

CME review

Local production of IgE in the respiratory mucosa and the concept of entopy: does allergy exist in nonallergic rhinitis?

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Objective: To review research regarding locally produced IgE and its impact on patients with chronic rhinitis.

Data Sources: PubMed search with the following keywords: *entopy*, *local IgE*, *nonallergic rhinitis*, *idiopathic rhinitis*, *vasomotor rhinitis*, and *allergic rhinitis*.

Study Selection: Articles were selected based on their relevance to entopy and locally produced IgE and its clinical effect and relationship to idiopathic rhinitis (IR).

Results: Local IgE has been found in a variety of tissues, including nasal and bronchial mucosa. IgE is produced in these local tissues and not simply the product of migration to the tissue from regional lymphoid tissue or blood. Local IgE has been identified in most of both atopic and nonatopic asthmatic patients and allergic rhinitis patients. Up to 40% of patients with IR and a positive nasal provocation test result have evidence of locally produced IgE, which has been coined *entopy*. Although patients with allergic rhinitis and IR show similar inflammatory patterns with increased activated mast cells, eosinophils, and T-cell subsets in some studies, other studies on IR patients are conflicting with regard to both inflammation and allergen-specific nasal provocation test results.

Conclusion: The concept of local allergy in IR patients is both intriguing and controversial. Studies have reported conflicting results, and currently there is no single best test to evaluate for entopy. It is known that there are a large number of IR patients for whom current treatment regimens are suboptimal. Therefore, further research elucidating the mechanisms of IR and the concept of localized IgE are needed to optimally diagnose this condition and treat this group of patients.

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INTRODUCTION

Rhinitis is defined as inflammation of the nasal mucosa with the clinical characteristics of nasal discharge, congestion, itching, sneezing, and postnasal drainage¹ and represents 1 of

the most common concerns of patients presenting to medical professionals.² Epidemiologic reviews^{2,3} of rhinitis have found that the prevalence of chronic rhinitis ranges from 17% to 83%, with up to 77 million affected individuals in the United States.

Allergic rhinitis (AR) symptoms are the result of a complex IgE-mediated response, and the diagnosis is made based on symptoms (eg, congestion, nasal discharge, itching, sneezing, and postnasal drainage) plus evidence of sensitization with allergen skin testing and/or serum specific IgE testing that correlate with allergen exposure.⁴ AR can further be divided into seasonal AR and perennial AR. A summary of numerous reports spanning a 30-year timeframe found that

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the reported prevalence of AR ranges from 9% to 42%³ and appears to be increasing,⁵⁻⁸ resulting in a significant burden on the health care system, with more than \$6 billion spent annually on medications alone for AR.⁹

Nonallergic rhinitis (NAR) has a similar clinical presentation as AR, but patients with NAR fail to have evidence of sensitization on allergen testing.¹⁰ It has recently been suggested that NAR can be classified into 9 subtypes: drug-induced rhinitis, gustatory rhinitis, hormonal-induced rhinitis, infectious rhinitis, nonallergic rhinitis with eosinophilia syndrome (NARES), occupational rhinitis, senile rhinitis, atrophic rhinitis, and vasomotor rhinitis (VMR) or idiopathic rhinitis (IR).¹⁰ VMR is the most frequent form of NAR observed clinically (up to 60%) and is a diagnosis of exclusion. VMR is used synonymously with IR, and it has been proposed to replace VMR with the term *nonallergic rhinopathy*.¹¹ Symptoms of VMR are typically elicited by environmental conditions, such as cold air, changes in temperature, barometric pressure and humidity, irritants, and strong odors.

An epidemiologic review reported the prevalence of NAR to be as high as 57%,³ with an estimated 19 million individuals affected in the United States.² Increasing data show that some patients with chronic rhinitis who do not have evidence of systemic sensitization, and who otherwise would be diagnosed as having NAR, may still have evidence of local production of allergen specific IgE in their respiratory mucosa.¹²⁻¹⁶ This concept has been coined *entopy*,¹⁶ and this review will summarize the literature on locally produced allergen specific IgE and entopy and place it in context with AR and NAR.

AR AND CLASS SWITCHING TO IgE

Symptoms of AR are typically a result of IgE-dependent activation of mast cells found in the respiratory tract mucosa.^{17,18} IgE is a classic immunoglobulin with 2 heavy chains and 2 light chains. The Fc portion of the antibody binds to the cell membrane receptor, and the Fab portion binds to specific antigen.¹⁹ IgE is produced by B cells and binds to the high-affinity receptor (FcεR1) on mast cells and basophils.²⁰ On exposure to an allergen to which an individual has been previously sensitized, cross-linking of adjacent, membrane-bound, allergen specific IgE molecules on mast cells can occur. This cross-linking can lead to an immediate hypersensitivity reaction, which results in cell degranulation and release of mediators (eg, histamine, tryptase, and leukotrienes)¹⁷ and cytokines (eg, interleukin [IL] 4 and IL-13),^{21,22} which all contribute to the “allergic” clinical findings.

B cells require 2 signals to undergo class switch recombination (CSR) to produce IgE. First, IL-4 and IL-13, which are produced principally by T cells (T_H2 subtype), provide an essential signal that activates IgE production by B cells.²³⁻²⁵ It is also known that these cytokines can be produced in mucosa by mast cells and eosinophils.²⁶ Second, T_H2 cells express CD40 ligand (CD154), which activates CD40 on B cells and allows CSR to continue. CSR to an ε heavy chain occurs in 3 general steps²⁷: ε germline gene transcription, DNA recom-

bination with heavy chain locus producing ε circle transcripts (εCTs), and the synthesis of ε chain messenger RNA (mRNA) that is translated into protein.²² In addition, activation-induced cytidine deaminase (AID) is a key enzyme required for class switching of immunoglobulins and affinity maturation. AID expression is positively influenced by IL-4.^{28,29}

LOCAL IgE FOUND IN TISSUES

Class switching to IgE was originally considered a process restricted to the germinal centers of lymphoid tissue, such as the regional lymph nodes and spleen.³⁰ The IgE found in local respiratory tissues, such as the nasal and bronchial mucosa, was believed to migrate from the regional lymphoid tissue or serum.^{21,31} The evaluation of locally produced IgE outside the regional lymph nodes began almost 70 years ago, when it was recognized that the nasal secretions of ragweed allergic individuals could be used to passively transfer a local reaction to previously nonallergic individuals.³² More in-depth studies in the 1970s reported ragweed specific IgE in the nasal washings of ragweed allergic patients³¹ and that the level of IgE in the nasal secretions corresponded to serum increases in IgE.³³ Later research demonstrated that specific IgE binding activity for rye grass antigen was elevated in the nasal secretions of rye grass allergic patients. This study also reported an increase in rye grass specific IgG and IgA in allergic patients' nasal secretions.³⁴

In 1975, Huggins and Brostoff¹² evaluated patients with dust mite allergy. They reported that all patients who had a history consistent with dust mite allergy, positive skin test results for dust mite, and positive dust mite specific serum IgE test results also had dust mite specific IgE in their nasal secretions. Interestingly, they also found that of the 14 patients who had a convincing history for dust mite allergy but had negative skin test results, only 2 patients had positive serum IgE test results but all had dust mite specific IgE in their nasal secretions. Thus, the concept of local specific IgE production in NAR was raised more than 30 years ago.

Local IgE has been reported in a diffuse range of tissues. Recently, it has been reported that local immunoglobulin CSR to IgE is increased in the esophageal mucosa of patients with eosinophilic esophagitis and that these patients had an increased number of IgE-bound mast cells in their esophageal mucosa.³⁵ In Japan, it has been reported that allergen specific IgE in tears increases and decreases with the coming and going of the pollen season as opposed to serum allergen specific IgE.³⁶ Also, local IgE has been located in the sinus mucosa of patients with atopic and nonatopic chronic sinusitis.³⁷

LOCAL IgE PRODUCTION IN THE LOWER AIRWAY

For some time it was unclear whether the local IgE found in these tissues was produced by resident cells or whether they migrated there after class switching in lymphoid tissue.^{21,31} Subsequently, researchers have investigated whether class switching actually occurs in the respiratory tract mucosa.

Focusing on the lower airway, Takhar et al²⁷ demonstrated that all of the necessary steps for IgE CSR in fact occur in the bronchial mucosa of asthmatic patients. They demonstrated from bronchial biopsy specimens that ϵ germline gene transcripts, which mark the first step in the dedication of a B cell to class switch to IgE, were detected in most of both atopic and nonatopic asthmatic patients compared with nonasthmatic controls (75% and 30%, respectively). They then looked at evidence for DNA recombination, ϵ CTs, which is evidence of an irreversible step in the synthesis of IgE. The ϵ CT was elevated in most of their asthmatic test patients, and none was found in the nonasthmatic control subjects (75% and 0%, respectively). Third, ϵ -mRNA, as evidence of IgE production, was measured and found in most of the asthmatic test patients (80%) compared with only 15% of controls. Finally, AID mRNA was detected in 60% of the samples from the asthmatic test patients and from 25% of the control patients. A similar finding was reported by Ying et al,³⁸ who found increases in ϵ germline gene transcripts and mature mRNA for the ϵ heavy chain in the bronchial mucosa of both atopic and nonatopic asthmatic patients when compared with controls.

In addition, Balzar et al³⁹ found mast cell-bound IgE to be present in the lower airway (proximal and distal lower airways) but not in the lung parenchyma using biopsy specimens. They concluded that the identification of local IgE in patients was associated with more severe asthma exacerbations and correlated with systemic IgE. However, because of the absence of mast cells in lung parenchyma demonstrating IgE binding, they concluded that the IgE process on mucosal surfaces is regulated locally and not influenced by systemic IgE. More recent reports have found that B-cell-activating factor of the tumor necrosis factor family of cytokines, which plays an important part in B-cell survival, maturation, and proliferation,^{40,41} can be identified in bronchial secretions after segmental allergen challenge in sensitized individuals.⁴² Others have reported that increases in both IL-4 and IL-13 can be identified in the bronchial mucosa of atopic and nonatopic asthmatic patients.^{43,44} These reports demonstrate not only that IgE can be found in the lower respiratory tract but that the IgE production actually can occur locally, regardless of atopic status.

LOCAL IgE PRODUCTION IN THE NASAL MUCOSA IN AR

Likewise, researchers have investigated the presence of IgE in the nasal mucosa that is produced locally in AR patients. The presence of T_H2 lymphocytes, B cells, IL-4, and IL-13 in the nasal mucosa indicate that the switch from IgM to IgE can occur locally. This is supported by Durham et al,⁴⁵ who detected CD20⁺ B cells expressing ϵ germline transcripts and C ϵ heavy chain RNA in the nasal mucosa of AR patients that increased after an allergen challenge. Likewise, nasal mucosa biopsy specimens of grass pollen allergic patients revealed IgE⁺ B cells and plasma cells in the epithelium and lamina propria. Although there were some (4 times less than allergic

patients) IgE⁺ B cells and plasma cells found in the lamina propria of the control patients (possibly because of smoking habits of these patients), only the allergic patients had allergen specific IgE⁺ cells identified.⁴⁶ Later, Coker and colleagues⁴⁷ sequenced IgE variable region heavy chain genes from B cells in the nasal mucosa and identified AID mRNA in the nasal mucosa of atopic patients during their allergen season. Others⁴⁸ identified upregulation of IL-4 and ϵ germline gene transcripts in nasal mucosa 24 hours after an allergen stimulation.

To investigate whether the IgE found in the nasal mucosa is a result of migration to the tissue from the serum or if it is actually produced locally, Takhar et al⁴⁹ used nasal biopsy specimens from grass pollen allergic patients to evaluate for evidence of CSR to IgE. They found ϵ germline gene transcripts in the nasal mucosa of every grass pollen allergic patient during the grass season. This finding was observed much less frequently in the same group when examined out of season. In addition, AID mRNA was detected in most samples from grass pollen allergic patients both in and out of the grass pollen season. Smurthwaite et al⁵⁰ developed a nasal tissue culture system and enzyme-linked immunosorbent assay to provide a direct and quantitative measurement of de novo IgE synthesis in the nasal mucosa of hay fever patients. They report that this allergen specific local IgE found in the nasal mucosa of their patients was synthesized locally, persisted between seasons, and was not the result of peripheral blood B cells contaminating the studied tissue. These data point to a direct correlation between allergen exposure and class switching to IgE in the nasal mucosa.

ENTROPY AS A CAUSE OF IR

Currently, patients who have rhinitis symptoms suggestive of AR yet have negative test results for allergy (ie, negative allergen specific serum IgE and negative allergen skin test results) are by definition diagnosed as having NAR. A cause of NAR can be difficult to identify. The differential diagnosis includes inflammatory, irritant, anatomical, environmental, drug-induced, infectious, or hormonal causes. When these causes are not implicated, the diagnosis of exclusion is IR or VMR.

Various investigators have studied whether allergy and local IgE production are playing a role in a subset of IR patients and have approached the concept in different ways. Some have focused on the presence of allergen specific IgE in nasal secretions,^{13,51} whereas others investigated the response to specific nasal allergen provocation testing (NAPT).^{13,51-53} Several groups have analyzed the inflammatory component of inferior turbinate biopsy specimens^{16,54,55} and the ability of the nasal mucosa to bind specific allergens.¹⁶

INFLAMMATION IN IR

This question of local evidence of IgE in the nasal mucosa of IR patients has been evaluated in several biopsy studies focusing on inflammation. Powe et al⁵⁶ studied full-thickness inferior turbinate nasal biopsy specimens of patients who

were diagnosed as having IR (n = 17) and compared them to biopsy specimens from AR patients (n = 11) and nonrhinitic controls (n = 9). Their findings showed that the mucosa of AR and IR patients demonstrate similar inflammatory changes having increased epithelial activated (degranulated) mast cells, increased superficial mucosa eosinophils, and increased IgE⁺ cells when compared with nonrhinitic controls. Plasma cells were similar between groups. This group further investigated IR patients using inferior turbinate specimens from patients with AR (n = 11), IR (n = 10), and healthy controls (n = 12) to compare intrinsic antigen-binding ("allergen capture") specific for dust mite and grass pollen in the nasal mucosa in these 3 groups. Six of the 11 AR samples (55%) stained positive for dust mite allergen, whereas none of the IR or healthy controls stained positive for dust mite. Seven of the 11 AR patients (64%) stained positive for grass pollen, and 3 of the 10 IR samples (30%) stained positive for grass pollen. None of the 12 control samples stained positive for grass pollen. The authors use this "allergen capture" in the nasal mucosa of 30% of the IR patients as further evidence of a localized allergic response and coined the term *entropy* to describe the process of a localized allergic mucosal response that is independent of systemic atopic responses.¹⁶

T-cell subtypes in the nasal mucosa were subsequently investigated by Powe et al.⁵⁴ Full-thickness inferior turbinate biopsy specimens were taken from patients with perennial AR (n = 21), patients with IR (n = 22), and nonrhinitic controls (n = 19) and evaluated for the presence of T-cell subtypes, antigen-presenting cells, mast cells, and basophils. CD4⁺ T-cell counts were similar across all 3 groups. The IR samples had significantly fewer antigen-presenting cells in the epithelium when compared with perennial AR samples ($P = .007$). The IR and perennial AR samples had a similar distribution of total T cells (CD3⁺), activated T cells (CD25⁺), and naive T cells (CD45RA⁺). The IR group had significantly more subepithelial CD8⁺ T cells compared with the control group ($P = .02$), which correlated with mucosal mast cell numbers. The authors concluded that both rhinitis groups (IR and perennial AR) show similarities between T-cell subsets and mast cells, suggesting a common pathway in persistent nasal inflammation.

Not all researchers agree that inflammatory cells are involved in IR. van Rijswijk and colleagues⁵⁵ compared nasal biopsy specimens from patients with IR (ie, negative skin prick test [SPT] result and serum specific IgE to dust mite, pollens, molds, dog, cat, and other animals, with active nasal symptoms for more than 1 year; n = 65) with those from nonrhinitic controls (n = 20). Specifically, they evaluated the nasal biopsy specimens for evidence of inflammatory cells and IgE⁺ cells. They reported that there were no significant differences between the 2 groups with respect to the numbers of T cells (CD3⁺, CD4⁺, CD8⁺, and CD25⁺), Langerhans cells, macrophages, monocytes, IgE⁺ mast cells, or eosinophils. Similarly, Blom et al⁵⁷ studied 40 patients with VMR using nasal biopsies and brush cytologic testing. They found

no difference in the number of eosinophils, mast cells, and IgE⁺ cells between the VMR patients and healthy controls. These results were in contrast to a prior study by Powe et al,⁵⁶ who demonstrated an increase in inflammatory cells and IgE⁺ cells.

There were several notable differences between the study by van Rijswijk et al⁵⁵ and the studies by Powe et al,^{54,56} which may explain the disparate conclusions: (1) type of biopsy specimen (full thickness in the studies by Powe et al vs partial in the study by van Rijswijk et al); (2) patient condition severe enough to require surgery in the studies by Powe et al, so presumably more severe; and (3) more patients in the studies by Powe et al had NARES vs only 2 of 65 (3%) in the study by van Rijswijk et al. One or more of these differences could explain the divergent findings.

ENTROPY AND SPECIFIC SEASONAL AND PERENNIAL ALLERGENS AS A CAUSE OF IR: STUDIES OF NAPT AND NASAL SPECIFIC IgE

Although the previous IR studies focused primarily on inflammation, the following studies investigated whether allergy is present in a subset of IR patients using specific NAPT and nasal specific IgE testing. Rondon et al,¹³ in an effort to better characterize IR patients, looked at 3 groups. The first group contained patients with IR symptoms exclusively during the spring pollen season who had negative skin test results (prick and intradermal) and serum specific IgE to grass and *Olea europea* (IR group). The second group included patients with persistent AR to pollens who had positive skin and/or serum test results and positive NAPT results to grass and/or *O europea*. The third group included patients with persistent AR to house dust mite with positive skin and serum test results and positive NAPT results. Nasal lavage samples were analyzed for markers of inflammation. No significant difference was found in the level of total IgE in the nasal secretions between the persistent AR group with positive NAPT results and the IR groups. The IR group was further broken down into those patients with a positive NAPT result (62.5% of IR group) and those who had a negative NAPT result. They reported that overall 35% of the IR patients with positive NAPT results had nasal specific IgE detected, and every patient with nasal specific IgE also had a positive NAPT result. However, 65% of patients from the IR group with positive NAPT results did not have IgE in their nasal secretions, suggesting another mechanism for their symptoms.

Rondon et al⁵¹ have further investigated these patients with entropy by measuring tryptase, eosinophilic cationic protein, and total and specific IgE in nasal secretions after NAPT. They described these patients as having local allergic rhinitis (LAR) and compared them with healthy controls. All LAR patients had negative SPT, intradermal skin test, and serum specific IgE test results to grass but a positive NAPT result to grass extract. During the study, the NAPT result was positive in 100% of the LAR patients but in none of the controls. After the NAPT, tryptase and eosinophilic cationic protein were detected in the nasal secretions of 40% and 43% of LAR

patients, respectively. Specific IgE to grass pollen was detected in 30% of patients, whereas an increase in total IgE was not detected. Of note, a significant difference was found in the levels of tryptase and eosinophilic cationic protein in patients with a positive NAPT result and positive specific IgE test results vs patients with positive NAPT and negative specific IgE test results ($P = .001$). The authors concluded that patients with LAR had not only local specific IgE production but also mast cell and eosinophil activation induced by nasal exposure to grass pollen.

These findings support earlier work by Carney et al,⁵⁸ who proposed that some or all patients with IR may have symptoms as a result of IgE-mediated nonatopic allergy. They performed NAPT with common perennial and seasonal allergens (eg, dust mite, cat, dog, grass pollen). They reported that 62% of IR patients studied had a positive allergen challenge result and 85% of those patients reacted to dust mite. The findings of these researchers suggest that NAPT may be a modality that can be used to identify entropic patients.

In addition to local IgE production being implicated in seasonal NAR, research has also demonstrated local specific IgE in persistent NAR (PNAR). Rondon et al⁵² compared nasal lavage and serum samples from PNAR patients ($n = 50$), AR patients ($n = 30$), and healthy nonatopic controls ($n = 30$). Specific inclusion criteria for the NAR patients were at least a 2-year history of persistent rhinitis, negative SPT and serum specific IgE test results to perennial aeroallergens, and a negative intradermal skin test result to dust mite. The persistent AR patients had to demonstrate at least 2 years of symptoms and have positive SPT results and/or positive serum specific IgE test results to dust mite and a positive response on the dust mite NAPT. The results revealed that 54% of the PNAR patients had a positive response on the dust mite NAPT, and of these 22% had dust mite nasal specific IgE. In addition, the researchers showed that this subset of patients had a similar leukocyte phenotype as the perennial AR group, with increased eosinophils, CD3⁺ T cells, and CD3⁺CD4⁺ T cells. Although this number did not reach significance, it demonstrates that a subset of NAR patients may have an allergic component to their disease.

However, not all studies have demonstrated that IR patients have positive NAPT results. Wierzbicki et al⁵³ used NAPT with several common aeroallergens to investigate the prevalence of localized allergy in patients with negative skin test results (PNAR). Twenty patients with perennial rhinitis and negative allergy skin test results and 3 positive control patients with AR underwent the NAPT. Four of the PNAR patients were excluded after they developed symptoms with the glycerin control. Five of the PNAR patients had a positive NAPT result after 1 or more nasal challenges. These 5 patients had the NAPT repeated 3 to 5 months later, and none of them had a subsequent positive NAPT result. Given this inability to reproduce the positive NAPT results in this small sample of patients, the authors concluded that this does not support the concept of localized allergy in the nose.

COMPARISON OF ENTROPY TO NARES

One of the differential diagnoses of IR is NARES. NARES is a clinical syndrome that presents similarly to AR but, like entropy, demonstrates an absence of atopy. Nasal cytologic testing demonstrates greater than 20% eosinophils. NARES also has anosmia as a prominent feature, which distinguishes it from AR. This syndrome is characterized also by chronic eosinophilic nasal inflammation and the eventual development of nasal polyposis.^{59,60} Although eosinophils have been reported in the nasal mucosa and nasal secretions of patients who have been characterized as having entropy, it appears that the degree of eosinophilia and the presence of comorbid conditions (eg, anosmia and polyposis) might be useful distinguishing features to the clinician when evaluating these patients. However, more research is needed to better separate these entities.

DISCUSSION

The concept of local allergy in IR patients is both intriguing and controversial. Although some of the aforementioned studies have found nasal specific IgE, positive NAPT results, and inflammatory cells in a subset of IR patients, the studies are conflicting. For example, studies on inflammation in IR have been contradictory.^{16,54–56} Powe et al demonstrated an increase in mast cells, eosinophils, and IgE⁺ cells,⁵⁴ a similar T-cell phenotype as AR patients,⁵⁶ and evidence of allergen binding in IR patients¹⁶ compared with controls. In contrast, van Rijswijk et al⁵⁵ found IR patients had a similar inflammatory profile as nonrhinitic controls. Differences in biopsy specimens and patient selection may explain these variable results.

Similarly, although several investigators have noted that a subset of IR patients (54%, 62%, 62.5%) have positive specific NAPT results,^{13,52,58} others have found all positive NAPT results in IR patients to be negative on repeat challenges.⁵³ Variability in nasal challenge techniques may partially explain these differing conclusions.^{12–14,26,51–53,58} Also, although studies by Rondon et al^{13,51,52} suggest that 22% to 35% of IR patients with a positive NAPT result have evidence of localized nasal specific IgE and Powe et al demonstrated 30% of IR patients have evidence of grass pollen allergen capture,¹⁶ this suggests that approximately 70% to 75% of patients are affected by other mechanisms.

In addition, although the machinery for CSR and somatic hypermutation has been identified in the nasal mucosa of AR patients, it has not been located in the nasal mucosa of IR patients.^{47,49} Finally, more specific to bronchial IgE production, it has been demonstrated that although class switching to IgE occurs in the lungs of both atopic and nonatopic asthmatic patients, it is also found in healthy control patients.²⁷

Given these conflicting results, there are multiple unanswered questions related to the concept of entropy. First, does this concept even exist? The aforementioned studies demonstrate contradictory results. Although inflammation may be similar in a subset of IR patients compared with AR patients,^{54,56} some investigators have concluded their inflamma-

tion is no different than controls.⁵⁵ In addition, because skin and serum specific IgE testing have limitations, it is possible that we are mislabeling AR patients in these studies with false-negative results on SPTs and serum specific IgE tests and then finding local IgE or positive NAPT results. Second, with NAPT and nasal specific IgE testing not widely available, the diagnosis would be difficult to make. Third, what is the natural history of entropy? A recent study¹⁴ suggested that some NAR patients will ultimately become AR patients, but this concept has not been specifically studied in patients with entropy or localized IgE.

CONCLUSION

A substantial percentage of IR patients have current treatment regimens that are suboptimal. In addition, a subset of IR patients has evidence of local allergen specific IgE production. Further work elucidating the mechanisms and causes of IR, including the concept of local IgE production or entropy, would ultimately enhance the ability to more precisely diagnose and optimally treat IR. If a percentage of IR patients are believed to have localized allergy, this may provide impetus for the investigation of conventional AR therapies in this subset of IR patients.

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