



IgE Test in Secretions of Patients with Respiratory Allergy

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Abstract

Purpose of Review IgE is a key player in multiple inflammatory airway diseases. Ample literature demonstrates its presence in mucosa of patients with allergic rhinitis (AR), local allergic rhinitis (LAR), asthma, or chronic rhinosinusitis with nasal polyposis (CRSwNP).

Recent Findings Current evidence shows that high-affinity IgE in blood stream of allergic individuals derives mainly from the mucosae. Also, mucosal synthesis of IgE can occur in the absence of systemic atopy, and may be relevant in atopic and non-atopic phenotypes of rhinitis as demonstrated in LAR. Specific IgE (sIgE) detection varies depending on technique used for sample collection and its measurement. sIgE detection is highly specific for diagnosis of LAR. Moreover, measurement of sIgE in secretions could be useful in monitoring response to allergen-specific immunotherapy in both AR and LAR phenotypes.

Summary This review will focus on recent developments in the role of IgE in respiratory diseases, and the clinical implications of its measurement in secretions.

Keywords Allergic · IgE · Local allergic rhinitis · Rhinitis · Allergen-specific immunotherapy

Introduction

Immunoglobulin E (IgE) is the less abundant class of immunoglobulins and is located predominantly in tissues, tightly bound to mast cells and basophils through its high-affinity receptor FcεRI. IgE constitutes a first line of defense against parasites and is a crucial mediator of many allergic reactions from food allergy to anaphylaxis [1].

IgE is also a key player in multiple inflammatory airway diseases such as allergic rhinitis (AR), local allergic rhinitis (LAR), asthma, or chronic rhinosinusitis with nasal polyposis (CRSwNP) [1]. Nevertheless, the presence of IgE in periphery (skin prick test (SPT) and/or specific IgE (sIgE) in serum) does

not always correlate with clinical allergy and does not give information about the status of local IgE in the target organ [2, 3].

This article represents a summary of the classic and recent developments in the role of IgE in respiratory diseases, clinical implications, and the measurement of this immunoglobulin in nasal secretions in patients with inflammatory respiratory diseases.

Synthesis of IgE in Respiratory Mucosa

The generation of high-affinity allergen-specific IgE requires the activation of the adaptive immune system. Germinal center (GC) B cells in the secondary lymphoid organs are stimulated to produce mature antibodies [4]. During immune responses, antigen-activated T cells provide help to GC B cells to carry out the class switch recombination (CSR) of their antibody, which results on a loss of IgM expression [5]. The process of CSR involves the change of the Fc portion of the heavy chains, thus altering the receptors the antibody can bind and affecting its functional specialization [4]. During CSR, the DNA in the locus of immunoglobulin heavy chain is rearranged to juxtapose distant DNA regions and to generate switch circles that will be ultimately eliminated. These switch circles are isotype-specific and can be transiently detected.

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Class switch recombination is followed by the somatic hypermutation of the antibody in order to increase its affinity for the cognate antigen [5]. After mutations in the genes of the variable regions of their antibodies, B cells migrate from the dark zone to the light zone of the GC. In the light zone, mutated B cells are re-exposed to their cognate antigens, and only those having increased their affinity will continue their maturation (positive selection) [5]. The processes of CSR and somatic hypermutation are driven by different genes codifying enzymes such as *activation-induced cytidine deaminase* (AID), *recombination activating gene* (RAG) 1 (RAG1), or 2 (RAG2) [4]. After CSR and somatic hypermutation, mature IgG+ or IgA+ B cells differentiate into long-lived plasma cells or memory B cells and exit the secondary lymphoid organs [5]. Plasma cells provide protection by the sustained production of high-affinity antibodies, whereas memory B cells rapidly proliferate upon antigen reencounter [5].

Class switch recombination to IgE (ϵ CSR) in GC B cells has a stronger dependence on T cell collaboration than other immunoglobulin isotypes [6]. The initiation of ϵ CSR requires the interaction of CD40L expressed on GC B cells with CD40 induced on activated Th2 cells, which also provide IL-4, the crucial inducer for the process [7]. Additional initiators of ϵ CSR include the stimulation of *proliferation-inducing ligand* (APRIL) and TLR4 on GC B cells by *B cell activating factor* (BAFF) and LPS respectively [8]. Globally, all these stimuli activate the transcription factor STAT6 which induces the gene changes resulting on ϵ CSR [7]. Nevertheless, the maturation of IgE affinity after ϵ CSR is the process displaying most differences with other immunoglobulin isotypes [6]. Immunoglobulin E+ GC B cells cannot efficiently traffic to the light zone in order to undergo the positive selection of the cells having increased their affinity after somatic hypermutation [8, 9]. This fact determines an increased apoptosis of GC IgE+ B cells in the dark zone and an impaired formation of IgE+ memory B cells. These factors result on a low frequency and an insufficient affinity maturation of GC-derived IgE antibodies [9, 10].

Nevertheless, high-affinity IgE can be produced by IgG+ memory B cells in the mucosae following ϵ CSR [7]. This sequential ϵ CSR (from IgM to IgG followed by from IgG to IgE) generates a switch circle different from that of direct ϵ CSR (from IgM to IgE) [8] and probably represents an additional checkpoint for IgE production reflecting that strong evolutionary pressure operates to limit, but not eliminate, the production of high-affinity IgE [6]. Even though the sequential ϵ CSR in mice seems restricted to IgG+ memory B cells [9], in the airway mucosa of humans, CSR from IgA to IgE has also been reported [11]. Markers of sequential ϵ CSR have been demonstrated in the mucosa of individuals with type 2 nasal inflammatory diseases such as AR [12–14] or CRSwNP [15], and sIgE has been detected in the nasal secretions of patients with both diseases [16, 17••]. In this regard, it is believed that high-affinity IgE in the blood stream of allergic

individuals derives mainly from the mucosae rather than from the secondary lymphoid organs [12, 13, 18]. In atopic subjects, mucosal high-affinity IgE might traffic through the lymphoid vessels to the blood stream where it would sensitize circulating basophils [18]. Interestingly, in the bronchial mucosa of both atopic and non-atopic asthma patients, markers of sequential ϵ CSR were also observed [19]. This observation implies that mucosal synthesis of IgE can occur in the absence of systemic atopy. Importantly, a proportion of subjects with LAR display detectable allergen-specific IgE in the nasal secretions [20, 21, 22•], and positive basophil activation test (BAT) responses [23, 24]. These findings suggest that the synthesis of IgE also occurs in the nasal mucosa of LAR individuals, yet markers of ϵ CSR at the tissue level of these patients have not been investigated to date (Fig. 1).

Evidence of Local IgE in Different Phenotypes of Respiratory Disease

Since the discovery of IgE, several studies tried to identify the source and location of this immunoglobulin. Early publications in the 1970s investigated the anatomical location of IgE+ cells, concluding that 70–80% of the IgE was synthesized locally [25, 26]. The evidence of local IgE in the most relevant phenotypes of respiratory disease is summarized below.

a) *Local IgE in AR*

Respiratory mucosa is a site of IgE production during allergic responses. Evidences of presence of sIgE in AR are numerous. Back in the 1970s, Tse et al. identified ragweed-specific IgE in nasal secretions [27]. Later on, Platts-Mills et al. were able to measure grass sIgE in nasal secretions of SPT+ patients, and they showed that 90% of this sIgE was produced locally [28]. A study performed in the 1990s demonstrated that house dust mite-specific IgE increased faster in the nasal secretions than in serum after allergen exposure [29]. Studies using turbinate mucosa of AR patients demonstrated the presence of IgE-positive mast cells, plasma cells, and B cells [12]. In nasal mucosal explants, de novo production of IgE has been also shown [30].

In AR patients, somatic hypermutation and CRS have been demonstrated in the nasal mucosa [11, 13, 14, 31], although GC formation has not yet been fully demonstrated. In a recent study in AR subjects, natural pollen exposure was associated with changes in IgE repertoires that were suggestive of ongoing GC reactions, and these changes were more apparent in nasal biopsies compared with peripheral blood [32•]. Moreover, the stimulus of the allergen in the mucosa might produce a sequential switching to IgE from IgG or IgA [11, 13, 14].

Interestingly, nearly all of the serum IgE may be derived from mucosal sites [18], and IgE-secreting B cell and plasma

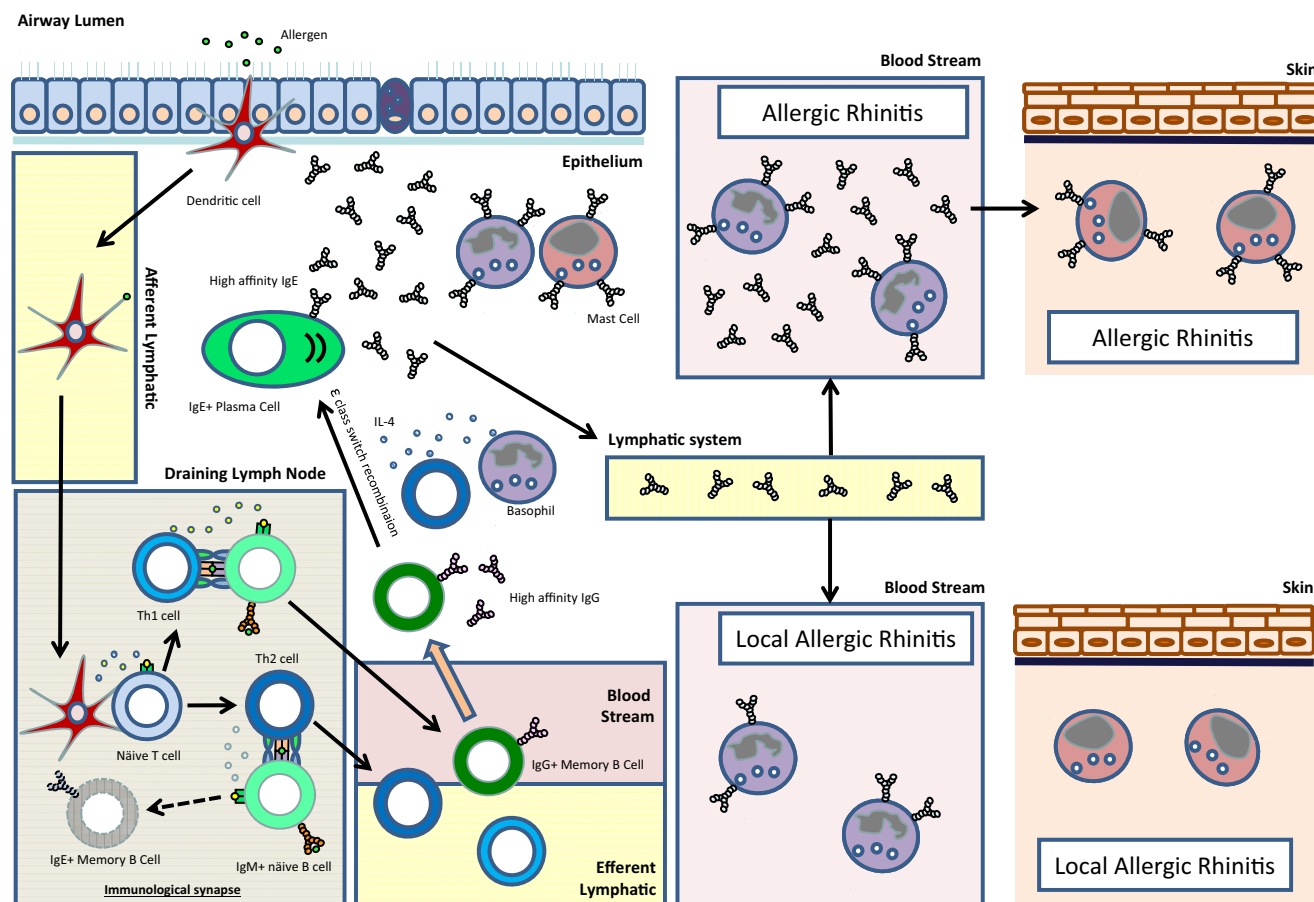


Fig. 1 Mucosal synthesis of IgE in allergic rhinitis and local allergic rhinitis patients. Allergen-activated dendritic cells traffic through the lymphatic vessels to the germinal center of the draining lymph nodes. In that location, dendritic cells activate allergen-specific naïve T cells to generate Th1 and Th2 cells. Th1 cells subsequently stimulate allergen-specific IgM+ naïve B cells which undergo class switch recombination (CSR) to IgG and somatic hypermutation to give rise to IgG+ plasma cells (not shown) and IgG+ memory B cells. Allergen-specific Th1 and IgG+ B cells exit the lymphoid system through the efferent vessels and reach the blood stream. Activated Th2 cells in the germinal centers also stimulate IgM+ naïve B cells which undergo CSR to IgE. Nevertheless, IgE+ B cells cannot efficiently carry out their somatic hypermutation and die by apoptosis before exiting the germinal centers. Conversely, Th2 cells reach the blood stream and extravasate at the lamina propria of the airway mucosa, together with Th1 cells (not shown) and IgG+ memory B cells. In the lamina propria, IgG+ memory B cells can

undergo sequential CSR to IgE upon allergen reencounter (not shown) and stimulation with IL-4 provided by Th2 cells and basophils among other cells. This process results on the generation of IgE+ plasma cells releasing vast amounts of high-affinity IgE to the lamina propria. Mucosal IgE can bind FcεRI on resident basophils and mast cells and sensitize them for activation upon allergen reencounter. After saturating the receptor system of the mucosa, free IgE can reach the blood stream through the lymphatic vessels. In the blood stream, IgE binds first to FcεRI on circulating basophils. In allergic rhinitis patients, IgE saturates the receptor system of blood basophils and subsequently binds FcεRI on mast cells residing at the different peripheral tissues including the skin. Moreover, after saturating the receptor system on mast cells, IgE can be found at a free state in serum of AR patients. In individuals with local allergic rhinitis, IgE is sometimes sufficient to sensitize circulating basophils, but it is not enough to sensitize skin mast cells or to be found at a free state in serum

cell populations suffer a much higher increase in nasal mucosa compared to the peripheral cell population [12]. In a study performed in tonsils, Ramadani et al. demonstrated that GC-derived B cells yielded the highest percentage of IgE(+) cells [33•]. The rate of local IgE production [30] is enough to saturate the whole IgE receptor system on resident mast cells, and subsequently to spill over into the circulation [1].

b) Local IgE in LAR

LAR is a clinical entity characterized by nasal itching, sneezing, rhinorrhea, and obstruction caused by a nasal allergic

response to aeroallergens (natural or by nasal allergen provocation test (NAPT)) in absence of atopy (negative SPT and undetectable sIgE in serum) [34, 35]. LAR is a new phenotype of AR that may start in childhood and tends to worsen over the years, developing comorbidities such as asthma [36•].

The physiopathology of LAR is only partially understood. The nasal mucosa of LAR patients shows a T2 allergic inflammatory pattern (increased levels of eosinophils, mast cells, and T cells), with nasal production of mediators such as tryptase and eosinophilic cationic protein (ECP) [20, 21, 37].

The clinical similarities between AR and LAR patients prompted the early investigators to examine the role of IgE

in the later disease. Brostoff and Huggins published the first evidence of sIgE in nasal secretions of patients with positive history of AR, absence of atopy, and positive response to NAPT [38]. Later on, Powe et al. demonstrated the presence of sIgE to grass pollen and house dust mites (HDM) in 30% of turbinate samples of patients with non-allergic rhinitis [39]. More recently, several authors have demonstrated presence of sIgE to different allergens (HDM, pollen, molds, epithelia) in both adults and pediatric LAR populations [20, 21, 40, 41, 42, 43].

A study from Rondón et al. showed sIgE antibodies against grass pollen and *D. pteronyssinus* during periods of non-exposure [20, 40]. Kinetic studies in LAR have shown that there is a fast and progressive increase of sIgE levels in the nasal secretions from 1 to 24 h after NAPT [21, 37].

Nasal sIgE can be detected in a variable percentage of LAR subjects, and numbers vary depending on the allergen and the population [20, 42, 43, 44]. The source of this sIgE is not clear, because the local synthesis of IgE has not been demonstrated yet. In this regard, it is tempting to speculate that in LAR individuals, IgE produced at the mucosal level can be enough to sensitize nasal effector cells, but not to reach skin mast cells or to be detected at a free state in serum. Of note, close to 50% of HDM-sensitized LAR individuals display positive IgE-mediated basophil activation test responses to house dust mites, suggesting that in those patients mucosal IgE has been able to reach the blood stream [23, 24]. Another indirect evidence in favor of an IgE-mediated mechanism for LAR is the good performance of allergen immunotherapy (AIT) in 70% of LAR individuals [45–47, 48]. Ongoing studies about the mechanism of IgE in LAR may help answer some of the questions remaining in the pathophysiology of this disease.

c) Local IgE in asthma

Classically, asthma has been categorized into allergic and non-allergic, based on routine test to measure systemic atopy such as SPT and serum sIgE [49]. Nevertheless, several studies showed that this classification does not relate to a distinct inflammatory pattern. Importantly, multiple similarities are present in the pathophysiological mechanisms of allergic and non-allergic asthma [50, 51].

In this regard, the cellular infiltrate of the bronchial mucosa of non-allergic asthmatic subjects is similar to that of allergic asthmatics [52], with increased expression of IL-4, IL-5, and IL-13 in both phenotypes [50, 52], along with higher expression of eotaxin-1, eotaxin-2, monocyte chemotactic proteins (MCP)-3 and -4, and CCR3 [53].

Moreover, as shown for rhinitis, IgE is also suspected to play a pivotal role in asthma. There is ample evidence for local IgE synthesis in asthmatic patients, regardless of their atopic

status. Several studies have demonstrated that non-atopic asthmatic individuals show local synthesis of IgE, increased expression of ϵ heavy-chain germ line, local ϵ CSR, and increased expression of Fc ϵ RI on residing immune cells of bronchial mucosa [19, 54]. Interestingly, a study demonstrated that local airway IgE-related processes are more relevant in determining the clinical outcomes of asthma than the systemic markers of atopy [55].

Nevertheless, the antigen-specificity of the bronchial IgE in asthma has not been investigated in depth, and it is unknown whether this IgE can bind aeroallergens as shown for nasal IgE in AR and LAR patients [28] and in CRSwNP individuals [16]. A single study demonstrated functional house dust mite-specific IgE in sputum samples from non-atopic asthmatic subjects after bronchial challenge with *D. pteronyssinus* (DP) [56]. However, these patients failed to develop a positive bronchial provocation test with house dust mite. Therefore, the clinical relevance of the allergen could not be confirmed. On the other hand, another study performed in bronchial biopsies of patients with atopic and non-atopic asthma showed that allergen-specific IgE could be only detected in allergic individuals [57]. All these aspects warrant further investigation.

d) Nasal Polyps

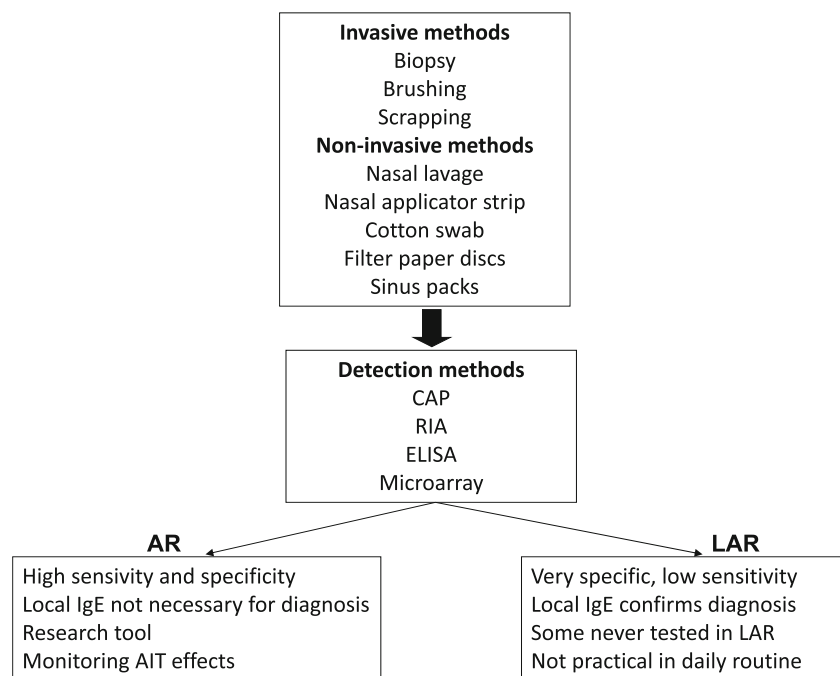
Large amounts of IgE are present in the nasal polyps of patients with CRSwNP along with tissue eosinophilia. The IgE can be synthesized in a polyclonal or in an allergen-specific manner [58]. The over-expression of polyclonal IgE is related with the presence of *Staphylococcus aureus* enterotoxins, which act as superantigens and activate resident B and plasma cells [15, 58]. This activation causes isotype switching, synthesis of low-affinity IgE, and polyclonal T cell activation [59].

Local allergen-specific IgE can also trigger mast cell degranulation. Nevertheless, vast amounts of polyclonal IgE can act as suppressors of mast cell reactivity by flooding Fc ϵ receptors on resident mast cells. This phenomenon explains why IgE level is independent of the atopic status of CRSwNP patients [17, 60].

Previous studies showed evidence of local switch to IgE in nasal polyp tissue, by means of local receptor revision, CSR, increase of IL-4, and B cell differentiation into IgE-secreting plasma cells [61, 62]. Also, there are high levels of free light chains that are able to mediate antigen-specific mast cell activation [61].

Total and specific IgE levels in CRSwNP patients can be measured in nasal biopsies and tissue homogenates (invasive), and in filter disks or sinus packs (non-invasive). Total IgE measured by non-invasive techniques strongly correlate with levels in tissue homogenates, but not specific IgE because sensitivity of the measurement in nasal secretions is lower compared to nasal tissue [16, 60].

Fig. 2 Techniques of measurement of specific IgE in allergic rhinitis and local allergic rhinitis



Relevance of Measurement of IgE in Secretions of Allergic Rhinitis Patients

Methods of Measurement and Clinical Implications

The synthesis of IgE in the nasal mucosa of AR patients has been reported in several studies [2, 62•, 63, 64]. Nasal IgE [1, 28, 38, 65] can be measured by several non-invasive and invasive methods such as nasal lavage [64, 66, 67], filter disks/cotton swabs/sinus packs [2, 17•], mucosal brush biopsy [68] or scrapping, among others (Fig. 2). It is noteworthy that serum IgE level is often considered a reliable diagnostic measurement in these patients [69, 70]. The evidence for local production of IgE in the nasal mucosa has resulted in a growing interest in developing validated methods for quantifying allergen sIgE in the nasal fluid. Moreover, nasal secretions can be collected in a non-invasive manner to allow reliable measurement of IgE.

The clinical history, SPT, and serum sIgE measured by ImmunoCAP system are the standard work-up for AR diagnosis and for deciding on AIT prescription [71–73, 74•]. Currently, two validated methods are available for the measurement of serum sIgE: the immunoassay capture test (ImmunoCAP) and the ImmunoCAP solid-phase allergen chip technology (ISAC). Both methods offer high specificity and sensitivity for IgE measurements. In particular, ISAC can be performed using very small volumes of serum (and potentially nasal secretions). The relevance of IgE measurement for AR diagnosis is reflected by the good correlation observed between the level of serum IgE and the skin and nasal provocation test results [75]. Moreover, allergen-specific IgE measurements offer a highly reproducible diagnostic tool as it remains unaffected by pharmacotherapy

treatments such as anti-histamines and anti-inflammatory drugs [76]. In contrast to allergen-specific IgE, the total IgE level is influenced by numerous factors; therefore, the quantification of elevated total IgE in serum or nasal secretions is of limited diagnostic value [77].

Monitoring Efficacy of AIT in Patients with AR

Monitoring of clinical efficacy of AIT can be performed using in vivo tests such as nasal, bronchial, and conjunctival provocation, which are laborious and challenging techniques. The use of antibody measurement that can be done in vitro to assess the effects of AIT on allergen-specific immune responses is therefore of high interest. Several studies have reported that following pollen immunotherapy (both subcutaneous and sublingual), sIgE levels are transiently increased during treatment, which is then followed by blunting of the seasonal increases [78]. In a study investigating serum IgE level and FcεRI expression in allergic patients, it was shown that serum IgE level correlated with FcεRI expression and IgE binding in conventional type 2 dendritic cells and basophils of allergic patients [79]. They further reported that patients treated with house dust mite subcutaneous AIT had elevated levels of serum IgE which was accompanied by elevated FcεRI in dendritic cells but not basophils. Further to this, a study involving subcutaneous AIT that observed the patients over a long period of time [80] reported that there was a gradual decrease in the level of specific IgE though this did not correlate with magnitude of the clinical response [81, 82]. In a recent double-blind, placebo-controlled immunotherapy trial performed in birch pollen-allergic patients, IgE and IgG levels were measured from sera to correlate

with clinical parameters using both ImmunoCAP and ISAC systems [83•]. The study illustrated that specific IgE antibody levels of patients who receive active treatment were significantly different when measured using the two systems. While immunoCAP measurements showed significant increases in Bet v 1-specific IgE antibodies following immunotherapy, ISAC measurements illustrated a significant reduction, which was associated with an increase in specific IgG antibodies. In support of this, another study also reported the reliable use of allergen microarray ISAC as a measure of house dust mite-specific IgE in nasal secretions [17]. Specific IgE to HDM extract was measured in serum and nasal secretion of patients with AR and it was found that the level was very comparable in the two samples, indicating the reliability of nasal IgE testing using microarray as a diagnostic tool of AR. Despite these promising observations, whether sIgE level measured by ISAC could be a true indication of absolute blocking effect associated with IgG antibody and clinical efficacy of immunotherapy remains to be fully validated.

Relevance of Measurement of IgE in Secretions of Local Allergic Rhinitis Patients

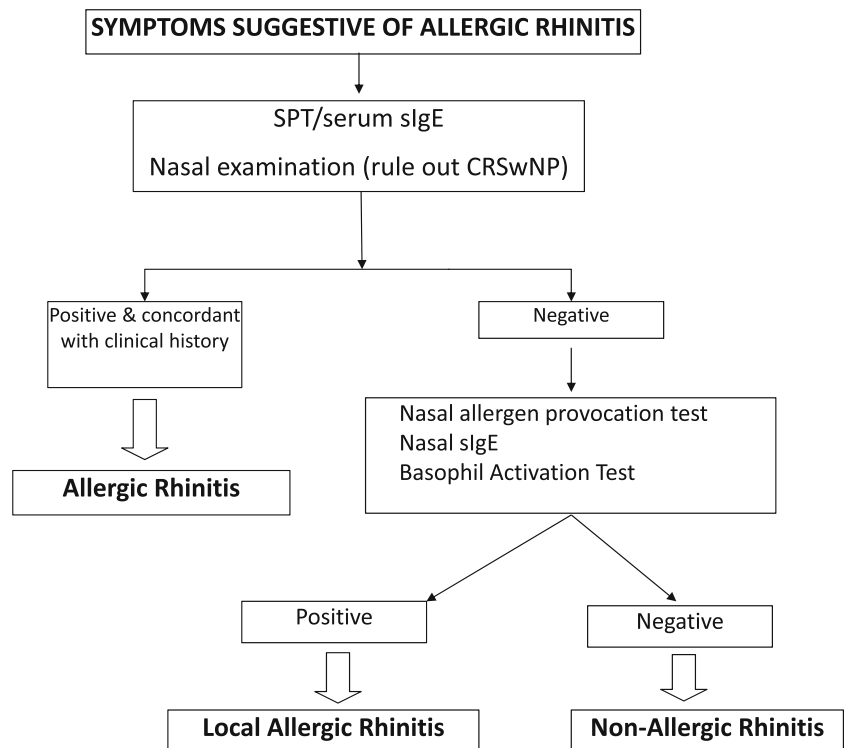
Local sIgE is detectable in nasal secretions of a percentage of patients with LAR. This fact has been demonstrated in many different populations (adult, pediatric, and elderly) from different genetic backgrounds [20, 21, 22•, 40, 42•, 43•, 64, 84–87, 88•, 89, 90]. Local sIgE seems to increase in nasal

secretions 1 h after NAPT reaching its maximum level 24 h after the allergen challenge [37]. In a recent study performed in children, levels of nasal sIgE increased 6 h after NAPT with pollen, and sIgE concentrations increased faster in patients with LAR compared with AR [43•].

Since the description of LAR, different investigators have focused their efforts on detecting sIgE in the nasal secretions as a mean to diagnose LAR. However, due to the lack of standardization in the measurement of sIgE, the variability among techniques, and the low sensitivity in its detection, the NAPT still remains as the gold standard for LAR diagnosis [91]. In any case, the identification of nasal sIgE in non-atopic patients with clear symptoms has a high specificity and can confirm LAR diagnosis [35, 91] (Fig. 3). Recently, a study performed in 53 allergic patients with non-allergic rhinitis with eosinophilia syndrome (NARES) reported the absence of nasal sIgE to 112 allergens (immunoassay-biochip technology), confirming that this entity is not associated with local allergy [92•].

Different investigators have reported variable percentages of positive results of nasal sIgE for HDM, pollens, and molds, ranging from 0 to 100% depending on the allergen or population [21, 42•, 43•, 44, 64, 86, 90, 93]. Many of the recent studies measuring sIgE in the nasal secretions have been performed in pediatric populations due to its non-invasive nature. In general, the frequency of positive nasal sIgE in LAR patients seems to be higher for pollen compared to other allergens [20, 21, 22•, 42•, 43•, 44]. In the study of Zicari et al. performed in non-atopic children, 16.7% of patients with positive NAPT to HDM had positive nasal sIgE to HDM and 100% with positive

Fig. 3 Diagnostic algorithm of local allergic rhinitis. AR allergic rhinitis, SPT skin prick test, sIgE allergen-specific IgE, NsIgE nasal allergen-specific IgE, BAT basophil activation test



grass pollen NAPT results had positive nasal sIgE for grass pollen [42]*. In the study by Buntarickpompan et al., nasal sIgE to DP could not be detected, although there were only 2 patients with positive NAPT [44]. A recent study including 26 non-atopic children with rhinitis detected a higher value of total IgE in the nasal lavage in 16 of them, with this finding leading to their classification in the LAR phenotype. This affirmation is not correct because the children were not challenged with allergens, and LAR diagnosis needs a confirmation of allergen sensitization (nasal sIgE) or reactivity (NAPT) [94].

Several methods have been published to collect and process nasal secretions and measure nasal sIgE (Fig. 2). Overall, these techniques display a low sensitivity compared to NAPT, potentially due to a dilutional effect in nasal secretions or to the extensive sample processing before quantification. Nasal lavage is a non-invasive method, can be performed in several ways (Greiff/Grünberg, Naclerio, spray), and has been widely used in the investigation of nasal sIgE. Of note, not all the nasal lavage methods have been tested in LAR patients [20, 42, 43, 87]. One study detected specific IgE in the nasal brushing samples from all non-atopic patients included, although the presence of LAR was not investigated by a NAPT [95]. Recently, our group reported an automated and non-invasive method involving very little sample manipulation to measure nasal IgE in LAR individuals. In this study, the solid phase of commercial ImmunoCAP® is placed in the mucosa of the lower turbinate after nasal provocation with *D. pteronyssinus*. This method showed a sensitivity of 42.8% with 100% specificity for a cut-off point of 0.1450 kU/L [22]. Spray and swab methods have been tested in children showing a good correlation between nasal and serum HDM-specific IgE. A lower cut-off point of 0.11 kIU/L was established but the investigators did not perform a NAPT in the patients and a control group was not included [87].

Recently, Bozeck et al. monitored nasal sIgE before and during a 2-year treatment with birch-AIT in patients with LAR [47]. The investigators observed a gradual decrease in nasal sIgE to Bet v 1 in patients treated with AIT as compared to the placebo group. This finding might constitute a biomarker for AIT effectiveness in LAR patients.

Conclusions

The current evidence confirms that IgE is mostly produced locally, and that serum IgE is a spillover from the mucosae. As it has been demonstrated in patients with LAR, IgE may be relevant in both topic and non-atopic phenotypes of rhinitis, and possibly of asthma. The detection of sIgE varies depending on the technique used for collecting the sample and for measurement. As shown in the literature, sIgE detection is highly specific for LAR diagnosis. Measurement of sIgE in nasal secretions could be useful in monitoring response to AIT in both AR and LAR phenotypes. Future studies should focus on developing

non-invasive and highly specific methods to quantify sIgE in nasal secretions.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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