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SPECIAL ARTICLE

Allergic Rhinitis and Its Impact on Asthma: An Evidence-Based Treatment Strategy for Allergic Rhinitis

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SUMMARY **The overall pathogenic view of respiratory allergy has deeply changed and evolved during the last ten years. Much emphasis has been laid to the relationship between rhinitis and asthma, which is between the upper and the lower respiratory airways. This strict link has been evidenced through clinical observations and epidemiological studies and also on the basis of immunological observations and outcomes of therapy. Furthermore, the frequent co-existence of rhinitis and asthma (up to 80 percent of asthmatic patients have co-existing allergic rhinitis, while up to 40 percent of allergic rhinitis patients have asthma, the coexistence of sinusitis and asthma, the presence of rhinitis as a risk factor for developing asthma, further emphasize this link and together lead to the operative definition of *Allergic Rhinobronchitis* or, *United Airways Disease (UAD)*. The strict link existing between upper and lower respiratory tract can be also regarded from the viewpoint of therapeutical outcomes.**

The more detailed knowledge of the intricate mechanisms sustaining allergic inflammation in the respiratory tract (i.e. antigen presentation, cytokines, chemokines and adhesion molecules) has clarified the functional relationships between nose and lung. Thus allergic rhinitis or asthma is not a disease confined to a specific target organ, but rather a disorder of the whole respiratory tract, with a range of clinical manifestations, leading to relevant diagnostic and therapeutic implications as indicated in the WHO Initiative ARIA, the first evidence-based guideline emphasizing the impact of allergic rhinitis on asthma and where a step-wise treatment strategy targeting both the upper and lower airway effectively has been proposed. Moreover, the use of novel potential therapies that target both rhinitis and asthma like antileukotrienes or anti-IgE are indeed a future strategy.

Allergic rhinitis is an IgE-mediated allergic inflammation of the nose occurring due to the interaction of allergen with IgE and resulting in the release of a variety of mediators that induce the typical symptoms of rhinorrhea, sneezing, itching and nasal blockage. Allergic rhinitis represents a global health problem. It is a common disease worldwide affecting about 10 to 50% of the population[1] and its prevalence is increasing. Although allergic rhinitis is not a fatal disease, it alters the social life of patients,[2] affects school learning performance[3] and work productivity.[4] Moreover, the costs incurred by rhinitis are substantial.[5] Finally, in recent years rhinitis has been recognized to be an important risk factor for asthma. These observations strongly suggest the importance of treating allergic rhinitis.

The International Consensus on Rhinitis, guidelines for the diagnosis and treatment of allergic rhinitis were developed and published in 1994. The International Consensus for Rhinitis guidelines[6] followed a stepwise approach in the treatment of allergic and non-allergic rhinitis, because this seemed to be the most practical approach for the general practitioner and for the specialist. However, in 1999, the European Academy of Allergy and Clinical Immunology (EAACI) proposed new guidelines[7] and, unlike the 1994 guidelines,[6] not only the mild and moderate cases were considered but also the severe ones. Yet, with the developments

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in our understanding of the mechanisms of allergic rhinitis, especially considering its link to asthma and the development of treatment strategies targeting these new mechanisms, the need for a comprehensive evidence-based international guideline and one that takes into consideration the patient globally, that is terms of the comorbidities of rhinitis, was recognized. This resulted in the development of the WHO initiative the Allergic Rhinitis and its Impact on Asthma (ARIA) which has been developed as a state-of-the-art document for the specialist as well as for the general practitioner, to update their knowledge of allergic rhinitis, highlight the impact of allergic rhinitis on asthma, provide an evidence-based documented revision on the diagnosis methods and the treatments available and propose a stepwise approach to the management of the disease.[8] The statement of evidence for the development of these guidelines has followed the WHO rules and is based on Shekelle *et al.*[9]

Epidemiology and genetics

Despite the recognition 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 in the prevalence of rhinitis and its possible risk factors. These include: 1) the second National Health and Nutrition Examination Survey (NHANES II);[10,11] 2) the European Community Respiratory Health Survey (ECRHS);[12] 3) the 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 the 6-7 years old and from 1.4% to 39.7% in the 13-14 years old;[1] 4) the Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA);[13] and 5) the Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen (SCARPOL).[14]

Overall, it is estimated that allergic rhinitis is present in 3 to 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 in the past 40 years.[15-17]

A genetic component in allergic rhinitis as well as in other allergic diseases has been shown.[18] For the past decade, various antigens of the HLA system have been identified as responsible for allergen reactivity. 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. The recent increase in prevalence of allergic rhinitis cannot be due to a change in gene pool. Environmental factors like air pollution, change in life-styles, dietary habits and a reduction in infections are among some of the possible contributing factors stressing the importance of environmental control in preventing the rise of allergic diseases.

Allergens and trigger factors

Allergens

Aeroallergens are very often involved in allergic rhinitis.[19] The increase in domestic allergens is partly responsible for the increase in the prevalence of rhinitis, asthma and allergic respiratory diseases.[20] Major indoor allergens are house dust mites, pets, insects or those derived from plant origin. Common outdoor allergens include pollens and moulds.

Occupational rhinitis is less well documented than occupational asthma but nasal and bronchial symptoms often co-exist in the same patients.[21] Latex allergy has become an increasing concern to patients and health professionals.[22]

Pollutants

Air pollution is a major environmental health problem in that it increases the outpatient visits due to respiratory illness, hospital admissions and the daily mortality (50,000-120,000 premature deaths are due to exposure to particulate matter in ambient and indoor environment, WHO 1999, Air quality guidelines). Transportation accounts for 1/4 of world energy use and 1/2 of world oil production and motor vehicles which account for nearly 80% of all transport related energy is the highest contributor to greenhouse gas emission and urban air pollution (UNEP, Global Environment Outlook 2000). Recent epidemiological evidence suggests an interaction between environmental pollutants and rhinitis. These may be involved in the aggravation of nasal symptoms in patients with allergic rhinitis[23,24] or in non-allergic subjects.[25] Moreover, diesel exhaust may enhance the formation of IgE[26] and allergic inflammation.[27]

Besides outdoor pollutants like that from automobile exhausts (principal atmospheric oxidant pol-

lutants include ozone, nitric oxides and sulfur dioxide) there is an increased exposure to indoor air pollutants. Indoor pollution includes domestic allergens and indoor gas pollutants,[29,30] among which tobacco smoke is the major source. In fact, an association between allergy and asthma, and parental smoking has also been researched upon.

Aspirin

Aspirin and other non-steroidal anti-inflammatory drugs (NSAID) commonly induce rhinitis and asthma.[28]

Mechanisms

Allergy is classically considered to result from a sustained overproduction of IgE to common environmental allergens like house dust mite, pets, insects, pollens, fungi and moulds. Allergic rhinitis is conventionally considered to be either seasonal (due to pollens from trees or grass) or perennial (due to house dust mite, pets, molds and fungi). Allergic 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 non-specific hyperreactivity.[29]

The chain of events that lead to a Type I allergic reaction includes the recognition of allergen by the APC, antigen presentation to T cells, activation of T cells resulting in the production and release of cytokines like IL-4 and IL-13, class switch of IgM^+ B cells to IgE^+ plasma cells, the production of IgE, binding of IgE to the high affinity IgE receptor (FcεRI) on the surface of mast cells, and the cross linking of the bound IgE-FcεRI complex with multivalent allergen on subsequent exposure to the allergen, resulting in the release of inflammatory mediators like histamine, leukotrienes and prostaglandins.[29] However, the allergic reaction in a Type I allergic disease, like allergic rhinitis or atopic asthma, comprises of two phases, an immediate phase reaction and a late phase allergic reaction. The immediate phase allergic reaction occurs as a result of crosslinking of the allergen specific IgE bound to the IgE receptor on the surface of mast cells by allergen resulting in the release of chemical mediators like histamine, leukotreines and prostaglandins. By contrast, the late phase allergic reaction is largely inflammatory occurring as a result of the inflammatory mediators released by the infiltrated cells.[29] Thus, allergic rhinitis is characterized by an inflammatory infiltrate made up of different cells. This cellular response includes the chemotaxis, selective recruitment and transendothelial migration of cells, release of cytokines and chemokines,[30,31] localization of cells within the different compartments of the nasal mucosa, activation and differentiation of various cell types including eosinophils, T-cells, mast cells, and epithelial cells,[32-35] as well as a prolongation of their survival, release of mediators by these activated cells (among these, histamine and cysteinyl-leukotrienes are the major vasoactive mediators), regulation of the local and systemic IgE-synthesis, communication with the immune system and the bone marrow. It is now, however, also appreciated that allergens, on account of their enzymatic proteolytic activity, may directly activate cells.[36]

Non-specific nasal hyperreactivity is an important feature of allergic and non-allergic rhinitis[37] and can be defined as an increased nasal response to normal stimuli resulting in sneezing, nasal congestion and/or secretion. The concept of "minimal persistent inflammation" is new but important.[38] It has been confirmed in perennial[39] and seasonal allergy.[40] In patients with perennial allergic rhinitis, the allergen exposure varies within the year and there are periods in which there is little exposure. However, these patients, even though they are symptom free, still present inflammation of the nose.

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

Co-morbidity and complications

Allergic inflammation does not necessarily limit itself to the nasal airway. Multiple co-morbidities have been associated with rhinitis.

Asthma

The nasal and bronchial mucosa share many similarities.[41] Epidemiological studies have consistently shown that asthma and rhinitis often co-exist in the same patients.[42-44] Eighty percent of patients with asthma have rhinitis and 40% of rhinitis patients have asthma, making allergic rhinitis as a risk factor for 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.[45] On the other

hand, smooth muscle is present from the trachea to the bronchioles and accounts for the bronchoconstriction in asthma.

Pathophysiological studies suggest that a strong relationship exists between rhinitis and asthma. The recent progress achieved in the cellular and molecular biology of airway diseases has documented that inflammation of nasal and bronchial mucosa plays a critical role in the pathogenesis of asthma and rhinitis. A similar inflammatory cell infiltrate,[46] the same pro-inflammatory mediators (histamine, **CysLT**), Th-2 cytokines, chemokines and adhesion molecules appear to be involved in nasal and bronchial inflammation.[47-53]

Endobronchial allergen challenge in patients with allergic rhinitis leads to an asthmatic response with recruitment of inflammatory cells and pro-inflammatory mediators.[54] Several mechanisms have been proposed to link uncontrolled allergic rhinitis and the occurrence or worsening of asthma.[55]

These data have lead to 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 co-morbidities

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

Classification

Rhinitis is classified as follows (Table 1): Symptoms of rhinitis include rhinorrhea, nasal obstruction, nasal itching and sneezing which are reversible spontaneously or under treatment. It is subdivided into "intermittent" or "persistent" disease (Table 2). The severity of allergic rhinitis can be classified as "mild" or "moderate-severe".

Previously, allergic rhinitis was subdivided, based on the time of exposure, into seasonal, perennial, and occupational. Perennial allergic rhinitis is most frequently caused by indoor allergens such as dust mites, moulds, insects (cockroaches) and animal danders. 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 it is often difficult to differentiate between seasonal and perennial symptoms, the exposure to some seasonal allergens is long-standing, the exposure to some perennial allergens is not similar over the year, and the majority of patients are now sensitized to pollen and perennial allergens.

Thus, a major change in the subdivision of allergic rhinitis was in the ARIA is "intermittent" and "persistent".

Diagnosis and assessment of severity

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

History and general ENT examination

Clinical history is essential to accurately diagnose rhinitis, assess its severity and response to treatment. In patients with mild intermittent allergic rhinitis, a nasal examination is optimal. All patients with persistent allergic rhinitis need a nasal examination. Anterior rhinoscopy, using a speculum and mirror, gives limited information and nasal endoscopy is more useful.

Diagnosis of Allergy

The diagnosis of allergic rhinitis is based on the coordination between a typical history of allergic symptoms and diagnostic tests. *In vivo* and *in vitro* tests to diagnose allergic diseases are directed towards the detection of free or cell-bound IgE. Skin tests are widely used to demonstrate an IgE-mediated allergic reaction and represent a major diagnostic tool in the field of allergy. If properly performed, they yield useful confirmatory evidence for a diagnosis of specific allergy. As there are many complexities for their performance and interpretation, it is recommended that they should be carried out by trained health professionals.[56]

The measurement of total serum IgE is only poorly predictive for allergy screening in rhinitis and should rarely be used as a diagnostic tool. In contrast, the measurement of allergen-specific IgE in serum is of importance and has a value similar to that of skin tests.[57,58]

Nasal challenge tests with allergen are recommended for research and, to a lesser extent, in clinical practice. They are, how-

Table 1 Classification of rhinitis

- Infectious: viral, bacteria, other infectious agents
- Allergic: intermittent, persistent
- Occupational: (allergic and non-allergic) intermittent, persistent
- Drug-induced: aspirin, other medications
- Hormonal
- Other causes: NARES, irritants, food, emotional, atrophic, gastrointestinal reflux
- Idiopathic

Table 2 Classification of allergic rhinitis

1. "Intermittent" means that the symptoms are present: less than 4 days a week and for less than 4 weeks.
2. "Persistent" means that the symptoms are present more than 4 days a week and for more than 4 weeks.
3. "Mild" means that none of the following items: sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work and troublesome symptoms.
4. "Moderate-severe" means that one or more of the following items are present: sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work and troublesome symptoms.

Table 3 Diagnostic tests for allergic rhinitis*

Routine tests: history, general ENT examination
Allergy tests: skin tests, serum specific IgE
Endoscopy: rigid, flexible
Nasal cytology
Nasal challenge: allergen, lysine, aspirin
Radiology: CT-scan
Optional tests (mainly for research)
- Nasal biopsy
- Nasal swab for bacteriology
- Radiology, CT scans, MRI
- Mucociliary function: nasal mucociliary clearance (NMCC), ciliary beat frequency (CBF), electron microscopy
- Nasal airway assessment: nasal inspiratory peak flow (NIPF), rhinometry (anterior and posterior), acoustic rhinometry
- Olfaction or nitric oxide measurement
- Testing for co-morbidities
- Asthma, conjunctivitis, otitis media, pharyngitis

*modified from (1)

ever, important in the diagnosis of occupational rhinitis. A subcommittee of the "International Committee on Objective Assessment of the Nasal Airways" has put forward guidelines for nasal provocation tests concerning indications, techniques and evaluation of the tests.[59]

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.[60] For atopic dermatitis, there are clinical scores of severity such as SCORAD.[61] However, for rhinitis, there is no internationally accepted objective measure of nasal obstruction. The nasal inspiratory peak flow (NIPF) has been extensively studied but results are not consistent among the different studies.[62-64] Moreover, the correlation between the objective measurement of nasal resistance and subjective reports of nasal airflow sensation is usually poor. In the WHO document, a clinical assessment of rhinitis has therefore been proposed (Table 2).

Management

The management of allergic rhinitis includes allergen avoidance, medications (pharmacological treatment), immunotherapy and education. Surgery may be used as an adjunctive intervention in a few highly selected patients. It is recommended to propose a strategy combining the treatment of both the upper and lower airway disease in terms of efficacy and safety.

a) Allergen avoidance: 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 clinical improvement. A meta-analysis of house mite avoidance trials indicated that this appro ch was doomed to failure in the treatment of asthma[65] suggesting that a single intervention may be insufficient. However, all asthma and rhinitis guidelines now suggest that allergen avoidance, including house mites, should be an integral part of a management strategy, but more data are needed to fully know the value of allergen avoidance.

b) Pharmacotherapy: Medications have no long-lasting effect when stopped. Therefore, in persistent disease, maintenance treatment is required. No tachyphylaxis usually occurs with prolonged treatment. Medications used for rhinitis are most commonly administered intra-nasally or orally. There are several advantages of intranasal medications since high concentrations can be delivered directly into the nose and the systemic effects are minimised. However, many patients with allergic rhinitis also have conjunctivitis and/or asthma and then medications need to be administered to various target organs. Medications for the treatment of allergic rhinitis include oral and topical (intranasal and ocular formulations) H1-antihistamines,[66] intranasal corticosteroids,[67] oral corticosteroids, chromones (intranasal/ocular formulations), oral and intranasal decongestants, oral decongestants combined with H1-antihistamines, intranasal anticholinergics and leukotriene receptor antagonists.[68] Some studies have compared the relative efficacy of these medications and intranasal corticosteroids were reported to be the most effective.[67] However, the choice for a treatment depends also on many other criteria.

The use of alternative care for the treatment of rhinitis is increasing. There is an urgent need for large, randomized and controlled clinical trials for alternative therapies of allergic diseases and rhinitis since scientific and clinical supports of these therapies are lacking.[69]

c) Allergen specific immunotherapy: therapeutic vaccines for allergic diseases: Several guidelines for specific immunotherapy with inhalant allergens have been published. The WHO document endorsed the conclusions of previous guidelines,[70] EAACI[71] with an update using newly published randomized, double-blind and placebo-controlled trials.

Subcutaneous immunotherapy alters the natural course of allergic diseases.[72,73] However, it raises contrasting efficacy and safety issues. Thus, the use of optimal doses of vaccines labeled either in biological units or in mass of major allergens has been proposed. Doses of 5 to 20 μg of the major allergen are optimal doses for most allergen vaccines.[70] The indications for this form of immunotherapy are similar to those published in 1998.[70] Also, specific immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. prevented the onset of new sensitizations in children.[72]

New studies have been published for high-dose sublingual-swallow immunotherapy and it has been confirmed that only doses at least 10 times greater than those used for subcutaneous immunotherapy are effective. Local nasal and high-dose sublingual-swallow

specific immunotherapy may be indicated in carefully selected patients with rhinitis, conjunctivitis and/or asthma caused by pollen and mite allergy, patients insufficiently controlled by conventional pharmacotherapy, patients who have presented with systemic reactions during injection specific immunotherapy, patients showing poor compliance with or refusing injections.

Finally, the strategy for the management of allergic rhinitis are as shown in Table 4. Also, the patient should be reassessed after 2 to 4 weeks:

If the patient does not improve, consider the following possibilities:

1) Failure to respond to intra-nasal glucocorticosteroids,

2) Inadequate compliance,

3) Patient (or doctor) misunderstanding of the dose/frequency of administration of intra-nasal glucocorticosteroids,

4) Severe nasal obstruction preventing drug delivery,

5) Additional nasal pathology (e.g. nasal polyps, sinusitis) or nasal septal deviation,

6) Heavy persistent allergen exposure (e.g. cat on the bed) and

7) A wrong diagnosis (see classification of rhinitis).

Possible solutions :

1) If the major symptom is nasal obstruction, double the dose of intra-nasal glucocorticosteroids

2) If the major symptoms are sneezing, itching or rhinorrhea, add: H1-antihistamines

3) If the major symptom is rhinorrhea, add ipratropium bromide

4) If the patient improves, a step down approach should be used.

However, a minimal duration of the treatment should be for at least three months or for the duration of the pollen season. In the step down treatment, low dose intra-nasal glucocorticosteroids may be required as a maintenance treatment to control symptoms.

Pediatric aspects

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 medications have to be adjusted and special considerations followed. Few medications have been tested in children under the age of two years.

Oral and intra-muscular glucocorticosteroids should be avoided when treating rhinitis in young children. Intra-nasal glucocorticosteroids are an effective treatment for allergic rhinoconjunctivitis, however their possible effect on growth for some but not all intra-nasal glucocorticosteroids is of concern.[74] Intra-nasal mometasone[75] and fluticasone did not affect growth in children with allergic rhinoconjunctivitis. Disodium cromoglycate is commonly used to treat allergic rhinoconjunctivitis in children because of the safety of the drug.

Special considerations in pregnancy and in elderly patients:

Rhinitis is often a problem during pregnancy since nasal obstruction may be aggravated by pregnancy itself.[76] Caution must be taken when administering any medication during pregnancy, as most medications cross the placental barrier. For most drugs, limited studies have been done only on small groups without long-term analysis.[77,78] Moreover, there are differences in regulation between countries.

With aging, various physiological changes occur in the connective tissue and vasculature of the nose which may predispose or contribute to chronic rhinitis.[79] Some drugs may induce specific side effects in elderly patients.

Future potential treatment modalities: Several novel approaches are currently under consideration for the treatment or prevention of allergic inflammation. These include a humanized monoclonal antibody against IgE which is in its latest phase of development.[80] Many novel treatments for allergy are based on an inhibition of eosinophil development or tissue recruitment, the inhibition of allergic inflammation (mast cells, T-cells) and new forms of immunotherapy.

Patient education

Education of the patient and/or the patient's care giver about the management of rhinitis is essential. Such education is likely to maximize compliance and the possibility of optimizing treatment outcomes.

Quality-of-life

In the last decade, the socio-economic 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.[2,81] Treatments for allergic rhinitis improve the quality of life.

The social economic impact:

Asthma and rhinitis are chronic conditions with a substantial economic impact on the affected subjects, their families, the health care systems and society as a whole. This includes direct and indirect costs associated with loss of economic productivity. It has also been shown that rhinitis increases the costs for asthma.[82]

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