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# Treatment of Allergic Rhinitis: ARIA Document, Nasal Lavage, Antihistamines, Cromones and Vasoconstrictors

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## 1. Introduction

Throughout history, various classifications of rhinitis have emerged, many of which originated from expert groups. We would have to go back to 1994 to find the “*International Consensus Report on Diagnosis and Management of Rhinitis*” (International Rhinitis Management Working Group, 1994), which was subsequently modified in the 2000 “*Consensus statement on the treatment of allergic rhinitis. EAACI Position paper*” (Van Cauwenberge et al, 2000). Of particular interest is the “*Executive Summary of Joint Task Force Practice Parameters on Diagnosis and Management of Rhinitis*” of 1998 (Dykewicz & Fineman, 1998). In 2001, a group of experts, the “*Allergic Rhinitis and its Impact on Asthma (ARIA) Workshop Expert Panel*”, met to develop guidelines on the diagnosis and treatment of rhinitis, which also dealt with other inflammatory processes interrelated/associated with asthma. The acronym “ARIA” comes from “Allergic Rhinitis and its Impact on Asthma”. ARIA is a document from a non-governmental organisation of the World Health Organization (WHO), endorsed by numerous scientific societies, such as the International Association of Allergology and Clinical Immunology (IAACI) and the World Allergy Organization (WAO) (Bousquet et al, 2001).

It was established as an educational program as the “Guidelines for recommendations for the diagnosis and comprehensive handling of patients with rhinitis”, associated with asthma and other interrelated processes (sinusitis, conjunctivitis and otitis).

## 2. The “United airway” concept

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness

that leads to recurrent episodes of wheezing, shortness of breath, chest tightness, and coughing. These episodes are associated with widespread and variable airflow obstruction within the lung, which is often reversible either spontaneously or with treatment (Global Initiative for Asthma, Update 2010).

There is increasing evidence that asthma is a complex syndrome made up of a number of disease variants, so-called asthma phenotypes, with different underlying pathophysiologies. Limited knowledge of the mechanisms of these disease subgroups is possibly the greatest obstacle in understanding the causes of asthma and improving treatment, and can explain the failure to identify consistent genetic and environmental correlations to asthma (Lötvall et al, 2011). It has been proposed that the asthma syndrome should be divided into distinct disease entities with specific mechanisms, which have been called "asthma endotypes." An "endotype" is considered to be a subtype of a condition defined by a distinct pathophysiological mechanism (Lötvall et al, 2011).

The ARIA document acknowledged the concept of a "single airway" or "one airway, one disease", in recognition of the indisputable epidemiological and etiopathogenic relationship that exists between asthma and allergic rhinitis (AR). Both are "a single disease whose basis is the chronic inflammatory process of the airway, a premise that must determine the diagnostic and treatment strategy (Bousquet et al, 2008).

The prevalence of allergic rhinitis in developed countries is between 10%-20%, almost three times the prevalence of asthma (Gergen & Turkettaub, 1991; Lester et al, 2001; Mannino et al, 2002). The concept "allergy; systemic disease" with clinical manifestations in various organs makes "one single airway" more accessible. This way, allergic rhinitis, rhinosinusitis, rhinitis with bronchial hyperresponsiveness, asthma, etc., may be reflections of different stages of the same chronic inflammatory disease of the airway.

In our settings, it is important to note that 20.4% of patients visit an allergist for the first time for rhinitis and asthma symptoms, as highlighted by the "2005 Allergological Study" (Spanish Society of Allergology and Clinical Immunology, 2006). Rhinoconjunctivitis (in allergy clinic settings), which was the main reason for visits in the 1992 Allergological Study (2,279 patients who represented the 57.4% of the sample) (Spanish Society of Allergology and Clinical Immunology, 1995), remains so in the 2005 Allergological Study (2,771 patients who represented the 55.5% of the sample) (Spanish Society of Allergology and Clinical Immunology, 2006). These absolute rates and figures reflect the importance of this disorder. In a study of 650 asthmatics from a health area of the Community of Madrid, 50% had an association with allergic rhinitis (Espinosa de los Monteros et al, 1999).

## **2.1 Why a new "ARIA document Update 2008" (Bousquet et al, 2008) and "Update 2010" (Brozek JL et al, 2010)?**

However, during the period between the first edition in 2001 (Bousquet et al, 2001) and the present (2012), the appearance of numerous studies have caused it to be revised, giving a dynamic and current outlook on the problem both from epidemiologic and therapeutic viewpoints. Thus, the most notable aspect is the inclusion of anti-leukotrienes (Philip G et al, 2004) and the first mention of Omalizumab (Anti-IgE). Successive meetings of experts, along with numerous studies of controlled clinical trials and evidence-based medicine, will produce new up-to-date revisions of this document (Bousquet et al, 2008) (Figure 1).

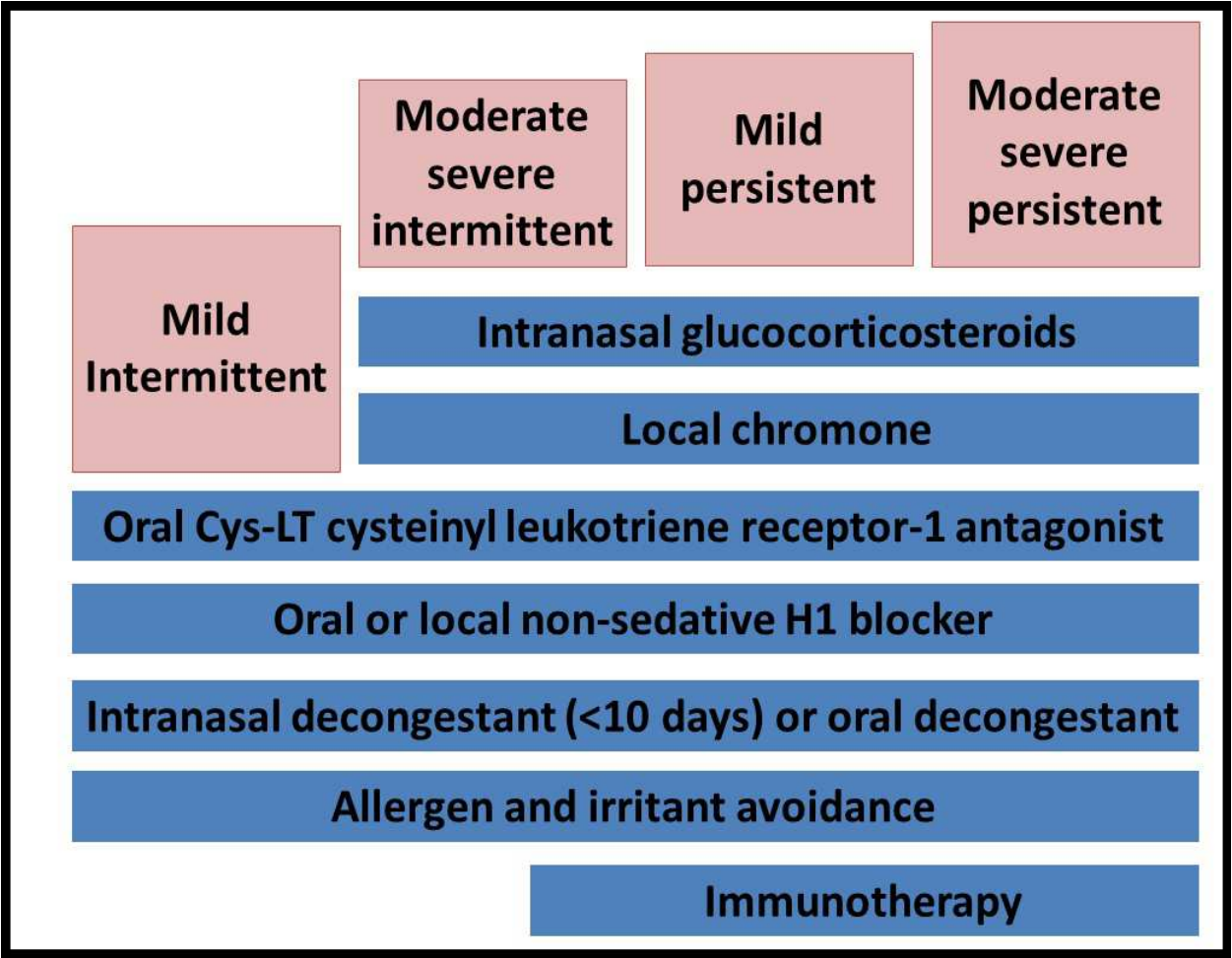


Fig. 1. Classification steps for the severity / persistence of allergic rhinitis symptoms with various therapy steps.

The update to the ARIA document is necessary because:

- a. During the period 2001-2012, knowledge of epidemiology, diagnosis, management and comorbidity of patients with allergic rhinitis broadened due to the considerable number of publications.
- b. The ARIA Recommendations that were proposed by an expert group must be validated in terms of classification and management.
- c. New evidence-based medicine systems will guide and include recommendations for safety, expenditure and efficacy of various treatments.
- d. Gaps in the understanding of the first ARIA document:
  - Certain aspects of treatment, such as complementary and alternative medicine.
  - Description of the relationship between upper and lower airways in developing countries.
  - The role of rhinitis in athletes.
  - The link between rhinitis and asthma in preschool aged children.

The rhinitis management (algorithm of the ARIA-Update recommendations 2008 and 2010) are shown in Figure 2.

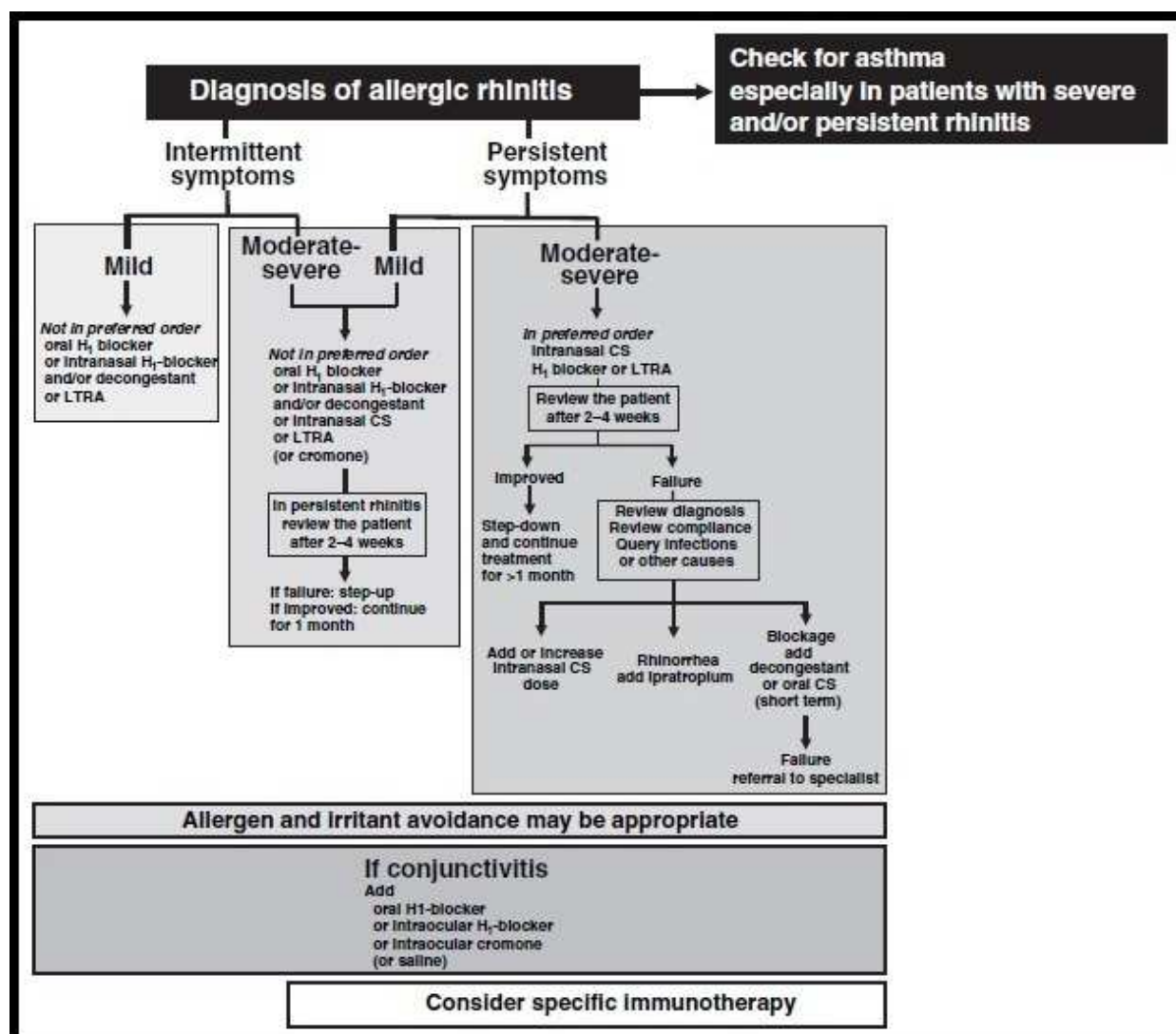


Fig. 2. Rhinitis management (algorithm of the ARIA-Update recommendations 2008 and 2010) (Bousquet et al, 2008; Brozek et al, 2010).

The **initial primary goal** of “education and implementation of the handling of allergic rhinitis based on the dissemination of information that exists about it, its relationship with asthma, as well as allowing scientific evidence (increasingly up-to-date) to be used for control, which results in the benefiting of more than 600 million patients who suffer from this pathology” has been supplemented by the following news:

Developments of the 2008- and 2010-ARIA document (Brozek et al, 2010):

- Confirm the clinical validity of the new allergic rhinitis classification.
- Better understand the impact of allergic rhinitis on patient quality of life starting with the management of rhinitis.
- Perform a review based on the scientific evidence of all available treatments (published trials), including anti-leukotrienes and omalizumab.
- Emphasize studies that highlight the relationship between rhinitis and asthma.
- Suggest a plan for implementing the recommendations in Europe (in collaboration with the EAACI).



- Provide an initial view of the magnitude of the problem with the first strategies in developing countries.

The following Figure 3 presents the degrees of evidence of the various studies in terms of each type of treatment (Shekelle et al, 1999; Custovic & Wijk, 2005; Bousquet et al, 2006; Passalacqua et al, 2006; Passalacqua & Durham, 2007).

| <i>Intervention</i>                            | SEASONAL RHINITIS |                 | PERENNIAL RHINITIS<br>(mostly applies for studies<br>≤ 4 weeks) |                 | PERSISTENT<br>RHINITIS |
|--|-------------------|-----------------|---|-----------------|------------------------|
|  | Adults            | Children        | Adults  | Children        |                        |
| H1-Antihistamines                              |                   |                 |   |                 |                        |
| - oral   | A                 | A               | A   | A               | A                      |
| - intranasal                                   | A                 | A               | A   | A               | No data                |
| - intraocular                                  | A                 | A               | B   | B               | No data                |
| Glucocorticosteroids:                          |                   |                 |   |                 |                        |
| - intranasal                                   | A                 | A               | A   | A               | No data                |
| - oral   | A                 | B               | B   | B               | No data                |
| - intramuscular                                | A                 | B               | B   | B               | No data                |
| Cromones:                                      |                   |                 |   |                 |                        |
| - intranasal                                   | A                 | A               | A   | B               | No data                |
| - intraocular                                  | A                 | A               | B   | B               | No data                |
| NAAGA topical                                  | B                 | C               | C   | C               | No data                |
| Antileukotriene                                | A                 | A over 6 years  |   |                 | No data                |
| Decongestants                                  |                   |                 |   |                 |                        |
| - intranasal                                   | C                 | C               | C   | C               | No data                |
| - oral   | A                 |                 |   |                 | No data                |
| - oral + H1-antihistamine                      | A                 | B               | B   | B               | No data                |
| Anticholinergic                                |                   |                 | A   | A               | No data                |
| Homeopathy                                     | D                 | D               | D   | D               | No data                |
| Acupuncture                                    | D                 | D               | D   | D               | No data                |
| Phytotherapy                                   | B                 | D               | D   | D               | No data                |
| Other CAM                                      | D                 | D               | D   | D               | No data                |
| Specific immunotherapy:<br>rhinoconjunctivitis |                   |                 |   |                 |                        |
| - subcutaneous                                 | A                 | A               | A   | A               | No data                |
| - sublingual                                   | A                 | A               | A   | A               | No data                |
| - intranasal                                   | A                 |                 |   |                 | No data                |
| Specific immunotherapy: asthma                 |                   |                 |   |                 |                        |
| - subcutaneous                                 | A                 | A               | A   | A               |                        |
| - sublingual                                   | A                 | A               | A   | A               |                        |
| Anti-IgE                                       | A                 | A over 12 years | A   | A over 12 years | No data                |
| Allergen avoidance:                            |                   |                 |   |                 |                        |
| - house dust mites                             | D                 | D               | D   | D               | No data                |
| - other indoor allergens                       | D                 | D               | D   | D               | No data                |
| - total avoidance of occupational agent        |                   |                 | A (for asthma)  |                 | No data                |
| - partial avoidance of latex                   |                   |                 | B   |                 | No data                |

Fig. 3. Level of evidence of different interventions in allergic rhinitis (AR) (Bousquet et al, 2008).

The recommendations follow criteria which may differ from country to country, and in Europe and at WHO another Shekelle method was commonly used (Shekelle et al, 1999) (Figure 3).

Strength of recommendation:

A: Category I evidence (meta-analysis of randomized-controlled trials (RCT); or at least one RCT).

B: Category II evidence (at least one controlled study without randomization; or at least one other type of study) or extrapolated recommendation from category I evidence

C: Category III evidence (nonexperimental descriptive studies) or extrapolated recommendation from category I or II evidence.

D: Category IV evidence (expert committee reports or opinions or clinical experience of respected authorities) or extrapolated recommendation from category I, II or III evidence.

### 2.3 Controversy in the treatment of allergic rhinitis

Rhinitis, or inflammation of the nasal mucosa, is currently recognised as a major cause of morbidity, which significantly deteriorates quality of life (ISAAC Steering Committee, 1998). Although the prevalence of rhinitis is highly variable, we can conclude that between 15% and 20% of the population suffers from rhinitis, based on various studies that are influenced by the questionnaires used and the geographical area in which they are carried out (Broder et al, 1974a; Broder et al, 1974b; Sibbald & Rink, 1991; Spanish Society of Allergology and Clinical Immunology, 1995; Spanish Society of Allergology and Clinical Immunology, 2006). Early intervention with appropriate treatment may improve patient quality of life and productivity, as well as prevent its evolution to asthma (European Academy of Allergology and Clinical Immunology, 1998). A few years ago, the goal of rhinitis treatment was to improve symptoms. Currently, the goal is to block pathophysiological mechanisms that cause chronic inflammation and that leave patients vulnerable to respiratory airway infections.

The therapeutic approach to allergic rhinitis (AR) entails comprehensive treatment of the allergic inflammation of the airways (ARIA). The selection and combination of the therapeutic arsenal is achieved by taking into account current clinical practice guidelines, and by individualising the treatment for each patient, depending on the frequency of discomfort (intermittent or persistent AR) and its repercussion on the quality of life (mild or moderate/severe AR) (Bousquet et al, 2001). Treatment cost-effectiveness must also be assessed, as well as safety and the fact that we are dealing with a chronic disease.

The protocol for managing rhinitis, according to the 1994 Consensus (International Rhinitis Management Working Group, 1994), proposes a phased approach for the treatment of both allergic and non-allergic rhinitis. The above protocol is not very clear about the indications for immunotherapy, which in the final summary is indicated exclusively for seasonal AR. The European Academy of Allergy and Clinical Immunology (EAACI) Position Paper for treatment of AR published in 2000 and created from consensus between experts of the Academy (van Cauwenberge et al, 2000), reviewed 185 articles on rhinitis, focusing exclusively on therapeutic issues. The proposed treatment guidelines in this review, differentiated for seasonal and perennial AR in children and adults, are too rigid. The indication for immunotherapy is envisioned in very advanced phases of the therapeutic range, and also in an undefined manner. The therapeutic approach in ARIA (Bousquet et al, 2001) is phased and not as rigid as in other consensus. Treatment guidelines are open and do not list directives, and

quality of life is assessed through the use of questionnaires. The recommendations for treatment depend on symptom severity along with repercussions on patient quality of life.

For the first time, therapy is approached using evidence-based medical criteria, reviewing controlled randomised studies, and performed according to the prior classification of seasonal and perennial rhinitis. These recommendations are based on meta-analysis studies regarding drug treatment and immunotherapy, and on a clinical practice guideline drawn up after an analysis of evidence available to date, based on the opinion of experts regarding the elimination of the antigen.

Of note are considerations regarding drug administration routes, and their advantages/disadvantages and indications/contraindications. There is special attention given to the intranasal route.

In 1995, the first manual portable controlled-dose inhaler, called the “Medihaler”, was introduced, which was the result of studies carried out in the Richer Co. laboratories (British Society for Allergy and Clinical Immunology, 2000). In the USA, a smaller inhaler was developed that was easier to handle than nebulizers and avoided the use of sedative antihistamines, which alter cognitive and motor functions. The inhaler was developed for the asthmatic daughter of Dr. G. Maison, chairman of the laboratories. The inhaler had a pressurized canister and metering valve. The use of topical medication in rhinitis has been developed to reduce systemic side effects as much as possible.

2.3 Allergen avoidance

Although there is disagreement as to the efficacy of eliminating the antigen, it must always be carried out using environmental control measures.

2.4 Therapeutics groups in the “ARIA-pharmaceutical”

Although there is disagreement as to the efficacy of eliminating the antigen, it must always be carried. In recent years, the pharmaceutical industry has researched new administration routes. It appears that the nose is a magnificent channel for drugs that until recently could only be administered systemically.

There are eight major therapeutic groups in the “ARIA-pharmaceutical market” available use (Table 1).

| Drugs   | Generic names  | Mechanism of action  | Side effects   | Comments   |
|---|--|--|--|--|
| Local H1-antihistamines (intranasal, intraocular) | Azelastine<br>Levocabastine<br>Olopatadine   | Blockage of H1 receptor.<br>Some antiallergic activity for azelastine. | Minor local side effects.<br>Azelastine: bitter taste.   | Rapidly effective (minor than 30 minutes) on nasal or ocular symptoms.                             |
| Intranasal glucocorticosteroids                   | Beclomethasone dipropionate<br>Budesonide<br>Ciclesonide<br>Flunisolide<br>Fluticasone | Potently reduce nasal inflammation.<br>Reduce nasal hyperactivity.     | Minor local side effects.<br>Wide margin for systemic side effects.<br>Growth concerns with BDP only.<br>In young children | The most effective pharmacologic treatment of allergic rhinitis.<br>Effective on nasal congestion. |



| Drugs  | Generic names  | Mechanism of action   | Side effects  | Comments  |
|--|--|---|---|---|
|  | propionate<br>Fluticasone<br>furoate<br>Metasone<br>furoate<br>Triamcinolone<br>acetonide  |   | consider the combination<br>of intranasal and inhaled<br>drugs.   | Effective on smell.<br>Effect observed after<br>12 hours but maximal<br>effect after a few days   |
| Leukotriene<br>antagonists                           | Montelukast<br>Pranlukast<br>Zafirlukast   | Blockage of<br>CystLT receptor.   | Excellent tolerance.  | Effective on rhinitis<br>and asthma.<br>Effective on all<br>symptoms of rhinitis<br>and on ocular<br>symptoms.  |
| Local cromones<br>(intranasal,<br>intraocular)       | Cromoglycate<br>Nedocromil<br>NAAGA  | Mechanism of<br>action poorly<br>known.                                       | Minor local side effects.   | Intraocular cromones<br>are very effective.<br>Intranasal cromones<br>are less effective and<br>their effect is short<br>lasting.   |
| Intranasal<br>anticholinergics                       | Ipratropium  | Anticholinergic<br>block almost<br>exclusively<br>rhinorrhea                  | Minor local side effects.<br>Almost no systemic<br>anticholinergic activity.  | Effective on allergic<br>and non-allergic<br>patients with<br>rhinorrhea.   |
| Oral<br>decongestants                                | Ephedrine<br>Phenylephrine<br>Phenylpropan<br>olamine<br>Pseudoephedri<br>ne<br>Oral H1-<br>antihistamine<br>decongestants<br>combinations | Sympathomimetic<br>drugs.<br>Relieve symptoms<br>of nasal<br>congestion.      | Hypertension.<br>Palpitations.<br>Restlessness.<br>Agitation.<br>Tremor.<br>Insomnia.<br>Headache.<br>Dry mucous membranes.<br>Urinary retention.<br>Exacerbation of glau-<br>coma or thyrotoxicosis. | Use oral decongestants<br>with caution in patient<br>with heart disease.<br>Oral H1-antihistamine-<br>decongestant<br>combination products<br>may be more effective<br>than either product<br>alone but side effects<br>are combined. |
| Intranasal<br>decongestants                          | Oxymethazoli<br>ne<br>Xylomethazoli<br>ne<br>Others  | Sympathomimetic<br>drugs.<br>Relieve symptoms<br>of nasal congestion          | Same side affects as oral<br>decongestants but less<br>intense.<br>Rhinitis medicamentosa<br>is a rebound phenome-<br>non occurring with pro-<br>longed use (over 10 days)                            | Act more rapidly and<br>more effectively than<br>oral decongestants.<br>Limit duration of<br>treatment to minor 10<br>days to avoid rhinitis<br>medicamentosa.  |
| Oral/intramuscu-<br>lar<br>glucocorticoster-<br>oids | Dexamethason<br>e<br>Hydrocortison<br>e<br>Methylprednis<br>olone<br>Prednisolone<br>Prednisone<br>Triamcinolone                           | Potently reduce<br>nasal<br>inflammation.<br>Reduce nasal<br>hyperreactivity. | Systemic side effects<br>common in particular for<br>intramuscular drugs.<br>Depot injections may<br>cause local tissue<br>atrophy.   | When possible,<br>intranasal<br>glucocorticosteroids<br>should replace oral or<br>intramuscular drugs.<br>However a short<br>course of oral gluco-<br>corticosteroids may be<br>needed of moderate<br>/severe symptoms.               |

Table 1. Therapeutic groups in the “ARIA-pharmaceutical market” (Bousquet et al, 2008).

Topical nasal drugs acts as both a preventive and a curative medication for rhinitis. It is very important that the application be performed appropriately, with the goal of achieving uniform distribution of the drug throughout the nasal mucosa, especially if rhinorrhoea is abundant.

### 3. Nasal lavage

Nasal lavage is a non-pharmacological treatment of rhinitis. Most authors agree that this is a well-tolerated, effective and inexpensive treatment.

#### 3.1 Efficacy in AR

Georgitis showed that the use of saline solution in nasal irrigation reduces inflammatory mediators (nasal histamine, prostaglandin D2 and leukotriene C4), while at the same time decreasing nasal symptoms (Georgitis, 1994). It observed that performing nasal lavage is important in the treatment of allergic rhinosinusitis.

Subiza et al, published one of the best and most complete articles in the JACI, which indicated that the action of nasal lavages is simple and known: cleaning of nasal secretions, with anti-inflammatory effect and reduction in basophils and other anti-inflammatory cells. It is a complementary technique for intranasal corticosteroids, but is effective and convenient. Saline irrigation of the nose and sinuses during the pollen season inhibits the IgE response to grass pollen (Subiza et al, 1999).

According to Tomooka et al, patients who use nasal lavage twice a day for 3-6 week periods have statistically significant improvement (23 of the 30 symptoms on The Quality of Well Being scale questionnaires improve or disappear) (Tomooka et al, 2000).

Garavello et al state that the use of nasal irrigation with hypertonic saline serum (3 times a day) decreases the consumption of antihistamines and significantly improves rhinitis, starting from the third week of treatment, and clearly in the fourth and fifth, with a significant reduction in the use of oral antihistamines (Garavello et al, 2003). The study was performed on 20 children, whose ages were not reported, with seasonal AR and sensitisation to *Parietaria judaica*. Irrigation with hypertonic serum was performed on 10 of the children 3 times at day during the entire pollen season (6 weeks). The other 10 were not administered lavages and were used as controls.

Degirmencioglu et al showed that saline irrigation with isotonic or hypertonic solutions improve symptoms during the pollen season (Degirmencioglu et al, 2004).

#### 3.2 Usefulness in sinusitis and chronic rhinitis

Lavages with isotonic and hypertonic saline serum are one of the mainstays of treatment of rhinosinus disease, as they are safe, inexpensive and effective. The weight of evidence is such that the Allergy Foundation published an International Consensus article in *Allergy* (International Rhinitis Management Working Group, 1994) recommending the routine performance of these lavages for rhinitis.

Different clinicians confirmed that nasal irrigations with a saline solution along with nasal steroids are the basis of treatment for chronic sinusitis (Aukema & Fokkens, 2004).

Nevertheless, is cautioned that nasal irrigation with saline solutions could no longer be considered a mere adjunct treatment of rhinosinusitis (Brown & Graham, 2004). Despite being effective and safe, it is underused.

Metson lends support to the conviction that saline irrigation improves breathing and adds, more importantly, that it lengthens the time between relapses (Metson, 2004). Daily saline irrigation improves the quality of life of patients with sinusitis, decreasing symptoms and the use of medication (Rabago et al, 2002).

Nasal irrigation is a simple and inexpensive treatment that improves symptoms of a variety of sinonasal diseases, reduces the use of resources and helps minimise resistance to antibiotics (Papsin & McTavish, 2003). Also, nasal lavage improves endoscopic imaging of nasal mucosa and the quality of life of patients with chronic rhinosinusitis (Taccariello et al, 1999). The nasal lavage increases mucociliary flow, dilutes thick secretions, relieves irritated mucous membranes, eliminates crusts and foreign bodies, facilitates the healing of mucous membranes, reducing the need for blowing and improving the sense of smell. The sinus irrigation by itself prevented the need for surgery in 58% of patients with chronic sinusitis over a year (Hartog et al, 1997)

#### **4. Antihistamines**

Histamine is one of the main mediators of allergic reactions occurring as a result of contact between the allergen and the nasal mucosa. Its actions are not limited to triggering of the signs and symptoms of the early phase of the allergic reaction but are also implicated in the release of multiple proinflammatory cytokines, with a vasoactive effect that favors arrival in the nasal zone of a range of cellular elements that characterize allergic inflammation.

Antihistamines inhibit the effects of histamine at H1 receptors. Histamine is a physiologically active, endogenous substance that binds to and activates histamine H1 and H2 receptors in the respiratory tract (including the nose), the gastrointestinal tract, brain, adrenal medulla, skin vasculature, and the heart (Golightly & Greos, 2005).

##### **4.1 Oral antihistamines**

The antihistamines exert a number of effects upon the histamine receptor. On one hand, it is now clear that all known antihistamines act as reverse agonists, inactivating the intracellular actions of the receptor. On the other hand, antiinflammatory effects have been demonstrated for these drugs, explained by modulation of nuclear factor NF- $\kappa$ B, such as the inhibition of ICAM-1 expression or action upon the bradykinins (Leurs et al, 2002).

Antihistamines are classified (Handley et al, 1998) as first generation (sedating, including chlorpheniramine, diphenhydramine, promethazine, and hydroxyzine) and newer. The newer antihistamines are sometimes referred to as second generation (relatively nonsedating, including terfenadine, astemizole, loratadine, cetirizine, and levocetirizine) and third generation (including fexofenadine, norastemizole, and descarboethoxyloratadine) (Table 2).

Antihistamine drugs are the most commonly used pharmaceutical group. The effective use of anti-H1 (in its oral, intranasal and ophthalmic presentations) for the treatment of AR

| Chemical class   | Functional class   |  |
|------------------|--|--|
|                  | First (old) generation   | Second (new) generation  |
| Alkylamines      | Brompheniramine, chlorpheniramine, dexchlorpheniramine, dimenthindene, pheniramine, triprolidine | Acrivastine  |
| Piperazines      | Bucizine, cyclizine, hydroxyzine, meclizine, oxatomide   | Cetirizine, levocetirizine   |
| Piperidines      | Azatadine, cyproheptadine, diphenylpyraline, ketotifen   | Astemizol, bepotastine, bilastine, desloratadine, ebastine, fexofenadine, levocabastine, loratadine, mizolastine, rupatadine, terfenadine, alcaftadine |
| Ethanolamines    | Carbinoxamine, clemastine, dimenhydrinate, diphenhydramine, doxylamine, phenyltoloxamine         |  |
| Ethylenediamines | Antazoline, pyrilamine, tripeleennamine  |  |
| Phenothiazines   | Methdilazine, promethazine   |  |
| Others           | Doxepin*   | Azelastine, emedastine, epinastine, olopatadine  |

\* Doxepin has dual H<sub>1</sub>- and H<sub>2</sub>- antihistamine activities and is classified as a tricyclic antidepressant.

Table 2. H1-antihistamines: chemical and functional classification (modified: Simons, 2004; Simons & Akdis, 2009; Simons & Simons, 2011).

(seasonal or perennial) in children or adults is backed by significant evidence from published clinical trials (ARIA).

In the new classification of rhinitis and in the clinical practice guidelines promoted in the ARIA document, oral anti-H1 is recommended for use in intermittent and persistent mild AR, and combined with topical corticosteroids in persistent moderate/severe AR. It shows good response in seasonal AR, where symptoms mediated by histamines predominate and ocular symptoms are common. In persistent AR, in which congestion is significant, anti-H1 has a moderate effect.

Oral antihistamines may cause subclinical side effects not noticed by the patient (somnolence, decreased coordination, etc.). This does not happen with the new non-sedating antihistamines, but generally up to 50% of patients self-medicate (Storms, 1997).

Treatment with antihistamines in AR is almost universally accepted. In fact, the treatment of seasonal AR in children: The results of placebo-controlled trials of cetirizine (Allegra et al, 1993; Masi et al, 1993; Ciprandi et al, 1997a; Ciprandi et al, 1997b; Pearlman et al, 1997) and fexofenadine (Wahn et al, 2003) demonstrated significant improvements in symptoms with the study drug compared with placebo. Active-control studies compared cetirizine (Charpin

et al, 1995) and loratadine (Boner et al, 1989) to first-generation antihistamines, with no significant differences between groups.

Various studies were identified which examined the efficacy of newer antihistamines among children with perennial AR (Baelde & Dupont, 1992; Jobst et al, 1994; Charpin et al, 1995; Pearlman et al, 1997; Sienra-Monge et al, 1999; Ciprandi et al, 2001; Yang et al, 2001; Lai et al, 2002; Wahn et al, 2003; Ciprandi et al, 2004; Hsieh et al, 2004). In three studies with active controls, cetirizine improved symptoms compared with placebo arms and compared with ketotifen and oxatomide (Lai et al, 2002). Cetirizine was comparable to montelukast in one study (Hsieh et al, 2004), but similar in efficacy in another (Chen et al, 2006). Three fair-quality, placebo-controlled studies (Baelde & Dupont, 1992; Jobst et al, 1994; Ciprandi et al, 2001) found cetirizine efficacious for nasal symptoms, particularly at a dosage of 10 mg daily (either at bed time or divided doses twice daily) for children 6 to 12 years.

## 4.2 Topical (intranasal) antihistamines

Up until the late 80s, antihistamines had not yet been developed for local application. In the last 20 years, several clinical trials have been carried out on local application of various new generation antihistamines. Their marketing and use started almost 15 years ago.

### 4.2.1 Azelastine

Azelastine hydrochloride was initially researched for use in bronchial asthma, and is currently used in the symptomatic treatment of seasonal AR and for acute exacerbations of perennial AR. It is administered in an aqueous solution as a nasal spray, and was initially administered orally.

Clinical evaluation of its efficacy and side effects were carried out in several multicentre studies (Weiler & Meltzer, 1997). It does not affect driving ability or handling of machinery, but may occasionally irritate the mucous membrane and cause epistaxis.

One of the first studies with azelastine was published by Dorow, who performed two studies with pollen-allergic patients. The first study compared azelastine with a double-blind placebo in 16 patients over one week. Significant improvement was noted in the group using the drug, with a decrease in sneezing ( $P < .01$ ) and nasal pruritus ( $P < .01$ ). There were no significant improvements in nasal congestion and hyrorrhoea (Dorow et al, 1993).

The second study was a double-blind comparison of 36 patients treated with either azelastine or budesonide for 15 days. There were no significant differences between the groups.

Weiler studied the effects of pre-treatment with azelastine in nasal provocation with grass pollens. Mean percent improvements in the total symptom complex severity scores for azelastine were statistically significant ( $P \leq .05$ ) or showed a trend toward statistical significance ( $P < .05$  or  $P \leq .10$ ) versus placebo from the second through the first ten hours after the initial dose and for each of the last five hours of the second day, demonstrating a rapid onset of action and sustained efficacy over the 2-day study period (Weiler & Meltzer, 1997).

Grossman performed a double-blind study of 199 patients with perennial AR for 8 weeks, obtaining significant improvement when compared to placebo (Grossman et al, 1994). Other



studies have compared azelastine nasal spray with other oral antihistamines, finding that its efficacy is similar and that it has fewer side effects.

Conde Hernandez et al compared the safety and efficacy of two antihistamines, azelastine in nasal spray and oral ebastine, for 14 days. Authors found no significant differences between the two treatments, considering both to be effective in the treatment of seasonal AR (Conde Hernández et al, 1995a; Conde Hernández et al, 1995b).

Berlin et al compared the efficacy of topical nasal corticosteroids with antihistamines in nasal spray (azelastine), and found that the results with topical nasal corticosteroids were clearly superior for managing nasal symptoms of rhinitis. The authors recommended topical nasal corticosteroids as a first-line treatment of perennial AR (Berlin et al 2000).

#### 4.2.1 Levocabastine

The first antihistamine developed for nasal application, levocabastine is a highly selective histamine antagonist of the H1 receptor, and acts immediately (Janssens et al, 1991). Since it is eliminated through the kidneys, it should be used with caution in renal patients. It does not sedate or boost the effects of alcohol. The dose is 2 applications of 0.5 mg each every 12 hours in each nostril. It is more powerful than chlorpheniramine (Dechant & Goa, 1991) and similar to other oral antihistamines [loratadine (Swedish GP Allergy Team, 1994) and terfenadine (The Livostin Study Group, 1993)] and disodium cromoglycate (Fisher, 1994).

In 1995, a study was published on 21 patients with AR sensitised to mites. The patients were treated with topical levocabastine, and a reduction of inflammatory mediators and nasal hyperreactivity was observed. The authors concluded that it was an effective antagonistic of H1 receptors, with immediate clinical response and few anti-inflammatory properties (de Graaf-in't Veld et al, 1995). Previously in 1991, other spanish authors showed the efficacy of levocabastine in seasonal AR using a double-blind study (Palma-Carlos et al, 1991).

### 5. Mast cell membrane stabilising drugs

Applied topically, these drugs are very useful in mild and moderate AR, as they lack systemic effects and are very well tolerated. To achieve effectiveness, appropriate application methods must be used so that an even distribution of the medication is achieved, especially if there is abundant rhinorrhoea (Okuda et al, 1985). The main drugs being used are:

#### 5.1 Disodium cromoglycate

Derived from the natural chromone Khellin, disodium cromoglycate (DSCG) is extracted from the *Ammi visnaga* plant, and was synthesised by Fisons (Cox, 1967).

It is a dual chromone joined by a flexible chain. The chromone chain has a hydrogen atom substituted by a sodium atom. It is a white powder that is barely water-soluble.

It is administered by inhalation because it is absorbed poorly orally. It has a plasma half-life of 80 minutes, and it reaches maximum levels in 20 minutes.

- *Mechanism of action:* DSCG has a stabilising effect on the mast cell membrane, preventing the release of the chemical mediators responsible for allergic reactions:

histamines and eosinophil/neutrophil chemotactic factors. It has no effect on basophils (Okuda et al, 1985). It increases the intracellular level of cyclic AMP, inhibiting phosphodiesterase and regulating the calcium retention mechanism.

- *Side effects:* Side effects are very infrequent. Symptoms may include epistaxis and dryness of nasal mucous, sometimes accompanied by sneezing. It is a safe drug, since no significant side effects have been reported in long-term treatments.

The dose is 20-40 mg every 6 hours in each nostril. Therapeutic non-compliance with the dosage is the main cause for the lack of spectacular results.

It is effective in the treatment of AR, especially in patients with high IgE (Okuda et al, 1985). It works to prevent sneezing and rhinorrhoea, but not obstruction.

DSCG performs better than placebo in studies on pollen-sensitized patients. In a double-blind study that included 104 patients and took place over 6 weeks, authors found significant improvement with minimal side effects (Handelman et al, 1977).

It is important to note that during administration:

- The container should be protected from light.
- The aqueous solution should not remain open for more than 30 days.
- Patient collaboration and discipline is necessary, since application every 6 hours is essential.
- The treatment must not be abandoned due to sneezing during administration, since it is usually temporary and lasts only a short time.
- The drug is mainly preventive and does not, therefore, provide control for patients with severe symptoms.

## 5.2 Nedocromil sodium

A pyrano quinoline dicarboxylic acid, nedocromil sodium has a half-life of 90 minutes, and is eliminated by the liver and kidneys. It acts extracellularly because it does not pass through the lipid membranes due to its physicochemical properties. It acts by blocking the chloride channels that are responsible for cellular activity. It inhibits the release of histamine, leukotriene C<sub>4</sub>, prostaglandin D<sub>2</sub> and chemotactic factors.

Although its mechanism of action is similar to DSCG, nedocromil sodium acts on other types of cells: eosinophils, neutrophil, macrophages, platelets and monocytes (Kaulbach et al, 1992).

Side effects are rare, similar to those of DSCG, although nausea, vomiting, dizziness and headaches have been reported. It is administered by inhalation in doses of 4 mg twice a day. This lower frequency of administration is an advantage over DSCG. Studies demonstrated its clinical efficacy in allergic rhinitis.

## 5.3 N-acetylaspartylglutamate acid

The magnesium salts of N-acetylaspartylglutamate (NAAGA) acid are effective in the treatment of seasonal allergic rhinitis.

Althaus performed a multicentre double-blind study for 4 weeks in pollen-allergic patients. Sixty-three patients were treated with NAAGA, 63 others with cromolyn sodium and 64

with placebo. The efficacy of NAAGA compared to placebo ( $P<.001$ ) and to cromolyn sodium ( $P<.03$ ) was demonstrated. Terfenadine was used as a rescue medication, requiring greater use for placebo than for NAAGA ( $P<.0001$ ) (Althaus & Pichler, 1994).

## 6. Vasoconstrictors ( $\alpha$ -adrenergics)

Vasoconstrictors are sympathomimetic drugs may act on  $\alpha$ -receptors, causing vasoconstriction, or on  $\beta$ -receptors (vasodilation). The use of  $\alpha$ -adrenergics in rhinitis is based on its ability to cause vasoconstriction, reducing blood flow in vessels and reducing secretions.

They are widespread in Spain, and should not be administered without medical supervision.

Those that are used topically are imidazole derivatives: oxymetazoline, naphazoline and xylometazoline. They should not be administered for more than 7 days as their prolonged use causes the onset of a rebound effect by secondary hyperaemia. This effect occurs a few hours after administration and may be interpreted by the patient as a sign of illness, which may make them increase the dose.

Vasoconstrictors have a significant effect on nasal obstruction, but continued use may cause drug-induced rhinitis, creating a dependence on nasal drops. Administration to children less than 1 year of age is dangerous.

Based on their study, Graf and Juto recommended avoiding the use of oxymetazoline in nasal spray for more than 10 days due to it causing hyperreactivity in the nasal mucosa, thus increasing susceptibility to histamines (Graf & Juto, 1994). These authors showed the lack of rebound with xylometazoline in nasal spray, when used at the recommended dosage, even over twice the recommended time period (Graf & Juto, 1995).

In the same time, other authors demonstrated the benefit of oxymetazoline above all, and xylometazoline somewhat less, in the topical treatment of nasal inflammation of rhinitis, due to its antioxidant properties (Westerveld et al, 1995).

Graf et al, in a study of oxymetazoline, benzalkonium chloride and placebo in nasal spray, found that prolonged use (more than recommended) induced an increase in nasal hyperreactivity and the feeling of nasal obstruction, developing into secondary drug-induced rhinitis. This may be related to the presence of benzalkonium in decongestant nasal sprays, which can produce or exacerbate drug-induced rhinitis (Graf & Hallen, 1996). Other authors performed a 4 to 8-week study with oxymetazoline and showed that it was safe, if used once a day, preferably at night (Yoo et al, 1997).

Moreover, it was confirmed that oxymetazoline and xylometazoline were beneficial in the treatment of upper respiratory tract inflammation, due to their dose-dependent inhibitory effects on nitric oxide synthase activity (Westerveld et al, 2000)

Stubner studied the efficacy of cetirizine associated with pseudoephedrine, comparing it to xylometazoline at 0.1% in nasal spray. With the exception of nasal obstruction, which improved quickly with xylometazoline nasal spray, the rest of the rhinitis symptoms (mainly the reduction of nasal secretions) clearly improved with the combination of anti-H1 and pseudoephedrine (Stubner et al, 2001).

Wellington compared the efficacy of the cetirizine-pseudoephedrine combination (5/120), administered twice a day with 100 micrograms of intranasal budesonide for 23 weeks. The study found that the cetirizine-pseudoephedrine combination was clearly more effective than monotherapy, significantly reducing the score symptoms for both allergic and perennial rhinitis, and was also well tolerated (Wellington & Jarvis, 2001).

## 7. Conclusions

Considering the reviewed data, and unifying the above-mentioned opinions on the treatment of AR, we provide the following guidelines:

- Aetiological treatment based on a correct aetiological diagnosis should always be achieved.
- Nasal lavage is a concomitant, non-pharmacological and economical treatment, useful in the treatment of AR and especially indicated in chronic rhinosinusitis.
- New generation antihistamines are the treatment of choice in AR and perhaps the only choice for intermittent mild rhinitis.
- Vasoconstrictors should only be used for a short time when combined with antihistamines and/or intranasal corticosteroids when nasal obstruction is not controlled.

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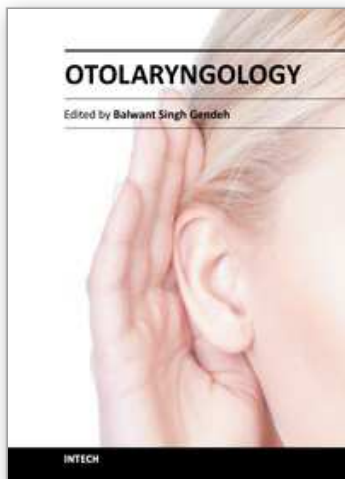
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This book emphasizes on different aspects of otolaryngology - the medical sciences of diagnosis and treatment of ENT disorders. "Otolaryngology" is divided into various clinical sub-specialities, namely otology, rhinology, laryngology, and head and neck. This book incorporates new developments, as well as future perspectives in otolaryngology. I would like to dedicate this book to those of you who will pick up the torch and by continued research, close clinical observation and the highest quality of clinical care, as well as by publication and selfless teaching, further advance knowledge in otolaryngology from this point forward. It is intended to be a guide to other books to follow. Otolaryngologists, researches, specialists, trainees, and general practitioners with interest in otolaryngology will find this book interesting and useful.

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