the administration of cromoglycate.[52]

One of the limitations of the use of disodium cromoglycate is the need to administer it four times a day, leading to less compliance over the long term. It is interesting that the use of disodium cromoglycate can be an option in milder cases or when it is desirable to withdraw steroids in a patient who responded well but who has been using the drug for a long time, and who might or might not do well without the medication.

Antileukotrienes

Montelukast is a type I cysteine selective leukotriene receptor antagonist found in human airways. It is known that leukotrienes act as inflammatory mediators and play an important role in the physiopathology of allergic rhinitis.

Clinical studies have demonstrated that the use of oral montelukast in the dose of 10 mg once a day (for adults) is well tolerated and brings significant relief of diurnal and nocturnal nasal symptoms, in addition to ocular symptoms of allergic rhinitis. The cost of the medication is an obstacle to part of the population, and its efficacy as monotherapy is low, being more often used as an adjuvant treatment in patients who do not respond satisfactorily to antihistamines and intranasal corticosteroids.[53,54]

Anti-IgE antibodies

The production of IgE is the principal mechanism of hypersensitivity reactions in patients with allergic rhinitis. It interacts with low and high affinity receptors. The use of monoclonal anti-IgE antibody has not been approved for the treatment of allergic rhinitis, although clinical trials have revealed its efficacy.[55,56]

Immunotherapy

Immunotherapy should be considered in cases of moderate/severe persistent allergic rhinitis that do

not satisfactorily respond to conventional therapy. It consists of a technique in which small quantities of allergen extract are periodically injected in the subcutaneous tissue over the course of a few years, aiming at minimizing the symptoms caused by the exposure to these allergens.[57]

One of the principal obstacles to the success of the immunotherapy treatment is the fact that these patients are usually allergic to more than one type of substance, thus making it difficult to identify the allergen to be used in the vaccine.

Controlled studies have shown that immunotherapy is efficacious in patients with hypersensitivity to insect bites, as well as in patients with allergic rhinoconjunctivitis and asthma.[58] The greatest risk in the use of specific immunotherapy is anaphylaxis. Therefore, patients who are submitted to immunotherapy need rigorous supervision by an experienced professional so that any prodromal manifestations of anaphylaxis are recognized and promptly treated. These patients are also at risk of asthma exacerbation.

Nasal corticosteroid inhalation for the simplified treatment of asthma and allergic rhinitis

Asthma and allergic rhinitis present direct morphological, epidemiological, pathophysiological and clinical interrelationships. Therefore, they have begun to be considered manifestations of the same pathological process: contiguous allergic inflammation of the airways. The efficacy of the unified treatment strategy, that is, nasal corticosteroid inhalation for the treatment of allergic rhinitis and asthma, which consists of the use of nasal metered-dose inhalers, with the aid of a facial mask attached to a large volume valve spacer, was demonstrated in two recent clinical trials.[58,59] Such findings indicate a reduction in costs and side effects, as well as the improvement of treatment compliance among patients with asthma and persistent allergic rhinitis.

Final comments

Allergic rhinitis presents high prevalence in Brazil, confirmed by recent epidemiological studies. The relationship with asthma is clear, and the approach to treatment should be integrated. In most cases, the clinical diagnosis suffices and can be confirmed by allergy tests. The use of antihistamines, preferably non-sedating, when necessary, is an alternative in intermittent and mild forms of allergic rhinitis. Intranasal corticosteroids should be reserved for use in patients with the persistent moderate or severe forms, which often require adjuvant treatment with antihistamines and, occasionally, with nasal decongestants.

The World Health Organization Global Alliance against Respiratory Diseases initiative, recently launched in Brazil and co-sponsored by the Brazilian National Ministry of Health, is aimed at improving the prevention and treatment of chronic respiratory diseases, including allergic rhinitis.

References

1. Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108(5 Suppl):S147-S334.
2. Holgate ST, Broide D. New targets for allergic rhinitis--a disease of civilization. Nat Rev Drug Discov. 2003;2(11):902-14.
3. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733-43. Erratum in: Lancet. 2007;370(9593):1128.
4. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J. 2004;24(5):758-64.
5. Solé D, Wandalsen GF, Camelo-Nunes IC, Naspitz CK; ISAAC - Brazilian Group. Prevalence of symptoms of asthma, rhinitis, and atopic eczema among Brazilian children and adolescents identified by the International Study of Asthma and Allergies in Childhood (ISAAC) - Phase 3. J Pediatr (Rio J). 2006;82(5):341-6.
6. International Consensus Report on the diagnosis and management of rhinitis. International Rhinitis Management Working Group. Allergy. 1994;49(19 Suppl):1-34.
7. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet. 1998;351(9111):1225-32.
8. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol. 1998;81(5 Pt 2):478-518.
9. Cruz AA. The 'united airways' require an holistic approach to management. Allergy. 2005;60(7):871-4.
10. Togias A. Rhinitis and asthma: evidence for respiratory system integration. J Allergy Clin Immunol. 2003;111(6):1171-83; quiz 1184.
11. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality

of Life Questionnaire. J Allergy Clin Immunol. 1999;104(2 Pt 1):364-9.
12. Juniper EF, Rohrbaugh T, Meltzer EO. A questionnaire to measure quality of life in adults with nocturnal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2003;111(3):484-90.
13. Juniper EF, Ståhl E, Doty RL, Simons FE, Allen DB, Howarth PH. Clinical outcomes and adverse effect monitoring in allergic rhinitis. J Allergy Clin Immunol. 2005;115(3 Suppl 1):S390-S413.
14. Raphael GD, Baraniuk JN, Kaliner MA. How and why the nose runs. J Allergy Clin Immunol. 1991;87(2):457-67.
15. Plaut M, Valentine MD. Clinical practice. Allergic rhinitis. N Engl J Med. 2005;353(18):1934-44.
16. Demoly P, Allaert FA, Lecasble M, Bousquet J; PRAGMA. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). Allergy. 2003;58(7):672-5.
17. Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. A comparison of topical budesonide and oral montelukast in seasonal allergic rhinitis and asthma. Clin Exp Allergy. 2001;31(4):616-24.
18. Naspitz CK, Solé D, Jacob CA, Sarinho E, Soares FJ, Dantas V, et al. [Sensitization to inhalant and food allergens in Brazilian atopic children by in vitro total and specific IgE assay. Allergy Project--PROAL] [Article in Portuguese] J Pediatr (Rio J). 2004;80(3):203-10.
19. Cruz AA, Carvalho EM. Citologia nasal quantitativa simplificada (CNQS). Rev Bras Alerg Imunopatol. 1997;20(2):56-74.
20. Medeiros D, Silva AR, Rizzo JA, Motta ME, Oliveira FH, Sarinho ES. Total IgE level in respiratory allergy: study of patients at high risk for helminthic infection. J Pediatr (Rio J). 2006;82(4):255-9.
21. Santos RS, Cipolotti R, D'Ávila JS, Gurgel RQ. Escolares submetidos a videonasofaringoscopia na escola: achados e aceitação. J Pediatr (Rio J). 2005;81(6):443-6.
22. Hilberg O, Jackson AC, Swift DL, Pedersen OF. Acoustic rhinometry: evaluation of nasal cavity geometry by acoustic reflection. J Appl Physiol. 1989;66(1):295-303..
23. Chan KO, Huang ZL, Wang DY. Acoustic rhinometric assessment of nasal obstruction after treatment with fluticasone propionate in patients with perennial rhinitis. Auris Nasus Larynx. 2003;30(4):379-83.
24. Wilson A, Dempsey OJ, Sims EJ, Coutie WJ, Paterson MC, Lipworth BJ. Evaluation of treatment response in patients with seasonal allergic rhinitis using domiciliary nasal peak inspiratory flow. Clin Exp Allergy. 2000;30(6):833-8.
25. Wihl JA, Malm L. Rhinomanometry and nasal peak expiratory and inspiratory flow rate. Ann Allergy. 1988;61(1):50-5.
26. Holmström M, Scadding GK, Lund VJ, Darby YC. Assessment of nasal obstruction. A comparison between rhinomanometry and nasal inspiratory peak flow. Rhinology. 1990;28(3):191-6.
27. Prescott CA, Prescott KE. Peak nasal inspiratory flow measurement: an investigation in children. Int J Pediatr Otorhinolaryngol. 1995;32(2):137-41.
28. Chatkin JM, Djupesland PER, Quian W, Haight J, Zamel N. Óxido nítrico exalado no diagnóstico e acompanhamento das doenças respiratórias. J Bras Pneumol. 2000;26(1):36-43.
29. Baraldi E, Azzolin NM, Carrà S, Dario C, Marchesini L, Zacchello F. Effect of topical steroids on nasal nitric oxide production in children with perennial allergic rhinitis: a pilot study. Respir Med. 1998;92(3):558-61.
30. Arnal JF, Didier A, Rami J, M'Rini C, Charlet JP, Serrano E, et al. Nasal nitric oxide is increased in allergic rhinitis. Clin Exp Allergy. 1997;27(4):358-62.
31. Kharitonov SA, Rajakulasingam K, O'Connor B, Durham SR, Barnes PJ. Nasal nitric oxide is increased in patients with asthma and allergic rhinitis and may be modulated by nasal glucocorticoids. J Allergy Clin Immunol. 1997;99(1 Pt 1):58-64.
32. Mello PR, Pinto GR, Botelho C. Influência do tabagismo na fertilidade, gestação e lactação. J Pediatr (Rio J). 2001;77(4):257-64.
33. Prietsch SOM, Fisher GB, César JA, Fabris AR, Mehama H, Ferreira THP et al. Doença aguda das vias aéreas inferiores em menores de cinco anos: influência do ambiente doméstico e do tabagismo materno. J Pediatr (Rio J). 2002;78(5):415-22.
34. Sole D. Poluição e doenças respiratórias. J Pediatr (Rio J). 1997;73(3):143-4.
35. Arruda LK. Controle ambiental na asma: recomendar ou não recomendar, eis a questão! J Bras Pneumol. 2005;31(1):3-4.
36. Jentzsch NS, Camargos PAM, Melo EM. Adesão às medidas de controle ambiental na asma. Rev bras alergia imunopatol. 2002;25(6):192-199.
37. Marinho S, Simpson A, Custovic A. Allergen avoidance in the secondary and tertiary prevention of allergic diseases: does it work? Prim Care Respir J. 2006;15(3):152-8.
38. Gore RB, Curbishley L, Truman N, Hadley E, Woodcock A, Langley SJ, et al. Intranasal air sampling in homes: relationships among reservoir allergen concentrations and asthma severity. J Allergy Clin Immunol. 2006;117(3):649-55.
39. Garavello W, Romagnoli M, Sordo L, Gaini RM, Di Berardino C, Angrisano A. Hypersaline nasal irrigation in children with symptomatic seasonal allergic rhinitis: a randomized study. Pediatr Allergy Immunol. 2003;14(2):140-3.
40. Garavello W, Romagnoli M, Gaini RM. Hypertonic or isotonic saline for allergic rhinitis in children. Pediatr Allergy Immunol. 2005;16(1):91-2.
41. Adam P, Stiffman M, Blake RL Jr. A clinical trial of hypertonic saline nasal spray in subjects with the common cold or rhinosinusitis. Arch Fam Med. 1998;7(1):39-43.
42. Papsin B, McTavish A. Saline nasal irrigation: Its role as an adjunct treatment. Can Fam Physician. 2003;49:168-73.
43. Passàli D, Damiani V, Passàli FM, Passàli GC, Bellussi L. Atomized nasal douche vs nasal lavage in acute viral rhinitis. Arch Otolaryngol Head Neck Surg. 2005;131(9):788-90.
44. Scadding GK. Corticosteroids in the treatment of pediatric allergic rhinitis. J Allergy Clin Immunol. 2001;108(1 Suppl):S59-S64.
45. II Consenso Brasileiro sobre Rinites. Rev Bras Alerg Imunopatol. 2006;29(1):29-59.
46. Bakker RA, Schoonus SB, Smit MJ, Timmerman H, Leurs R. Histamine H(1)-receptor activation of nuclear factor-kappa B: roles for G beta gamma- and G alpha(q/11)-subunits in constitutive and agonist-mediated signaling. Mol Pharmacol. 2001;60(5):1133-42.
47. Leurs R, Church MK, Taglialatela M. H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. Clin Exp Allergy. 2002;32(4):489-98..
48. Stempel D. Improving the value of care for allergic rhinitis. Drug Benefit Trends 1996;8(1):11-2.
49. Juniper EF, Ståhl E, Doty RL, Simons FE, Allen DB, Howarth PH. Clinical outcomes and adverse effect monitoring in

allergic rhinitis. J Allergy Clin Immunol. 2005;115(3 Suppl 1):S390-S413.
50. Mygind N. Local effect of intranasal beclomethasone dipropionate aerosol in hay fever. Br Med J. 1973;4(5890):464-6.
51. International Consensus Report (ICR) of the diagnosis and management of rhinitis. Allergy 1994;49(1):1-36.
52. Meltzer EO; NasalCrom Study Group. Efficacy and patient satisfaction with cromolyn sodium nasal solution in the treatment of seasonal allergic rhinitis: a placebo-controlled study. Clin Ther. 2002;24(6):942-52.
53. Nayak AS, Philip G, Lu S, Malice MP, Reiss TF; Montelukast Fall Rhinitis Investigator Group. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. Ann Allergy Asthma Immunol. 2002;88(6):592-600.
54. Ribeiro JD, Toro AA, Baracat EC. Antileukotrienes in the treatment of asthma and allergic rhinitis. J Pediatr (Rio J). 2006;82(5 Suppl):S213-21.
55. Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA. 2001;286(23):2956-67.
56. Sarinho E, Cruz AA. Anti-IgE monoclonal antibody for the treatment of the asthma and other manifestations related to allergic diseases. J Pediatr (Rio J). 2006;82(5 Suppl):S127-S32.
57. Wilson DR, Torres Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis. Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD002893. DOI: 10.1002/14651858.CD002893.
58. Camargos PA, Rodrigues ME, Lasmar LM. Simultaneous treatment of asthma and allergic rhinitis. Pediatr Pulmonol. 2004;38(3):186-92.
59. Camargos P, Ibiapina C, Lasmar L, Cruz AA. Obtaining concomitant control of allergic rhinitis and asthma with a nasally inhaled corticosteroid. Allergy. 2007;62(3):310-6.