# Local allergic rhinitis: Diagnosis and management protocol

Review Article


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## Abstract

Aim: Propose a protocol for diagnosis and management of Local Allergic Rhinitis.
Material and Methods: Literature review of articles published in english on PubMed database, between 2000 and 2021.
Results: Clinically Local Allergic Rhinitis manifestations are similar to allergic rhinitis, however prick tests and specific-IgE serum levels are negative. The diagnosis requires a positive response during a Nasal Allergen Provocation Test. The therapeutic algorithm consists of allergen avoidance measures and pharmacotherapy. When these measures are insufficient to control symptoms, specific immunotherapy can be administered to Local Allergic Rhinitis patients.
Conclusions: Local Allergic Rhinitis is a new rhinitis phenotype and is underdiagnosed, affecting a significant proportion of patients diagnosed with non-allergic rhinitis.
The implementation of Nasal Allergen Provocation Test in rhinitis diagnostic algorithms is essential for early recognition of Local Allergic Rhinitis and management of the correct therapeutic approach.


Keywords: allergic rhinitis; local allergic rhinitis; rhinitis diagnostic methods; rhinitis therapeutic approaches.


## Introduction

Rhinitis is an inflammation of the nasal mucosa, which is associated with symptoms such as nasal congestion, sneezing, rhinorrhea, and nasal itching. Noninfectious rhinitis is classified into allergic rhinitis (AR) and non-allergic rhinitis (NAR) after considering the clinical history, response to the skin prick tests (SPT), and serum levels of immunoglobulin E for specific inhaled allergens (sIgE)[1].

AR is the most common noninfectious rhinitis. However, NAR is also very prevalent[1].

Some European centers have suggested that 47% to 62.5% of patients with symptoms of perennial or seasonal rhinitis have undetected specific serum IgE antibodies and negative

SPT. Most of these patients receive a diagnosis of idiopathic rhinitis or non-allergic rhinitis with eosinophilia syndrome (NARES)[2-5].

Recent evidence indicates that the classic approach to rhinitis is incomplete because many patients diagnosed with NAR may be classified as having a local allergic rhinitis (LAR) phenotype[2-6].

The first evidence of a localized allergic response in the nasal mucosa, with local production of IgE antibodies in patients with NAR, was reported in 1975 by Huggins and Brostoff[9]. In 2001/2002, an Australian group[2] also reported an increase in the local production of IgE antibodies in the nasal mucosa of patients with AR and NAR. This phenomenon was described as "entopy", or an allergic response restricted to the nasal mucosa in the absence of a systemic allergic response[1-2]. These findings led to the identification of a distinct phenotype, LAR, which was initially considered NAR (with negative SPT)[1-6].

LAR is a localized nasal allergic response in the absence of systemic atopy. It is characterized by the local production of specific IgE antibodies and a pattern of $T_H2$ inflammatory response during exposure to aeroallergens, as well as a positive response to nasal allergen provocation tests (NAPT) with the release of inflammatory mediators in the nasal secretions (tryptase and eosinophil cationic protein)[8].

According to the literature, the prevalence of LAR is higher in southern European countries (Portugal, Spain, Italy, and Greece), accounting for 50% to 75% of the rhinitis cases initially diagnosed as NAR. However, it remains an underdiagnosed clinical entity[3-6]. The estimated prevalence of LAR in Asian countries is not higher than 20%[9-10].

## Materials and Methods

This was a systematic review of the literature published on LAR, with an emphasis on diagnostic and therapeutic approaches, to establish a protocol. The search was conducted in the online database PubMed and included articles published between January 2000 and December 2021. The following keywords were used: "allergic rhinitis", "local allergic rhinitis", "rhinitis diagnostic methods", "rhinitis therapeutic approaches".

The review was restricted to studies published in English. The eligible articles were selected in three stages, based on a sequential review of the title, abstract, and full-text publication.

The publications included review articles, meta-analyses, systematic reviews, practice protocols, and cross-sectional and cohort studies. Studies with one or more of the following characteristics were excluded: studies with non-standardized methods, duplicate and overlapping studies, and studies published in languages other than English.

After the application of the inclusion criteria, 19 articles were used to establish our protocol.

## Results

**1. Definition and classification of rhinitis:**

The etiologic classification of non-infectious rhinitis divides it into AR and NAR. The exact prevalence of NAR is unknown, as it corresponds to a heterogeneous group of diseases with nasal manifestations that are associated with a specific triggering factor ("trigger") in some cases. However, its cause is unknown in most cases and NAR is categorized as idiopathic or vasomotor rhinitis.

NARES is deemed a distinct nosological entity, in which a subgroup of patients with NAR has eosinophilia in the nasal mucosa, with a good response to topical treatment with nasal corticosteroids[9]. In recent years, several authors have shown that a significant percentage of patients with a negative SPT and negative serum specific IgE, who would be classified as having NAR, present with nasal symptoms after NAPT[3-4]. More recent studies have suggested that in these patients, production of specific IgE occurs locally in the nasal mucosa; therefore, a new phenotypic entity has been proposed – LAR, which has led to a new etiologic classification of rhinitis[3-6,11] (Table 1).

**Table 1**
Etiologic classification of rhinitis (adapted from Rondón *et al.*[11])

| |
|---|
| **1. Allergic Rhinitis** |
| **Allergic Rhinitis (with systemic atopy)** |
| Classic Classification |
| Time of exposure to the aeroallergen: perennial, seasonal, occupational |
| ARIA Classification[1] |
| Duration of the symptoms: persistent, intermittent |
| Severity of the symptoms: mild, moderate, severe |
| **Local Allergic Rhinitis (without systemic atopy)** |
| Classic Classification |
| Time of exposure to the aeroallergen: perennial, seasonal, occupational |
| ARIA Classification[1] |
| Duration of the symptoms: persistent, intermittent |
| Severity of the symptoms: mild, moderate, severe |
| **2. Nonallergic Rhinitis** |
| Infectious |
| Occupational |
| Induced by drugs |
| Hormonal |
| Irritant |
| Gustatory |
| Emotional |
| Atrophic |
| NARES |
| Idiopathic |

**2. LAR – Epidemiology and pathophysiology:**
LAR is more prevalent in Mediterranean countries than in northern European and Asian countries[12]. The prevalence of LAR among children has been little studied; however, the existing studies show that it is similar to that among adults[12-14].
The allergens most frequently associated with LAR are house dust mites (Dermatophagoides pteronyssinus), grasses, Alternaria alternata, and, less frequently, animal hair and Olea europaea (olive)[3-5]. Nasal reactivity to several aeroallergens can occur, similar to what occurs in AR[3,5,15].
Rondón *et al.* demonstrated that patients with LAR exhibit an eosinophilic infiltrate in the nasal mucosa after exposure to an aeroallergen, as well as a sudden increase and subsequent decrease in tryptase in the nasal secretions, while the concentration of eosinophil cationic protein (ECP) increases gradually in the following 24 hours[3,6]. Moreover, patients with LAR exhibit a significant increase in IgEs in the nasal secretions within 24 hours after exposure to the aeroallergen[3]. These immunological findings indicate an underlying IgE-mediated pathological mechanism.
The presence of IgE in nasal secretions of patients with LAR after exposure to aeroallergens is detected in 22% to 35% of patients[3,4]. This low detection rate of IgE may be explained by the low sensitivity of the diagnostic method used; therefore, the measurement of IgE in nasal secretions is used solely for research purposes and not as a diagnosis method in clinical practice[3,4,16].
The analysis of nasal secretions by flow cytometry in patients with LAR exposed to aeroallergens demonstrated a pattern of inflammatory infiltrate similar to that seen in AR, with increased levels of eosinophils, basophils, mast cells, and $CD3^+$ and $CD4^+$ T cells, suggesting a $T_H2$/IgE-mediated inflammatory response[3,4].

**3. Clinical manifestations:**
The symptoms of LAR are similar to those of AR. Patients may present with nasal congestion, rhinorrhea, sneezing, and nasal itching. The latter three are more frequently reported in LAR[3-5] (Table 2). These patients may also exhibit other extra-nasal diseases such as conjunctivitis and asthma. Most patients with LAR report having persistent moderate to severe symptoms, associated with conjunctivitis and asthma (in up to 50% of patients)[3-4,11].

**Table 2**
Clinical manifestations of local allergic rhinitis

| Local Allergic Rhinitis – Clinical manifestations |
|---|
| Anterior rhinorrhea |
| Sneezing |
| Nasal itching |
| Nasal congestion |

**4. Diagnosis:**

Some manifestations of NAR mimic symptoms of AR but it is very important to distinguish them because the treatment approach of these two conditions may differ.

Rondón *et al.*[11] proposed a new diagnostic approach in patients with symptoms of AR who have a negative SPT and sIgE (Figure 1).

The diagnosis of LAR can be confirmed through the detection of IgE in nasal secretions and/or through a positive response to NAPT. However, NAPT is the gold standard method for the diagnosis of LAR due to its high specificity, sensitivity, and reproducibility[3-6,8].

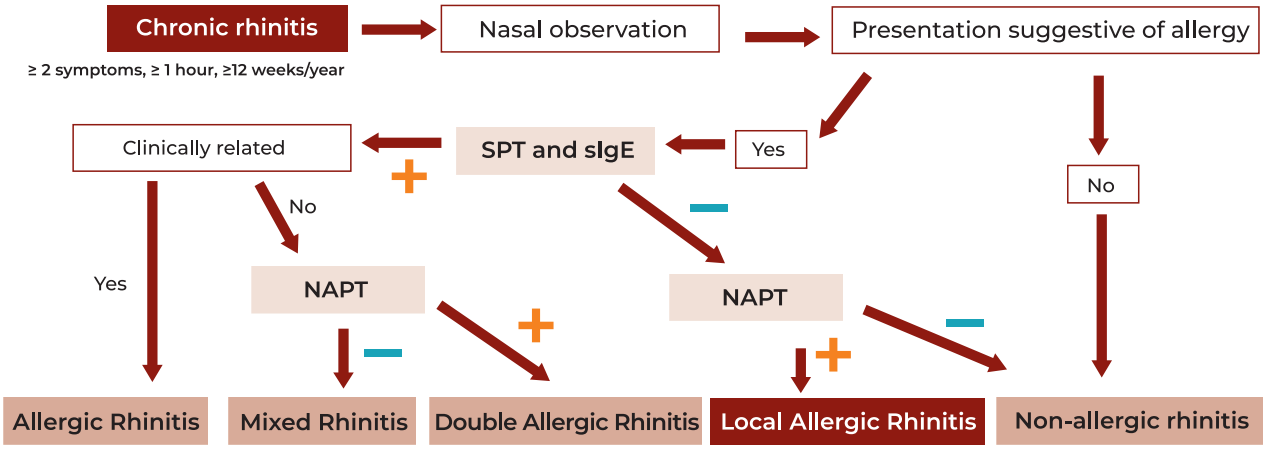
**4.1 NAPT:**

The NAPT is a safe and well tolerated technique, both through nasal administration and using a micropipette[17]. This technique has high diagnostic precision, because of the standardized and validated method for the cut-off parameters[18]. In addition to being used for the diagnosis of LAR, the NAPT can also be used in other clinical situations[19] (Table 3). There are absolute contraindications for performing the NAPT, including acute viral or bacterial rhinosinusitis, acute exacerbation of the allergic disease, previous anaphylactic reaction to an allergen, systemic diseases with reduced lung capacity, and pregnancy. Relative contraindications that warrant the delay of NAPT are as follows: episodes of AR exacerbation (wait 2-4 weeks), nasal surgery (wait 6-8 weeks), and treatment with: antihistaminic drugs (wait 3 days), topical nasal corticosteroids (wait 1 week), oral corticosteroids at a dose higher than 10 mg (1-2 weeks), nonsteroidal anti-inflammatory drugs (1 week), centrally acting antihypertensives

**Table 3**
Indications for performing the NAPT

| Indications for performing the nasal allergen provocation test (NAPT)[19] |
|---|
| Diagnosis: |
| Persistent allergic rhinitis |
| Intermittent allergic rhinitis |
| Local allergic rhinitis |
| Occupational allergic rhinitis |
| Correlation with extra-nasal symptoms |
| Differential diagnosis of ocular symptoms |
| Increasing the evidence for the diagnosis of food allergies |
| Clinical monitoring of the efficacy of immunotherapy |

**Figure 1**
Diagnostic approach to local allergic rhinitis




Abbreviations: SPT, skin prick tests; sIgE, serum levels of Immunoglobulin E specific for inhaled allergens; NAPT, nasal allergen provocation test; "-"if negative; "+"if positive

(3 weeks), and tricyclic antidepressants (1 week)[19-20]. The solution used in the NAPT is composed of an allergen extract at a predefined concentration, diluted in an isotonic solution at neutral pH[19-20]. Rondón *et al.*[18] established a NAPT protocol with multiple allergens, in which they used the following concentrations of the aeroallergens most commonly associated with LAR: solutions of *Dermatophagoides pteronyssinus* at 4 µm/mL, *Alternaria alternata* at 0.25 µm/mL, *Olea europaea* at 0.6 µm/mL, and grasses at 0.1 µm/mL.

### 4.2 Protocol for the NAPT (Figure 2):

Certain conditions need to be met for performing the NAPT to ensure its reproducibility and similarity with daily life conditions:

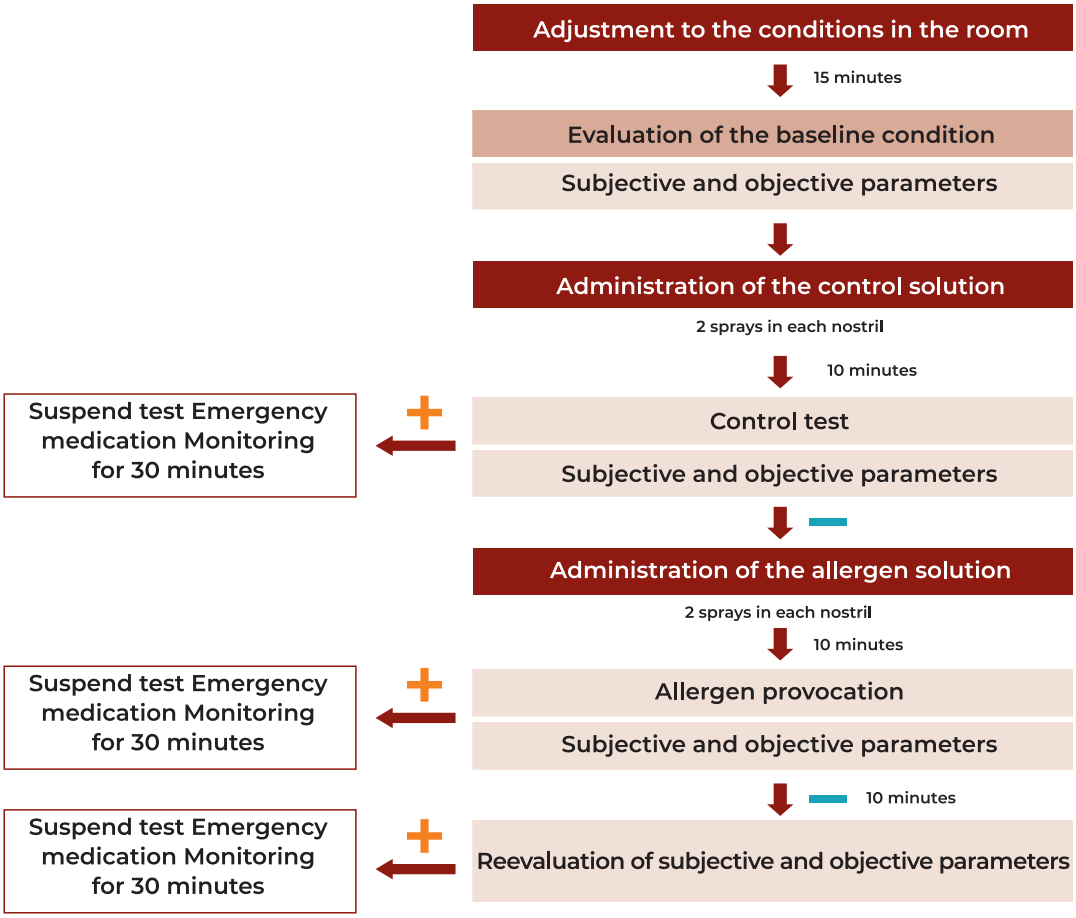
**a) Conditions of the test room**

The patients should be adjusted to the conditions of the room where the NAPT will be performed for 15-30 minutes before the start of the test. The room should be at a temperature of 20+/-1.5 °C with humidity between 40% and 60%[15,19-20].

**b) Qualified staff and emergency medication**

The patients should sign an informed consent form before undergoing the NAPT. The site of the test should be located at less than a 30-minute distance from an emergency room and intensive care unit. There should be an emergency medicine kit in the room[19].

**Figure 2**
Protocol of the Nasal Allergen Provocation Test (NAPT)




Subjective parameters: symptoms reported by the patient (nasal congestion, rhinorrhea, sneezing, nasal itching, ocular symptoms), classified according to their severity (0 – none; 1 – mild; 2 – moderate; 3 – severe). Objective parameters: evaluation of nasal permeability through active anterior rhinomanometry.

c) Allergens

The allergens are available in the form of standard solutions. The solutions used in the NAPT should be isotonic and at neutral pH[15,19-20].

d) Allergen administration technique

The most reproducible and easiest form of allergen administration is the nasal spray, because it allows the delivery of a similar standard amount of the allergen to patients, with a precise dose of 50 µL per spray being administered. Allergen administration is performed with two sprayings in each nostril, one at the level of the inferior meatus and the other toward the middle meatus[19-20]. Inclination toward the nasal septum should be avoided. The following measures should be taken during spray application to prevent allergens from reaching the lower airway: 1. Deep inhalation, 2. Stop breathing during spray application, 3. Deep exhalation after spray application[15,19].

e) Evaluation of the results

All patients undergo an evaluation through a questionnaire on symptoms, rhinoscopy, anterior rhinomanometry, and/or acoustic rhinometry to establish the patient's baseline status. After the period of adjustment in the test room, a test is performed with saline solution (two sprayings in each nostril) to exclude hyperreactivity of the nasal mucosa. The parameters of the baseline evaluation are retested 10-15 minutes after this initial test. If no changes occur, the NAPT can then be performed. The parameters are reevaluated 10-15 minutes after allergen provocation. When the test is finished, the patients remain under observation for 30 minutes to check for any allergic reaction.

f) Criteria of positivity in the NAPT

For evaluating the response to the NPT, both subjective (symptoms) and objective (nasal permeability) parameters after allergen provocation are considered.

The ideal assessment of the subjective parameters is that proposed in the Position Paper by Augé *et al.*[19], which was based on the Total Nasal Symptom Score as well as the Linder and Lebel scores, and considers five symptoms: sneezing, nasal itching, rhinorrhea, nasal congestion, and ocular symptoms (Table 4). The reported symptoms are classified according to the severity described by the patient (0 – none; 1 – mild; 2 – moderate; 3 – severe). The scores given to each symptom are added to obtain the total score, which is compared before and after the NAPT.

**Table 4**
NAPT: Subjective criteria

| Subjective criteria |
|---|
| Nasal congestion |
| Rhinorrhea |
| Sneezing |
| Nasal itching |
| Ocular symptoms |

Nasal permeability is evaluated using the following objective methods: peak nasal inspiratory flow (PNIF), active anterior rhinomanometry, acoustic rhinometry, or four-phase rhinomanometry[19] (Table 5). In this protocol, the authors used active anterior rhinomanometry due to its sensitivity and high specificity and because it is the standard internationally accepted method for the objective assessment of nasal permeability[19].

The evaluation of nasal permeability through active anterior rhinomanometry is performed before NAPT and is repeated 10 minutes after it. Then, the variation in nasal permeability between the two tests is determined.

The NAPT is considered positive (Table 6) when one of the following criteria is met[19]:

- Significant change in the subjective parameters (≥5);
- Significant change in the objective parameters (≥40%);
- Moderate changes in the subjective (≥3) and objective (≥20%) parameters.

**Table 5**
NAPT: Objective criteria – Complementary diagnostic procedures

| Objective criteria | |
|---|---|
| Peak nasal inspiratory flow (PNIF) | - Easy to execute, inexpensive<br>- Dependent on the patient's collaboration and lung capacity |
| Acoustic rhinometry | - Easy and fast execution<br>- Not dependent on the patient's collaboration |
| Active anterior rhinomanometry | - Sensitive, high specificity<br>- Standard method for measuring nasal permeability |
| Four-phase rhinomanometry | - Most reliable method to evaluate nasal permeability and ventilation |

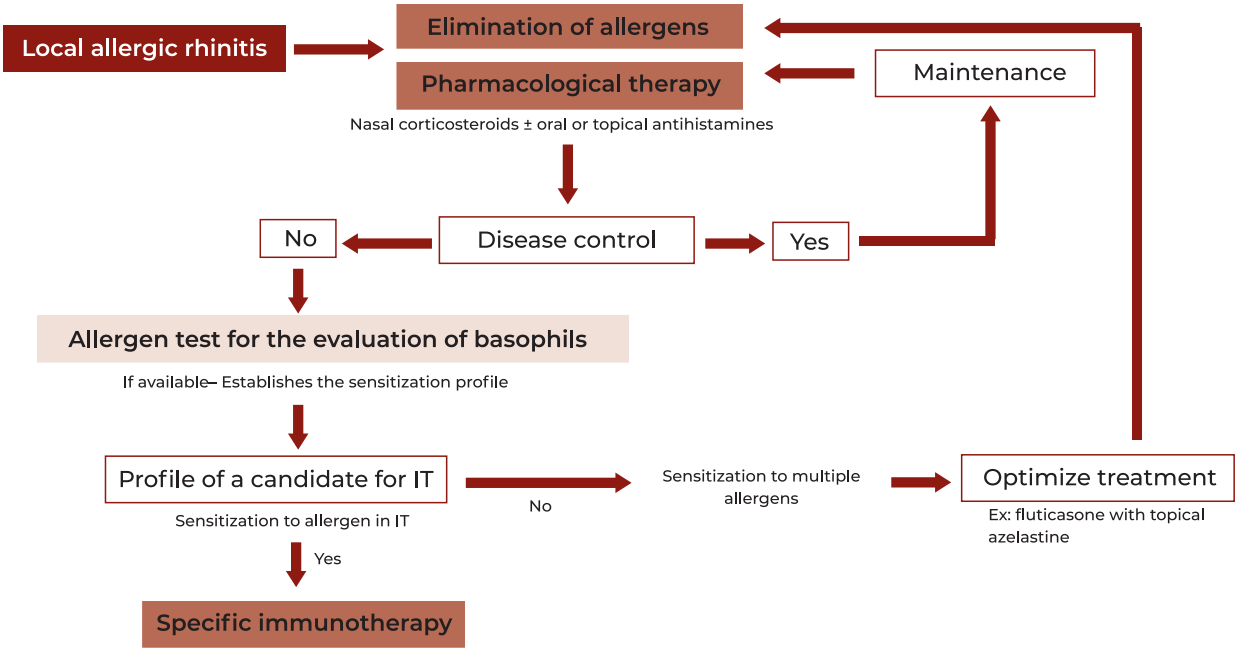
**Table 6**
Positivity in the Nasal Allergen Provocation Test (NAPT)

| Method | Significant change | Moderate change |
|---|---|---|
| **Subjective** (symptoms) | Increase of ≥ 5 points in the total score of the classification of symptom severity | Increase of ≥ 3 points in the total score of the classification of symptom severity |
| **Objective** | Decrease of ≥ 40% in nasal permeability | Decrease of ≥ 20% in nasal permeability |

## 5. Treatment

An accurate distinction between LAR and NAR is important for the correct therapeutic approach to LAR (Figure 3). Despite the absence of a study on the efficacy of allergen elimination and pharmacotherapy in patients with LAR, an improvement in the symptoms has been reported with topical nasal corticosteroids and oral and topical antihistamines[3-4,10]. This is a phenotypic characteristic of LAR that contrasts with NAR and may be explained by the clinical and pathophysiological similarities between LAR and AR, which include eosinophilic inflammatory infiltrate and reactivity to allergens. An observational study and four double-blind clinical trials, controlled by placebo,[21-24] showed an improvement in LAR with the use of specific immunotherapy (IT)

**Figure 3**
Therapeutic approach to local allergic rhinitis IT, immunotherapy.



Six months after IT, there was a reduction in patients' symptoms (nasal, ocular, and lung symptoms) and use of emergency medication, as well as a greater tolerance to allergens and improved quality of life. The success of IT in LAR is associated with an increase in the serum levels of specific $IgG_4$ and a decrease in IgE in the nasal secretions. However, it has not been reported whether the use of IT in LAR modifies the clinical course of the disease[16].

## Discussion

The diagnosis of AR is based on the clinical history, positive response in SPT, and positive serum specific IgE. However, a structured clinical history along with directed sIgE increases the diagnostic precision in AR, compared with clinical history alone.

However, this diagnostic approach does not allow the diagnosis of LAR in which the SPT and sIgE are negative, and it is thus necessary to perform the NAPT[2-6]. The fact that the patients diagnosed with LAR already have an extended follow-up and monitoring period, without progression to AR, supports the notion that LAR is a separate entity from AR, despite the similar symptoms and therapeutic response[8]. Some authors advocate IgE testing in nasal secretions during natural exposure to allergens or after the NAPT because the in vitro detection of sIgE has high specificity, despite having low sensitivity (between 22% and 40%). Its low sensitivity may be explained by the effect of dilution, a non-specific response to house mites, or other not yet identified factors[8]. Given its low sensitivity, IgE detection in nasal secretions is not a good method for the diagnosis of LAR and is reserved for research purposes[3-4,16].

The NAPT is a very useful diagnostic tool as it is more sensitive than other diagnostic methods such as the detection of sIgE, tryptase, ECP, or the basophil activation test, although its execution is time consuming[3-6].

Rondón et al.[15] defined a protocol for the testing of several allergens in a single session (NAPTm), using a panel of four allergens most commonly involved in LAR. They concluded that this method was as useful, specific, sensitive, and reproducible as testing with a single allergen, as well as less time-consuming. In addition, they demonstrated that NAPTm is in total agreement with the results of the NAPT and is safe, with no exacerbated inflammatory response compared to the NAPT. In a previous study by Wierzbicki et al.[25], in which a panel of multiple allergens was also used in the NAPT for the diagnosis of LAR in patients initially classified as perennial NAR, there were seven false positive results. These discordant results may be explained by the use of a different control solution (may trigger a nasal irritant response) or by the fact that the test was performed in only one nasal cavity. Some allergen solutions contain preservatives that react with the nasal mucosa and it is thus essential to have control by conducting a test with the dilution solution in the nasal mucosa to exclude nasal hyperreactivity[19].

On the other hand, in their protocol, Wierzbicki *et al.*[25] also used a concentration of allergen (namely D. pteronyssinnus) lower than that recommended to trigger a positive response in the nasal mucosa. Although NAPTm is essential for the diagnosis of patients with LAR who are mono- and polysensitized to allergens, it is not possible to measure the intensity of the nasal allergic response. This is only possible through a NAPT with a gradual increase in the concentration of the allergen administered during the provocation until a target concentration that triggers the allergy symptoms is reached[3-4].

For the evaluation of the response to NAPT, several scales exist that facilitate the subjective assessment of allergy symptoms.

The classification of the response may be based on the patient's report of nasal symptoms, such as the Likert scale (0 – none, 1 – mild, 2 – moderate, 3 – severe) or the visual analogue scale (VAS) may be used for reporting the severity of the symptoms (mild: 0-30 mm; moderate: 31-70 mm; severe: 71-100 mm). The Total Nasal Symptom Score (TNSS) is a scale that assesses four symptoms (rhinorrhea, nasal congestion, sneezing, and

nasal itching). In the Position Paper by Augé et al.[19] it was suggested that the ideal scale to evaluate the symptoms of AR should consider the following symptoms: rhinorrhea, nasal congestion, sneezing, nasal itching, and ocular symptoms. Although there is no study on the effect of allergen elimination or medical treatment in patients with LAR, they exhibit a good response to treatment with topical nasal corticosteroids and topical or oral antihistamines, such as in AR[16]. Unlike NAR, this good response to pharmacological treatment may be explained by the similarities in the nasal inflammatory pattern of patients with local and allergic symptomatology.

In recent years, it has been suggested that IT has a role in LAR. The use of IT in LAR was supported by one observational study and four double-blind clinical trials, controlled by placebo[21-24]. These studies have shown that IT allows control of nasal, conjunctival, and bronchial symptoms and possibly reduces rescue medication use in patients with LAR sensitized to grass pollens, birch pollen, and house dust mites. Moreover, IT improves the quality of life and nasal and bronchial tolerance to the allergen in patients with LAR. IT is a safe treatment, with only a few mild and moderate reactions having been observed during its administration, both with the allergen and placebo solutions[14]. It has not yet been possible to determine the long-term effects of IT in patients with LAR or its ability to modify the natural course of the disease. However, in cases of LAR refractory to preventive measures and/or corticosteroids and oral or nasal antihistamines, IT may be administered to reduce symptoms, reduce the need for rescue medication, and improve the quality of life[16].

## Conclusion

LAR is a phenotype that differs from the described classical rhinitis and remains an underdiagnosed condition that affects a significant proportion of patients classified as having NAR (negative SPT and serum specific IgE).

The implementation of the NAPT in the diagnostic algorithms of rhinitis is essential for the early recognition of LAR and adequate treatment prescription. Unlike NAR, LAR responds well to medical treatment with nasal corticosteroids and/or oral or topical antihistamines.

In moderate to severe cases of LAR refractory to medical treatment, subcutaneous IT with a specific allergen is a safe treatment and has good results, including control of symptoms, reduced need for rescue medication, and improved quality of life.

### Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

### Data Confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

### Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.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### Availability of scientific data

There are no datasets available, publicly related to this work.

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