

# Local IgE Production in Nonatopic Nasal Polyposis

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## ABSTRACT

**Introduction:** Chronic rhinosinusitis with nasal polyposis (CRSwNP) represents an eosinophilic T-helper 2 inflammatory response. Local production of IgE within nasal polyps (NPs) has been demonstrated, suggesting a role for local IgE in the pathogenesis of NP in atopic CRS patients. We hypothesized that local IgE specific to inhalant allergens may also play a role in the genesis of NP in nonatopic CRS patients.

**Methods:** Sinus and inferior turbinate tissue was obtained from nonatopic CRSwNP patients ( $n = 7$ ), chronic rhinosinusitis without nasal polyps (CRSSNP) patients ( $n = 15$ ), and healthy controls ( $n = 9$ ) at the time of surgery. ImmunoCAP analysis (Phadia AB, Portage, MI) for 14 common inhalant antigens was performed on tissue homogenates to determine the antigen-specific response.

**Results:** Total IgE levels did not differ in sinus or turbinate tissue between CRSwNP, CRSSNP, or control patients. CRSwNP sinus tissue had higher levels of specific IgE for cockroach and plantain ( $p = .03$ ) than other groups and elevated *Alternaria* IgE levels when compared with CRSSNP sinus tissue ( $p < .05$ ). No significant differences were found for any of the other antigen-specific IgE levels. Fifty-seven percent of CRSwNP polyps demonstrated a polyclonal IgE response, whereas the other 43% had no demonstrable antigen-specific IgE. In contrast, only 17% of CRSSNP patients demonstrated a polyclonal response within sinus tissue, whereas 67% had no detectable antigen-specific IgE. There was no significant difference in levels of IgE in inferior turbinate tissue between the groups ( $p > .05$ ).

**Conclusions:** Localized mucosal IgE specific to common inhalant allergens appears to play a role in a subset of CRSwNP patients without evidence of systemic atopy.

## SOMMAIRE

**Introduction:** La rhinosinusite chronique (RC) accompagnée d'une polypose nasale (PN) est une réaction inflammatoire éosinophile médiée par les lymphocytes T auxiliaires 2. Comme la production locale d'immunoglobulines E (IgE) dans les polypes nasaux a déjà été établie, cela donne à penser que les IgE locales jouent un rôle dans la pathogénie de la PN dans le contexte de la RC atopique. Aussi avons-nous émis l'hypothèse selon laquelle les IgE locales, spécifiques d'allergènes inhalés pouvaient également jouer un rôle dans l'apparition de la PN dans le contexte de la RC non atopique.

**Méthode:** Des prélèvements de tissu ont été effectués dans les sinus et les cornets inférieurs de sujets souffrant d'une RC avec PN non atopique ( $n = 7$ ) ou d'une RC sans PN ( $n = 15$ ) et de témoins en bonne santé ( $n = 9$ ) au moment de l'intervention. Une analyse de 14 antigènes souvent inhalés a été réalisée à l'aide d'ImmunoCAP (Phadia AB, Portage, MI) sur des homogénats de tissu afin de déterminer la réaction spécifique de l'antigène.

**Résultats:** Il n'y avait pas de différence quant au taux d'IgE totales dans les tissus des sinus et des cornets inférieurs entre la RC avec PN, la RC sans PN et les tissus sains. Le tissu sinusal dans le groupe de la RC avec PN présentait un taux plus élevé d'IgE spécifiques de la coquerelle et du plantain ( $p = .03$ ) que dans d'autres groupes et un taux élevé d'IgE *Alternaria* comparativement au tissu sinusal dans le groupe de la RC sans PN ( $p < .05$ ). Aucun écart significatif n'a été relevé en ce qui concerne le taux des autres IgE spécifiques de l'antigène. Cinquante-sept pour cent des polypes dans la RC avec PN ont montré une réaction polyclonale d'IgE, tandis

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que les 43% restants n'ont pas montré d'IgE spécifiques de l'antigène. En revanche, 17% seulement des personnes atteintes d'une RC sans PN ont montré une réaction polyclonale dans le tissu sinusal, tandis que 67% des personnes du groupe avaient un taux indétectable d'IgE spécifiques de l'antigène. Il n'y avait pas de différence importante entre les groupes quant au taux d'IgE dans le tissu des cornets inférieurs ( $p > .05$ ).

**Conclusion:** La présence locale d'IgE dans la muqueuse, spécifiques des principaux allergènes inhalés semble jouer un rôle dans le sous-groupe de personnes atteintes d'une RC avec PN mais ne présentant pas de signes atopiques généraux.

**Key words:** *chronic rhinosinusitis, IgE, local production, nasal polyps, specific IgE*

Chronic rhinosinusitis (CRS) is typically divided into chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP). In the European position paper on rhinosinusitis and nasal polyps (NPs), CRS is considered to represent a spectrum of disease, with CRSwNP representing a subgroup of this continuum.<sup>1</sup> The etiology of NPs in patients with CRS is multifactorial. Histologic and immunohistochemical studies have shown increased levels of eosinophils, plasma cells, and mediators of the T-helper 2 inflammatory cascade in CRSwNP compared with CRSsNP.<sup>2</sup>

The abundance of eosinophils in NPs has led to the suggestion that atopy results in a predisposition to the development of NPs in susceptible individuals. Positive skinprick tests to common allergens are frequent in both CRSwNP (71%) and CRSsNP (68%).<sup>3</sup> However, it remains unclear why a subset of CRS patients develop NPs, whereas other CRS patients do not. In addition, the theory of atopy in association with NPs does not explain the etiology of NP in patients with negative skinprick tests.

In previous work, we have found increased levels of local IgE specific for fungal and nonfungal allergens in the NPs of patients with allergic fungal rhinosinusitis (AFRS) compared with CRSsNP patients and controls,<sup>4</sup> thus demonstrating overexpression of local IgE in patients with systemic allergies. Other authors reported increased levels of local NP tissue IgE in CRSwNP patients with low levels of systemic allergen reactivity, suggesting a heightened local tissue-allergic response.<sup>5</sup> In the present study, we hypothesized that patients with CRSwNP without evidence for systemic atopy would also have increased levels of local mucosal IgE specific to common aeroallergens and that polyp IgE would be elevated and may play a role in anatomic localization of NP formation. To investigate this, we studied sinus and inferior turbinate tissue for the presence and levels of specific IgE in CRS patients with and without NPs, as well as in healthy control subjects.

## Methods

### Subjects

Eligible patients were undergoing endoscopic sinus or skull base surgery at the Medical University of South Carolina. The subjects were divided into three groups: (1) patients with CRSwNP with negative systemic allergy testing, either via skinprick testing or serum IgE measurements; (2) patients with CRSsNP; and (3) control patients without inflammatory sinus disease. The latter group consisted of patients undergoing endoscopic sinus surgery as an approach to skull base pathology, such as cerebrospinal fluid leak repair. Exclusion criteria included patients with cystic fibrosis, Samter triad, ciliary dyskinesia, known immunodeficiency, or systemic corticosteroid use in the last 30 days. All CRSwNP patients underwent systemic allergy testing, which was negative. Allergy testing was not routinely carried out on CRSsNP or control patients as this was not clinically indicated. Prior to undergoing sinus surgery, all participants in the study signed a written informed consent form. The study was approved by the Institutional Review Board of the Medical University of South Carolina.

### Nasal Biopsy

All biopsies were performed at the time of surgery. In patients with CRSwNP, polypoid tissue from the middle meatus or ethmoid infundibulum was taken. In patients with CRSsNP, edematous mucosa was collected from the ethmoid infundibulum, maxillary sinus, or anterior ethmoid sinuses. From control patients, mucosa from the anterior ethmoid or maxillary sinus was sampled. In all patients, a biopsy was also taken of the inferior turbinate, just posterior to the head of the inferior turbinate. The tissue specimens were immediately snap-frozen in liquid nitrogen or placed in Tissue-Tek O.C.T. (Sarkura Finetek, Torrance, CA) and frozen for immunohistochemical analysis. Frozen sinus tissue specimens were stored at  $-80^{\circ}\text{C}$  until processed.

### Total and Antigen-Specific IgE Quantification

Specimens were processed as previously described.<sup>4</sup> Briefly, frozen specimens were thawed in 1 mL of sterile phosphate-buffered saline and processed in a tissue homogenizer, yielding single-cell suspensions. These suspensions were transferred to 1.5 mL microcentrifuge tubes and centrifuged for 5 minutes at 10 000 rpm (4°C). The supernatant from each vial was decanted into a 5 mL snap-top vial and stored on ice prior to analysis. Lysate total protein concentration was determined by BCA protein assay (Thermo Scientific, Rockford, IL).

One-millilitre samples of each lysate were submitted for specific IgE analysis via commercially available ImmunoCAP methodology (Phadia AB, Portage, MI). Concentrations determined by ImmunoCAP analysis were standardized using the original protein concentrations determined previously. Specific IgE analysis panel included the following antigens: Bermuda grass, Timothy grass, white oak tree, red maple tree, cocklebur, plantain, ragweed, *Cladosporium*, *Aspergillus*, *Alternaria*, dust mite, cockroach, cat, dog, and total IgE.

### Immunohistochemistry

Immunohistochemical staining was performed on sinus mucosa and inferior turbinate tissue biopsies as previously described.<sup>4</sup> Briefly, tissue sections were cut using a Leica CM1850 cryostat (Wetzlar, Germany) and fixed to poly-L-lysine-coated slides. Endogenous peroxidase activity was quenched using 0.6% hydrogen peroxide, and nonspecific antibody staining was blocked with Vectastain ABC blocking agent (Vector Labs, Burlingame, CA). Slides were then incubated with commercially available antibodies to IgE (Invitrogen/Zymed, Carlsbad, CA). Positive staining cells were visualized by processing with Vectastain ABC immunoperoxidase kit (Vector Labs). Patients with AFRS served as positive controls, as previously described.<sup>4</sup> Counterstaining was performed with hematoxylin, and isotype controls were performed for all staining protocols. Pictomicrographs were taken with a Zeiss Axiovert 200M microscope (Carl Zeiss, Inc., Germany). Given the high percentage of patients with no detectable IgE on ImmunoCAP analysis, immunohistochemistry was performed to confirm the absence of any significant IgE in the specimens, and separate statistical analysis of immunohistochemical results was not performed.

### Statistical Analysis

Statistical analysis was performed using *Winstat for Excel* version 2001.1. Because the data were not distributed

normally, nonparametric tests were used. A Kruskal-Wallis *H*-test was used to test for significant differences between the three groups. A Mann-Whitney *U* test was used to test for significant differences between each pair of groups. Significant differences in IgE levels between sinus and turbinate tissue were tested using a Wilcoxon ranked-pairs test.

### Results

Thirty-one patients were included in the study. Seven patients had CRSwNP, 15 had CRSsNP, and 9 were control patients. All CRSwNP patients had negative systemic allergy testing (Table 1). Adequate turbinate tissue was available for analysis for all patients. Three patients in the CRSsNP group did not have adequate sinus tissue for analysis. Total and antigen-specific IgE levels for each of the 14 antigens in both sinus and turbinate tissue are shown in Table 2 and Table 3.

#### Sinus Tissue

ImmunoCAP analysis of sinus tissue was completely negative in 5 of 9 (56%) control patients, 8 of 12 (67%) CRSsNP patients, and 3 of 7 (43%) CRSwNP patients. Immunohistochemistry confirmed the absence of IgE in all of these cases. In all 4 of the 7 CRSwNP patients with detectable tissue IgE, a polyclonal response was present, with positive antigen-specific IgE to at least 9 of the 14 antigens tested (Table 4).

The mean levels of total and antigen-specific IgE in sinus tissue in each of the three groups is shown in Table 2. There was no difference in total IgE levels between the groups ( $p = .74$ ). Significant differences between antigen-specific IgE levels among the groups were detected by the Kruskal-Wallis *H*-test for cockroach and plantain ( $p = .03$ ). When each pair of groups was analyzed, CRSwNP patients had significantly higher levels of specific IgE for cockroach and plantain than either control patients ( $p = .046$ ) or CRSsNP patients ( $p = .025$ ). CRSwNP patients also had higher levels of *Alternaria*-specific IgE

**Table 1.** Patient Demographics

|               | Controls | CRSsNP | CRSwNP |
|---------------|----------|--------|--------|
| Number        | 9        | 15     | 7      |
| M:F           | 6:3      | 6:9    | 4:3    |
| Mean age (yr) | 47       | 36     | 42     |

CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyposis.

**Table 2.** Mean (Median) IgE in Sinus Tissue

| Specific IgE (mUA/mg) | Control (n = 9) | CRSwNP (n = 7)   | CRSsNP (n = 12) |
|-----------------------|-----------------|------------------|-----------------|
| Bermuda grass         | 35.35 (0)       | 200.39 (0)       | 28.26 (0)       |
| Timothy grass         | 32.94 (0)       | 531.33 (36.03)   | 176.29 (0)      |
| White oak tree        | 66.68 (0)       | 961.38 (36.66)   | 211.20 (0)      |
| <i>Cladosporium</i>   | 52.22 (0)       | 854.66 (36.66)   | 83.37 (0)       |
| Red maple tree        | 0 (0)           | 277.56 (0)       | 26.81 (0)       |
| Dust mite             | 93.20 (0)       | 584.64 (30.98)   | 170.08 (0)      |
| Cockroach             | 6.01 (0)        | 500.22 (32.24)*† | 30.07 (0)       |
| Ragweed               | 0 (0)           | 6.77 (0)         | 24.28 (0)       |
| Plantain              | 29.73 (0)       | 673.65 (36.03)*† | 39.49 (0)       |
| Cocklebur             | 46.60 (0)       | 598.67 (51.84)   | 83.67 (0)       |
| <i>Aspergillus</i>    | 74.72 (0)       | 397.97 (35.40)   | 71.93 (0)       |
| <i>Alternaria</i>     | 190.38 (0)      | 692.95 (30.34)†  | 32.97 (0)       |
| Cat                   | 114.65 (0)      | 3.25 (0)         | 38.41 (0)       |
| Dog                   | 102.19 (0)      | 450.90 (0)       | 24.28 (0)       |
| Total IgE (mIU/mg)    | 1537.34         | 2448.23          | 1366.12         |

CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyposis.

\*Significant difference with control ( $p < .05$ ).

†Significant difference with CRSsNP ( $p < .05$ ).

than CRSsNP patients ( $p = .025$ ); however, these levels were not significantly higher than those seen in control patients ( $p = .18$ ). No other significant differences were detected among the groups for any of the remaining allergens tested.

### Inferior Turbinate

ImmunoCAP analysis of inferior turbinate tissue was completely negative in 5 of 9 (56%) control patients, in 13

of 15 (87%) CRSsNP patients, and in 5 of 7 (71%) CRSwNP patients (71%). Immunohistochemical staining for IgE confirmed the absence of IgE in all of these cases. The mean levels of total and antigen-specific IgE in turbinate tissue in each of the three groups are shown in Table 3. Kruskal-Wallis  $H$ -test showed no significant difference between the three groups for any of the 14 allergens tested. Furthermore, there were no significant differences in total or antigen-specific IgE levels between any pair of groups.

**Table 3.** Mean (Median) IgE in Inferior Turbinate Tissue

| Specific IgE (mUA/mg) | Control (n = 9) | CRSwNP (n = 7) | CRSsNP (n = 15) |
|-----------------------|-----------------|----------------|-----------------|
| Bermuda grass         | 23.08 (0)       | 0 (0)          | 0 (0)           |
| Timothy grass         | 25.34 (0)       | 0 (0)          | 25.8 (0)        |
| White oak tree        | 54.66 (0)       | 0 (0)          | 31.59 (0)       |
| <i>Cladosporium</i>   | 44.92 (0)       | 0 (0)          | 10.14 (0)       |
| Red maple tree        | 11.03 (0)       | 0 (0)          | 0 (0)           |
| Dust mite             | 63.38 (0)       | 0 (0)          | 24.64 (0)       |
| Cockroach             | 21.6 (0)        | 0 (0)          | 0 (0)           |
| Ragweed               | 18.46 (0)       | 21.77 (0)      | 0 (0)           |
| Plantain              | 26.29 (0)       | 0 (0)          | 10.14 (0)       |
| Cocklebur             | 31.28 (0)       | 12.86 (0)      | 0 (0)           |
| <i>Aspergillus</i>    | 118.24 (0)      | 0 (0)          | 0 (0)           |
| <i>Alternaria</i>     | 123.99 (0)      | 8.16 (0)       | 0 (0)           |
| Cat                   | 44.9 (0)        | 0 (0)          | 12.17 (0)       |
| Dog                   | 21.23 (0)       | 0 (0)          | 0 (0)           |
| Total IgE (mIU/mg)    | 839.15          | 209.91         | 0               |

CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyposis.

**Table 4.** Specific IgE (mUA/mg) Levels in Chronic Rhinosinusitis with Nasal Polyposis Sinus Tissue ( $n = 7$ )

| Patient | Bermuda<br>Grass | Timothy<br>Grass | White<br>Oak | Cladosporium | Red<br>Maple | Dust<br>Mite | Cockroach | Ragweed | Plaintain | Cocklebur | Aspergillus | Alternaria | Cat   | Dog     |
|---------|------------------|------------------|--------------|--------------|--------------|--------------|-----------|---------|-----------|-----------|-------------|------------|-------|---------|
| A       | 0                | 0                | 0            | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0     | 0       |
| B       | 0                | 0                | 0            | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0     | 0       |
| C       | 0                | 0                | 0            | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0     | 0       |
| D       | 23.39            | 36.03            | 36.66        | 36.66        | 27.18        | 30.98        | 32.24     | 47.41   | 36.03     | 51.84     | 35.40       | 30.34      | 22.76 | 28.45   |
| E       | 0                | 204.35           | 330.43       | 269.57       | 0            | 221.74       | 173.91    | 0       | 278.26    | 195.65    | 165.22      | 243.48     | 0     | 0       |
| F       | 0                | 1333.33          | 2454.55      | 2151.52      | 0            | 1272.73      | 1303.03   | 0       | 1757.58   | 1606.06   | 1090.91     | 1818.18    | 0     | 1212.12 |
| G       | 1379.31          | 2145.59          | 3908.05      | 3524.90      | 1915.71      | 2567.05      | 1992.34   | 0       | 2643.68   | 2337.16   | 1494.25     | 2758.62    | 0     | 1915.71 |

**Table 5.** Specific IgE (mUA/mg) Levels in Chronic Rhinosinusitis without Nasal Polyposis Sinus Tissue ( $n = 12$ )

| Patient | Bermuda<br>Grass | Timothy<br>Grass | White<br>Oak | Cladosporium | Red<br>Maple | Dust<br>Mite | Cockroach | Ragweed | Plaintain | Cocklebur | Aspergillus | Alternaria | Cat    | Dog    |
|---------|------------------|------------------|--------------|--------------|--------------|--------------|-----------|---------|-----------|-----------|-------------|------------|--------|--------|
| A       | 0                | 0                | 0            | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0      | 0      |
| B       | 0                | 0                | 0            | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0      | 0      |
| C       | 0                | 0                | 0            | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0      | 0      |
| D       | 0                | 0                | 0            | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0      | 0      |
| E       | 0                | 0                | 0            | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0      | 0      |
| F       | 0                | 0                | 0            | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0      | 0      |
| G       | 0                | 0                | 0            | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0      | 0      |
| H       | 0                | 0                | 0            | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0      | 0      |
| I       | 0                | 0                | 169.57       | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0      | 0      |
| J       | 0                | 0                | 1190.87      | 0            | 0            | 0            | 0         | 0       | 0         | 0         | 0           | 0          | 0      | 0      |
| K       | 0                | 1576.29          | 504.41       | 491.80       | 0            | 493.97       | 0         | 0       | 0         | 643.13    | 567.47      | 0          | 0      | 0      |
| L       | 339.13           | 539.13           | 669.57       | 508.70       | 321.74       | 1586.96      | 360.87    | 291.30  | 473.91    | 360.87    | 295.65      | 395.65     | 460.87 | 291.30 |

CRSwNP patients tended to have higher levels of specific IgE in sinus tissue than in turbinate tissue for several allergens (timothy grass, white oak, *Cladosporium*, house dust mite, cockroach, *Aspergillus*); however, the difference was not significant ( $p = .07$  in all cases). For CRSsNP patients, the differences in specific IgE levels between sinus and turbinate tissue were not significant.

## Discussion

A variety of etiologies have been proposed for CRSwNP, to include biofilms,<sup>6</sup> bacterial superantigens,<sup>7</sup> leukotriene metabolism disorders,<sup>8</sup> abnormalities in innate immunity,<sup>9</sup> and local allergic responses.<sup>5</sup> It is likely that CRSwNP is a multifactorial, heterogeneous subset of CRS. However, just why a subset of patients with CRS develops NP, whereas others do not, is unclear.

The relationship between systemic allergy and NP has been widely debated. A high proportion of CRSwNP patients are reported to have positive skinprick tests to inhalant allergens (35–72%).<sup>3,10,11</sup> This is higher than the incidence seen in control patients (20–43%).<sup>3,12</sup> On the other hand, several authors have reported that the incidence of systemic atopy in CRSwNP is not significantly higher than that seen in CRSsNP (41–68%).<sup>3,13</sup> Furthermore, only 0.5 to 4.5% of patients with positive skinprick tests to common allergens develop NP, which compares with the incidence of NP in the general population.<sup>1,14–16</sup> Finally, the systemic allergic theory fails to explain why a substantial proportion of CRS patients with negative skinprick tests go on to develop NP. Thus, epidemiologic evidence does not support a role for systemic allergic responses as a cause of NP for many patients.

AFRS is a subset of CRSwNP with well-defined criteria.<sup>17</sup> It exhibits unique demographics and clinical aggressiveness, in contrast to other types of CRSwNP.<sup>18,19</sup> Even within individual patients, the manifestations of AFRS are frequently highly localized. It is unclear why AFRS can be unilateral or only affect certain sinuses. We recently found that AFRS polyps have significantly increased levels of IgE specific to fungal and nonfungal allergens than seen in control or CRSsNP patients.<sup>4</sup> With this in mind, we hypothesized that a similar local IgE response to inhalant allergens might play a role in the pathophysiology of NP in non-AFRS patients who lacked evidence of systemic atopy.

Previous studies investigating local tissue production of IgE to inhalant antigens in CRSwNP have shown mixed results. Hirschberg and colleagues found that nonatopic polyps had more IgE than control tissue, but this was only a trend and not statistically significant.<sup>20</sup> Suh and

colleagues demonstrated tissue-specific IgE to dust mite in weakly atopic patients but did not find dust mite-specific IgE in nonatopic patients.<sup>5</sup>

In contrast, Bachert and colleagues examined a limited IgE panel in NP patients (seven were nonatopic) and divided them into three groups. Group 1 (29% of the nonatopic patients) had no detectable tissue IgE. Group 2 had tissue IgE to only dust mite and included only one patient. Group 3 (over 50% of their nonatopic NP patients) demonstrated tissue IgE to all antigens tested (grass mix, dust mix, mould mix, and *Staphylococcus* superantigen).<sup>21,22</sup> Similar to Bachert and colleagues' results, we found tissue IgE in 57% of our nonatopic NP patients. We expanded on their work by examining a more extensive panel focused on inhalant allergens. We found specific IgE for cockroach (mean of 10-fold higher than other groups), as well as at least 9 of 14 common inhalant antigens, indicating polyclonal upregulation of tissue IgE. As our protocol focused on inhalant antigens, we did not test for IgE to *Staphylococcus* superantigen, and it is unclear if this was also elevated. Polyps generally demonstrated elevated IgE compared with turbinate within the CRSwNP group, but this trend did not reach significance. Similar to Bachert and colleagues, we found a significant subset of nonatopic NP patients (43%) with no detectable tissue IgE.<sup>21</sup> It appears that a non-IgE-mediated mechanism plays a role in the development of their NPs.

In contrast to CRSwNP, we found that only 2 of 12 CRSsNP patients demonstrated polyclonal local antigen-specific IgE production within sinus mucosa. Two patients had positive antigen-specific IgE to only one antigen, whereas 8 of 12 (67%) patients had no detectable tissue IgE.

## Conclusions

Our study demonstrates that approximately half of nonatopic NP patients have a significant localized IgE specific to multiple common inhalant allergens. Identification of these tissue-specific IgEs may play a role in elucidating the cause of NP formation in a subset of CRSwNP patients. Although tissue IgE may play a role in the development of some nonatopic NPs, this appears to be a heterogeneous disorder, and non-IgE mechanisms probably play a role in some patients.

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