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ABSTRACT

In the past years several investigators have demonstrated the existence of local nasal responses in some patients with typical allergic rhinitis symptoms but without atopy, and have defined a new phenotype called local allergic rhinitis (LAR) or “*entopy*”. In a percentage of LAR subjects, the upper airway disease is also associated with lower airway symptoms. After the description of this phenotype, the differential diagnosis between LAR and non-allergic rhinitis (NAR) has become a challenge for the clinician.

To correctly identify LAR patients is of high importance for treatment and management of these patients, and for an appropriate inclusion of patients in clinical trials and genetics studies. The treatment of LAR patients, in contrast with NAR is oriented to allergen avoidance and specific treatment. Allergen immunotherapy, the aetiological specific treatment for allergic respiratory diseases, has demonstrated to be an effective and safe treatment in LAR, increasing immunological tolerance, and reducing the clinical symptoms and the use of medication.

In this article, the important and novel aspects of LAR in terms of mechanisms, diagnosis and treatment will be discussed. Also, the involvement of the lower airway and the potential role of IgE in the bronchial disease will be also reviewed.

KEYWORDS: allergen immunotherapy; asthma; local IgE; local allergic rhinitis; non-allergic rhinitis

ABBREVIATIONS:

ACT:	Asthma control test
AIT:	Allergen immunotherapy
AR:	Allergic rhinitis
BAT:	Basophil activation test
CRS:	Chronic rhinosinusitis
CSR:	Class switch recombination
DBPCCT:	Double-blind placebo-controlled clinical trial

FcεRI:	Human high affinity receptor for IgE
FEV ₁ :	Forced expiratory volume in 1 second
GC:	Germinal centers
GETE:	Global evaluation of treatment effectiveness
LAR:	Local allergic rhinitis
MCP:	Monocyte chemotactic proteins
NAR:	Non-allergic rhinitis
NAPT:	Nasal allergen provocation test
SCIT:	Subcutaneous immunotherapy
sIgE:	Specific IgE
SHM:	Somatic hypermutation
SPT:	Skin prick test

INTRODUCTION

Rhinitis is a highly prevalent disease that represents an important medical and economical burden. This term includes several different phenotypes, and to properly identify each of these subtypes is not always an easy task (1).

Classically, rhinitis has been divided in allergic rhinitis (AR) and non-allergic rhinitis (NAR) based on a basic allergological evaluation. NAR comprises an ample group of diseases characterized by the presence of at least two nasal symptoms (obstruction, rhinorrhea, sneezing, pruritus) in the absence of sensitization to allergens. The diagnosis is based mostly by exclusion (1, 2).

Due to the recent research studies, many advances have been made in the field of NAR. Several investigators in the past years have demonstrated the existence of local nasal responses in some patients with typical allergic rhinitis symptoms but without atopy, and have defined a new phenotype called local allergic rhinitis (LAR) or “*entopy*” (3-6). In an important percentage of LAR subjects, the upper airway disease is also associated with lower airway symptoms (7). After the description of this phenotype, the diagnosis of NAR has become a challenge for the clinician, since a variable percentage of patients initially labelled as NAR will be in fact LAR patients(3-6, 8, 9). To correctly

identify LAR patients is of high importance for the treatment and management of these patients will be, in contrast with NAR, oriented to allergen avoidance and specific treatment of the disease {Campo, 2015 #6; (10). In addition, a correct rhinitis phenotype is essential for the design and interpretation of the results of genetic studies and the study of pathophysiological mechanisms involved in airway diseases.

In this article, the important and novel aspects of LAR in terms of mechanisms, diagnosis and treatment will be discussed. Also, the involvement of the lower airway in these patients and the potential role of IgE in the bronchial disease will be also reviewed.

LAR vs. NAR: TWO DIFFERENT RHINITIS PHENOTYPES

LAR is a distinct rhinitis phenotype characterized by symptoms suggestive of allergic rhinitis (AR) due to a localized allergic response in the nasal mucosa in the absence of atopy assessed by conventional diagnostic tests such as skin prick test (SPT) or determination of specific IgE (sIgE) in serum (11, 12). The immunological characteristics of LAR are a nasal Th2 allergic inflammation (3-6), with positive response to nasal allergen provocation test (NAPT) (5-7, 9, 13), and nasal production of sIgE (3-6, 14, 15) and inflammatory mediators (14, 16, 17). A better understanding of the underlying immune mechanisms of this disease is essential for developing diagnostic methods and targeted therapies (10).

Similar to AR, LAR can be classified as seasonal, perennial, intermittent, persistent and mild, moderate and severe (18). Patients with LAR have shown a tendency toward worsening over time, with impairment in quality of life, an increase in rhinitis persistence and severity, the use of emergency assistance, and new associations with conjunctivitis and asthma (18).

After the description of LAR, the diagnostic workup in patients with rhinitis has changed (11, 12), and new epidemiological studies are required for establishing the clinical phenotype, comorbidities and natural evolution of LAR and NAR.

NAR is a heterogeneous group of nasal conditions with chronic nasal symptoms including at least 6 sub-phenotypes: drug-induced rhinitis, gustatory rhinitis, hormone-induced rhinitis, rhinitis of the elderly, atrophic rhinitis, and idiopathic rhinitis (2, 19). The diagnosis of NAR is made by clinical history, and by exclusion of an endonasal infection and signs of AR and LAR (20, 21). The differentiation between LAR and NAR is necessary for accurate therapeutic management of patients and for an appropriate inclusion of patients in clinical trials and genetics studies.

Studies performed well-phenotyped LAR and NAR patients have identified several clinical-demographic markers or risk factors that may be useful for identifying LAR patients among those subjects with rhinitis symptoms and absence of atopy (22) (Table 1).

LOCAL IgE IN RHINITIS

Specific IgE is a major contributing factor in multiple airway allergic diseases. However, their presence on the surface of skin mast-cells or as free molecules circulating in serum—as assessed by SPT or in vitro tests—indicates sensitization, but fails to give information about the allergic response in the target organ (11, 12, 23). In fact, up to 50% of the health population may have positive SPT/serum sIgE without any clinical manifestations of allergy (24). In contrast, the absence of sIgE in the nasal mucosa seems to be more related with the absence of symptoms in most healthy sensitized subjects (23).

From 1947 (25) to present, multiple studies have demonstrated the presence of IgE in the target organs of AR (5, 6, 26-32) and LAR (3, 5, 6, 14-17, 33). A majority production of sIgE in target organs can explain the reason for some atopic subjects of developing rhinitis, and others asthma, conjunctivitis, and/or eczema alone or in combination (34).

In 1979 Platts-Mills et al. (28) first proposed the local production of sIgE to rye grass pollen in AR. After demonstration of elevated concentrations of allergen sIgE in serum and nasal secretions, but not in saliva they suggested that the nasal mucosa was the source of allergen-specific IgE in the patients'

sera. In 1994 Sensi et al. (35) compared the concentrations of house dust mite-specific IgE in the nasal fluid and serum in alternative periods of allergen avoidance and re-exposure. Interestingly the rates of the decrease after avoidance and increase following re-exposure were strongly faster in the nose than in the serum. These observations suggested a local origin of the allergen-specific IgE in AR (35). The slower changes in the serum may be the reflect of the half-life of plasmablasts migrating out of the nasal mucosa and associated lymphoid tissue during the allergic response, followed by cell death or migration to the bone marrow to become long-lived IgE-secreting plasma cells (36). In 1997 Durham et al. (27), detected interleukin 4 and epsilon gene transcripts by in situ hybridization in B cells in the nasal mucosa of AR patients supporting the local IgE synthesis (Figure 1).

More recently ex-vivo stimulation of mucosa obtained from allergic patients leads to an increase in IgE, confirmed the local mucosa production of sIgE in allergic patients (29). In LAR, elevated concentration of nasal sIgE has been confirmed after allergens natural exposure (5, 6, 37), after controlled exposure by NAPT, (14-17) and in non-exposure (16, 17). Kinetics studies in patients with LAR after NAPT with grass pollen (17) and *D. pteronyssinus* (16) revealed that aeroallergen exposure induces local sIgE production, mast-cells and eosinophil activation with nasal secretion of tryptase and eosinophil cationic protein (ECP) (Figure 2). In these studies the presence of nasal sIgE antibodies against grass pollen and *D. pteronyssinus* during periods of non-exposure and their fast and progressive increase from 1- 24 hours after NAPT demonstrated the existence of a persistent nasal production of the sIgE that rapidly increases after allergen specific stimulation in the nasal mucosa (Figure 2)(16, 17). Cellular studies in AR have confirmed the expression of epsilon germline gene transcripts and messenger RNA for the epsilon heavy chain of IgE in nasal mucosal B cells (26). In addition, the localization of free light chains of IgE in tissue and nasal secretions of patients with AR and with NAR suggests that they could mediate immune responses involving mast-cells (Figure 3)(11, 38).

LOCAL IgE IN ASTHMA

The definition of non-allergic asthma comprises a subset of subjects with asthma where allergic sensitization cannot be demonstrated, since asthma, like rhinitis, has been traditionally classified as allergic or non-allergic based on the presence or absence of atopy (negative skin prick test/ *in vitro* specific-IgE test to a panel of seasonal and perennial allergens) (39, 40). Many investigators have studied the characteristics of each type of asthma, and surprisingly, epidemiological studies yielded important similarities in the pathophysiology of allergic and non-allergic asthma (41-46). In some studies performed in bronchial biopsies, similarities in the inflammatory cellular infiltrate of the bronchial mucosa have been described (47, 48). Moreover, there is an elevated expression of key cytokines such as IL-5, IL-4 and IL-13 in the bronchial mucosa of both atopic and non-atopic asthmatics compared with controls (41, 45, 49). Also, in both atopic and non-atopic asthmatics an elevated expression of eosinophil chemotactic chemokines such as eotaxin, eotaxin-2, RANTES, monocyte chemotactic proteins (MCP-3, MCP-4), and also of the CCR3 receptor has been demonstrated (50, 51). Although many of the immunopathologic features of non-allergic asthma are comparable between both types of asthma, some differences exist, including a higher expression of RANTES in mucosa and bronchoalveolar lavage fluid, as well as a higher GM-CSF receptor alpha expression in non-atopics (52, 53).

Regarding the role of IgE in non-atopic asthma. Different studies have demonstrated the local synthesis of IgE in the bronchial mucosa of atopic and non-atopic asthmatics, with increased expression of the IgE epsilon heavy-chain germ line and mature gene transcripts compared with controls, and local IgE class switching (44, 46). Non-atopic as well as atopic asthmatics also show up-regulation of the high-affinity IgE receptor FcεRI in the bronchial mucosa (42). This has led to the hypothesis that the respiratory mucosa may be a major site of IgE synthesis, and that IgE-mediated mechanisms may participate in the pathogenesis of both atopic and non-atopic asthma. However, the way this local IgE production is related to the airway cellular inflammatory profile is still not well known.

An important question is if the IgE in the lung could be allergen-specific, as has been demonstrated in the nose of AR and LAR patients (6, 28), and in nasal polyp tissues from non-atopic patients (54). In an interesting study, functional IgE antibodies to house dust mites allergens were detected in sputum from patients with non-atopic asthma after bronchial challenge with *D. pteronyssinus*, despite the fact that these patients did not clinically respond to the challenge (55). Recently, studies performed in bronchial mucosa of atopic asthmatics, non-atopic asthmatics and controls showed an elevated median total IgE in both asthmatic groups. However, allergen-sIgE determined by microarray was only demonstrated in atopic subjects (56). Therefore, the specificity and functional activities of IgE in both types of asthma should be further investigated.

ASSOCIATIONS BETWEEN LAR & ASTHMA

Patients with rhinitis frequently present asthmatic symptoms associated (57). In several studies performed in LAR patients, this same association has been demonstrated (5-7, 58, 59). In the aforementioned studies, the frequency of lower airway symptoms ranges from 18.8 to 47%, but there are no studies demonstrating the real prevalence of asthma by objective measurements (e.g. methacholine test) in this population, since data is mostly from self-reported symptoms. In a follow-up study of 176 LAR subjects for a period of 5 years ($p=0.464$), asthma was the second most commonly associated disease at the initial evaluation (18.8%) after conjunctivitis (52.3%). After 5 years, the number of patients of the patients with lower airway respiratory symptoms increased to 24.4% although it was not significant ($p=0.195$). The analysis of the use of medical emergency services during those first 5 years revealed a significant increase in the percentage of patients who required emergency assistance due to asthma attacks triggered by natural exposure to aeroallergens (initial, 11.4%; fifth year, 22.2%; $p= 0.007$). Lung function explored by forced expiratory volume in 1 second (FEV_1), which was normal at the initial evaluation in 94.1% of the patients, showed no significant change during the study period (18).

Evidence suggests that IgE may be important in non-atopic asthma and that it may be generated in the bronchial mucosa, as it is in the nasal mucosa in LAR. However, it is still not clear what is the role of allergens in the asthmatic symptoms in patients with LAR, and the allergen immunotherapy either (Figure 4). As mentioned before, one study has demonstrated the presence of sIgE to *D. Pteronyssinus* in sputum of non-atopic asthmatics after bronchial challenge with house dust mite extract. This study also showed that the sIgE is functional, although the subjects did not clinically respond to the allergen (55). A study has been performed in 16 subjects with LAR and perennial bronchial symptoms where asthma was confirmed by methacholine test. All subjects underwent bronchial challenge with *D. pteronyssinus* extract, showing in 8/16 a positive response with a decrease in $FEV_{1\geq 20\%}$ and a significant increase in PC_{20} methacholine 24 hours after challenge. Moreover, the analysis of induced sputum after allergen bronchial provocation test revealed similar increases of eosinophils and eosinophils cationic protein in both LAR subjects and AR controls, providing more evidence for a possible equivalent to LAR in the lower airways (60).

HYPOTHESIS ON WHY LOCAL MUCOSAL IgE PRODUCTION OCCURS

Respiratory mucosa is a site of IgE production during allergic airway inflammation. Classically, an immune response is primed in germinal centers (GC) located in secondary lymphoid tissues, whereas the effectors function of antibodies is peripheral, e.g. mucosal. B cells in the GC undergo antibody affinity maturation by means of a diversity of reactions including somatic hypermutation (SHM), class switch recombination (CSR), clonal expansion, and selection (61). However in allergic rhinitis patients, SHM and CRS occur in the nasal mucosa (26, 29, 46, 62, 63), as reflected that the majority of circulating sIgE antibodies are not derived from IgE-producing cells in the blood (64) and, that the nasal mucosal IgE-secreting B cell and plasma cell populations increase up to 1000 times compared to the blood cell population (31). In nasal mucosa allergen stimulates IgG- or IgA-expressing B cell to switch to IgE (sequential switching), and this is the predominant pathway for local IgE production in AR (26, 29, 63).

Serum IgE in allergic rhinitis may be derived from nasal mucosal production. The rate of local IgE production (65) is 100 times more than required to saturate all the IgE receptors on mast-cells in the tissue, and to spill over into the circulation (66, 67).

Next generation sequencing of expressed immunoglobulin genes in AR has revealed the clonal amplification, diversification and selection of IgE-expressing B cells in the nasal mucosa (68, 69).

NON-BIOPSY BIOMARKERS FOR LAR: LOCAL IgE, BASOPHIL ACTIVATION TEST, PERIOSTIN, TOTAL IgE

The classical approach for diagnosing rhinitis patients, in which subjects are classified based on the results of skin test and/or serum sIgE to aeroallergens, has been shown to be insufficient, leading to the misdiagnose of a fair percentage of patients with apparent NAR that end up being finally labelled as LAR (36). Evidence collected in several studies show a variable frequency of detection of LAR among rhinitis patients without atopy, ranging from 0 to 69.4%. These differences are due probably to the use of different diagnostic methodology and each population intrinsic characteristics (7, 8, 10, 70) (Table 2).

Up to date, the identification of LAR patients relies on the demonstration of an allergen-specific nasal response by means of NAPT and/or sIgE in nasal secretions or tissue (5-7, 18, 21, 36). Previously, a thorough clinical history must be done along with a nasal exploration that includes endoscopy and CT scan to rule out other diseases that produce IgE locally such as chronic rhinosinusitis (CRS) and nasal polyps (Figure 4)(61).

NAPT is considered the gold standard for AR and LAR diagnosis, with a high sensitivity and specificity for allergens such as house dust mites and pollens (7, 11, 71, 72). Recently it was demonstrated that LAR subjects also respond to purified allergens (10/12 (83%) LAR patients challenged with nOle e 1 (59)) as had been shown previously in AR (73). NAPT is time-consuming but a provocation with multiple allergens is available and may be useful as a screening method for LAR and NAR (71).

The presence of nasal sIgE has been demonstrated in LAR but its measurement is highly variable depending on the technique used (5, 6, 8). When measured by nasal lavage sIgE sensitivity is low (22% to 40%) but very specific (5, 6, 16, 17, 74). Other techniques such as a cellulose device coupled to the allergen directly applied to the nose (8), nasal brushing (75) or sinus packs (61) have been shown useful in nasal detection of sIgE but still need to be tested in LAR. Recently Becker et al. (76) have measured sIgE using sinus packs and ISAC® detection in 53 AR and 19 non allergic NARES patients, being able to detect sIgE in all AR samples and in none of NARES, and obtaining a good correlation with results obtained by UniCAP®. This new approach has to be explored in LAR as well.

The basophil activation test (BAT) has demonstrated its utility supporting the LAR diagnosis (Figure 4). In patients with LAR to *D. pteronyssinus* the BAT has shown a sensitivity of 50% with high specificity (77). Moreover, in LAR subjects sensitized to *Olea Europaea* the sensitivity is higher (66%) with >90% specificity (59). More studies are needed in bigger cohorts and other allergens need to be tested but studies so far have shown that BAT can be a useful tool to diagnose LAR to inhalant allergens.

There are several biomarkers that have been thoroughly explored in other respiratory diseases such as asthma. Periostin is an extracellular matrix protein that is over expressed in many respiratory diseases in response to epithelial injury. Periostin is known to be a marker of Th2 inflammation in asthma, it is involved in airway remodelling and many other aspects of pulmonary pathophysiology (78). There are only a few studies done in nasal disease, mostly in CRS with nasal polyps (79, 80), allergic fungal rhinosinusitis (81), allergic rhinitis (79) and NSAID-exacerbated respiratory disease (82). This biomarker has not been yet explored in LAR populations.

Other marker such as total serum IgE has been identified as characteristic of presence of asthma in the absence of atopy (83). However, in most LAR subjects from our cohort the serum total IgE is typically lower than 100 UI/ml irrespective of the presence or absence of asthma (6, 59, 74), although this fact is only an observation made in limited cohorts.

THERAPEUTIC IMPLICATIONS

The therapeutic approach in AR and LAR patients, in contrast with NAR (Figure 5), is oriented towards allergen avoidance measures, pharmacological treatment with intranasal corticosteroids, oral and intranasal antihistamines, and allergen immunotherapy (AIT) (74, 84, 85). The recent results of anti-IgE treatment in non-atopic asthmatic patients highlight the need to evaluate the response to omalizumab in subjects with local allergic respiratory disease affecting both upper and lower airways (Figure 4).

Allergen immunotherapy in Local allergic rhinitis with/without asthma

Allergen immunotherapy (AIT) is the aetiological specific treatment for allergic respiratory diseases. It has the ability to modify the natural course of AR, increasing immunological tolerance, and reducing the clinical symptoms and the use of medication (84, 86). ARIA guideline recommends the use of AIT in children and adults with moderate-severe, persistent or intermittent AR and/or allergic asthma (84, 87, 88).

The evidence of a localized allergic response in LAR patients suggested that specific AIT would be beneficial in these patients. Moreover when LAR patients commonly suffer from persistent, moderate to severe nasal symptoms associated with conjunctivitis and/or asthma and impairment of their quality of life (7, 18).

An observational study evaluated the potential role of grass pollen subcutaneous immunotherapy (SCIT) in LAR patient. The results of this study showed that grass SCIT is a safe and effective treatment induced significant improvement in nasal tolerance to NAPT, clinical symptoms and reduced use of rescue medication (74). These findings have been recently confirmed in the first phase II randomized double-blind placebo-controlled clinical trial (DBPCCT) with *D. pteronyssinus* SCIT (85). In this study immunotherapy resulted in a fast and sustained reduction in symptom and rescue medication, and increased the number of medication-free days (85). The immunological effects of AIT induced the production of allergen specific-IgG4 and a decrease in serum sIgE with a

strong improvement in nasal allergen tolerance. At the end of the study 2/3 of patients treated with AIT tolerated a nasal concentration of *Der p1* >10 times higher by NAPT than basal concentration, and NAPT was negative in 50% of patients (85). These results provided the indication for AIT in LAR.

Anti-IgE treatment in non-allergic asthma

Omalizumab is a humanized murine monoclonal antibody that recognizes the Cε3 domain of human IgE, which is the portion of the IgE molecule that binds to the receptors of the mast-cells and basophils. The treatment with omalizumab leads to a fast decrease in free serum IgE, induces down-regulation of human high affinity receptor for IgE (FcεRI) on basophils, dendritic cells and monocytes and decreasing serum, tissue, and sputum eosinophilia (89). Omalizumab has shown clear benefits in patients with allergic asthma and chronic spontaneous urticaria (90). Moreover, recent studies have also shown its efficacy in non atopic asthma (90-93). The exact mechanism is still unknown, but it may be due to IgE produced locally in the airway in the absence of systemic measurable allergen-specific or the production of sIgE in response to Staphylococcal enterotoxins (90).

Initially there were isolated case reports of non-atopic asthmatic patients with significant improve of asthmatic symptoms after treatment with omalizumab (91, 92). Later on, the effect of omalizumab on a serie of 29 severe non-atopic asthmatic patients gathered in collaborating centers were compared with 266 patients with severe atopic asthma also treated with omalizumab. In both groups, anti-IgE treatment led to similar improvements in symptoms, global evaluation of treatment effectiveness (GETE), asthma control test (ACT) and exacerbations (93). There is also a randomized, DBPCCT that evaluated the anti-IgE treatment in 41 patients with severe non-atopic asthma. Omalizumab-treated patients had an improvement in lung functions despite no significant changes in exacerbations or asthma control symptoms. Also, a significant decreases the expression of FcεRI on basophils and plasmacytoid dendritic cells. All patients treated with decrease of higher than 50% in the expression

of FcεRI in basophils (94). These results support the possible role of IgE in non-atopic asthma although further studies in larger populations are needed.

CONCLUSIONS

The ongoing research on LAR and its associated lower airway disease is helping to understand this complex phenotype that represents the expression of allergic inflammation mostly localized in the target organs despite the fact that in a percentage of subjects a positive basophile activation test can be detected. Still, there are many questions regarding the mechanism of the disease that there are still unknown, especially in the lower airway where the evidence of functional specific IgE antibodies is still scarce. Future research will focus on the study of the pathophysiological mechanisms of local allergic rhinitis and asthma, the development of *in vitro* tests for diagnosis in the clinical setting, improvement of sIgE detection and AIT with other allergens.

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TABLES AND LEGENDS OF FIGURES

IMPORTANT NOTE:

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Table 1. Risk and protective factors of LAR

A multiple logistic regression analysis performed in 140 LAR patients and 140 non-atopic rhinitis patients identified 6 risk factors and 2 protective factors of LAR.

	Clinical features	β	Exp (β)	P value	I.C. 95% for Exp (β)
Risk factors	Female gender	1.741	5.703	0.035	1.133 – 28.710
	Family atopy	1.992	7.328	0.001	2.175 – 24.695
	Childhood onset	2.029	7.610	0.004	1.930 – 30.011
	Asthma	2.125	8.376	0.005	1.911 – 36.709
	Seasonal rhinitis	2.027	7.588	0.015	1.494 – 38.534
	Severe symptoms	2.895	18.086	0.006	2.259 – 144.782
Protective factors	Mucous rhinorrhea	-1.974	0.139	0.001	0.043 – 0.451
	Irritant smells	-1.881	0.152	0.007	0.039 – 0.597
	constant	-3.792	0.023		

Table 2. LAR epidemiological studies

(a) Adinoff AD, Tsai KS, Steffen M. Entopy: Where Art Thou Entopy? J Allergy Clin Immunol 2015;135 (2):AB190.

(b) Jang TY, Kim YH. Nasal provocation test is useful for discriminating allergic, nonallergic, and local allergic rhinitis. Am J

Author	Year	Country	Study groups	Group Age	Allergens	Positive NAPT response (n,%)
Carney et al (REF)	2002	UK/Australia	21IR (perennial)	Adults	DP/DF Cats/dogs Grass	13/21 (61.9%)
Wedback et al (REF)	2005	Sweden	15IR (seasonal)	Adults	Birch Timothy	7/15 (46.7%)
Rondon et al (REF)	2007	Spain	50 IR (perennial)	Adults	DP	27/50 (54%)
Rondon et al (REF)	2008	Spain	32 IR (seasonal)	Adults	Grass Olive	21/32 (65.6%)
Fuiano et al (REF)	2012	Italy	36 IR (perennial)	Children (4-18y)	Alternaria	25/36 (69.4%)
Cruz Niesvaara et al (REF)	2012	Spain	30 IR (perennial)	Adults	DP	19/30 (63.3%)
Rondon et al (REF)	2012	Spain	158 IR (seasonal/perennial)	Adults	DP Alternaria Grass Olive Cat Dog	110/158 (69.6)
Cheng KJ et al (REF)	2013	China	147 IR (perennial)	Adults	DF	12/147 (8.1%)
Chang et al (REF)	2014	Korea	62 IR	Adults	DP	22/62 (35.5%)
Bozek et al (REF)	2015	Poland	131 IR (perennial)	Adults >65 yrs	DP Phleum Molds Trees Cat	46/131 (35.1%)
Klimek et al (REF)	2015	Germany	2 IR (perennial)	Adults	Alternaria	2(case report)
Adinoff et al (REF)	2015	USA	30 IR (seasonal/perennial)	Adults/Children	Trees Weeds Timothy grass Cat	11/30 (36.7%)
Jang TY et al (REF)	2015	Korea	110 IR (perennial)	Adults	DP	12/110 (10.9%)
Buntarickpornpan et al (REF)	2015	Thailand	25 IR (perennial)	Children (8-18y)	DP	0/25 (0%)
Refaat et al (REF)	2015	Egypt	40 IR	Adults	DP	25/40 (62.5%)
Blanca-López (REF)	2016	Spain	61 IR (seasonal)	Adults/Children	Phleum	37/61 (61%)

Rhinol Allergy. 2015 Jul-Aug;29(4):e100-4. doi: 10.2500/ajra.2015.29.4214. PubMed PMID: 26163237.

(c) Buntarickpornpan P, Veskitkul J, Pacharn P, et al. The Prevalence and Clinical Characteristics of Local Allergic Rhinitis in Thai Children J Allergy Clin Immunol 2015;135 (2):AB282.

(d) Refaat M, Melek N, Shahin R, et al. Study for Assessing Prevalence of Local Allergic Rhinitis Among Rhinitis Patients. J Allergy Clin Immunol 2015;135 (2):AB140.

DP: D. Pteronyssinus; IR: idiopathic rhinitis; LAR: local allergic rhinitis; NAPT: nasal allergen provocation test

(Reproduced from Campo P, Salas M, Blanca-López N, Rondón C. Local allergic rhinitis. Immunology and Allergy Clinics of North America. DOI: <http://dx.doi.org/10.1016/j.iac.2015.12.008>). (NEED PERMISSION)

Figure 1. Immunohistology and *in situ* hybridization images of nasal biopsies. (A) CD20⁺ B cells, (B) IL-4 mRNA⁺ cells, (C) IgE Cε⁺ cells after NAPT colocalized to CD20⁺ cells, (D) by use of double immunohistochemistry/*in situ* hybridization. (Reproduced from Durham SR, Gould HJ, Thienes CP, et al., Expression of epsilon germ-line gene transcripts and mRNA for the epsilon heavy chain of IgE in nasal B cells and the effects of topical corticosteroid. Eur J Immunol 1997;27: 2899-2906) (NEED PERMISSION)

Figure 2. Kinetic of local production of inflammatory mediators and sIgE after nasal allergen provocation test with grass pollen (A) and with *D. pteronyssinus* (B).

(Figure 2A) Reproduced from Rondon C, Fernandez J, Lopez S, Campo P, Doña I, Torres MJ, Mayorga C, Blanca M. Nasal inflammatory mediators and specific IgE production alter nasal challenge with grass pollen in local allergic rhinitis. J Allergy Clin Immunol 2009;124:1005-11. (NEED PERMISSION)

(Figure 2B) Reproduced from López S, Rondón C, Torres MJ, Campo P, Canto G, Fernandez R, Garcia R, Martínez-Cañavate A, Blanca M. Immediate and dual response to nasal challenge with Dermatophagoides pteronyssinus in local allergic rhinitis. Clin Exp Allergy 2010 Jul;40(7):1007-14. (NEED PERMISSION)

Figure 3. Immunohistochemistry images of nasal biopsies showing free light chain (FLC) localized to stromal cells adjacent to submucosal glands (G) in nasal mucosa of allergic rhinitis patients (A) and idiopathic rhinitis patients (B), compatible with localization to plasma cells (arrow). FLC staining are shown (arrow) in the epithelium (C) and in granulated cells with morphologic features of mast-cells (arrow) in the superficial lamina proprium. Reproduced from Powe DG, Groot Kormelink T, Sisson M, Blokhuis BJ, Kramer MF, Jones NS, Redegeld FA. Evidence for the involvement of free light chain immunoglobulins in allergic and nonallergic rhinitis. J Allergy Clin Immunol. 2010 Jan;125(1):139-45.e1-3. (NEED PERMISSION)

Figure 4. Immunologic features, diagnostic and specific therapeutic approaches in the local allergic response of the upper and lower airways

Figure 5. Therapeutic approach in allergic and non-allergic rhinitis





