

Mucosal brush biopsy of the oral cavity to detect local, peanut-specific immunoglobulin E

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Background: This study compares the ability of mucosal brush biopsy (MBB) from 2 separate locations in the oral cavity to detect peanut-specific immunoglobulin E (IgE) in patients who report adverse oral cavity reactions when ingesting peanuts.

Methods: Twenty patients who reported a history of oral cavity itching or swelling when ingesting peanuts underwent either MBB of the dorsal tongue ($n = 10$) or the vestibule ($n = 10$). Serum testing for total and peanut-specific IgE, using standard immunofluorescent assay, was obtained for all patients. Total and specific IgE for each location were compared. Additionally, the correlation between MBB and peanut-specific IgE on serum was determined using Fisher's exact probability testing.

Results: Peanut-specific IgE was detected in 3 of 10 (30%) MBB specimens from the dorsal tongue and in 10 of 10 (100%) MBB specimens from the vestibule. The mean peanut-specific IgE on MBB (kU/L) in the dorsal tongue group was 0.03 vs 0.17 in the vestibule group ($p = 0.0002$).

No significant association was noted for peanut-specific IgE between MBB and serum testing ($p = 1.0$).

Conclusion: This study demonstrates for the first time that peanut-specific IgE can be detected using MBB in the oral cavity of patients who are symptomatic when consuming peanuts. The vestibule was a superior location compared to the dorsal tongue for oral cavity MBB, correlating very well with self-reported symptoms. Peanut-specific IgE on MBB overall did not correlate well with serum testing for peanut-specific IgE. © 2013 ARS-AAOA, LLC.

Key Words:

mucosal brush biopsy; peanut allergy; antigen; oral cavity; IgE

How to Cite this Article:

Reisacher WR, Cohen JC. Mucosal brush biopsy of the oral cavity to detect local, peanut-specific immunoglobulin E. *Int Forum Allergy Rhinol.* 2013;3:636-641.

The Center for Disease Control and Prevention estimates the prevalence of food allergy in children less than 18 years of age in the United States to be approximately 4% to 8%, with an estimated 18% increase from 1997 to 2007.^{1,2} These concerns are also relevant for adults, with an estimated 4% prevalence of food allergy.³

In the United States, most food-associated allergic reactions are related to milk, egg, peanut, and tree nut ingestion.⁴ Reactions to foods may range from mild oral cavity itching to life-threatening anaphylactic reactions, which are responsible for approximately 200 deaths per year in the United States.⁵

The optimal test to diagnose immunoglobulin E (IgE)-mediated food allergy is currently unknown. The double blind, placebo-controlled food challenge has been considered the gold standard for diagnosing food allergy but this is difficult to perform on small children, is time-consuming, and carries a risk of severe reaction.⁶ Skin-prick testing (SPT) is easy to perform and has good sensitivity, but only has a 50% positive predictive value.³ Food-specific serum IgE levels, like SPT, can be used to help predict the likelihood of a severe allergic reaction, but is more expensive and also has a poor predictive value. Moreover, both SPT and in vitro testing are invasive procedures, which represent an obstacle for many patients and their families. Therefore, an alternative, less invasive test for diagnosing food allergy would be beneficial.

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Funding sources for the study: Research grant from the American Academy of Otolaryngic Allergy Foundation (AAOAF).

Potential conflict of interest: None provided.

Presented at the American Academy of Otolaryngic Allergy (AAOA) Annual Meeting, September 7, 2012, Washington, DC.

Received: 29 November 2012; Revised: 23 January 2013; Accepted: 10 February 2013

DOI: 10.1002/alar.21164

View this article online at wileyonlinelibrary.com.

Mucosal brush biopsy (MBB), which is able to harvest epithelial cells using a standard cytology brush, has been used in the nasal cavity for the study of ciliary ultrastructure⁷ and viral culture,⁸ and in the oral cavity for DNA analysis.⁹ In a study examining inferior turbinate tissue, antigen-specific IgE was shown to be present in epithelial cells after surgical biopsy.¹⁰ In 2012, Reisacher¹¹ first demonstrated the ability to detect local, antigen-specific IgE to airborne allergens in an MBB sample from the inferior turbinates of patients with allergic rhinitis (AR). Testing the oral cavity for locally-present IgE to food allergens with MBB represents a logical extension of this finding because, in certain cases such as peanut allergy and oral allergy syndrome (OAS), the oral cavity may be the primary area of the body affected by ingestion.¹²

This study is designed to assess the ability of an epithelial brush biopsy of the oral cavity to detect locally-present, peanut-specific IgE in patients who report local reactions to peanut ingestion. Peanut was chosen as a model food antigen because of the higher likelihood of systemic reactions, the strong oral cavity reactions that result from contact and the tendency of peanut allergy to persist into adulthood.^{13,14} It has been shown that within the oral cavity, the highest concentration of mast cells are present in the gingival and vestibular regions, whereas the lowest amount are found in the dorsal tongue.¹⁵ The primary goal of this study is to compare the levels of total IgE and peanut-specific IgE from the dorsal tongue and vestibule mucosa of symptomatic patients using MBB. Additionally, we explore the possibility of a correlation between the presence of peanut-specific IgE from MBB vs peanut-specific IgE from standard in vitro assay.

Patients and methods

Patient sample

Approval for this study was obtained from the Institutional Review Board of Weill Cornell Medical College, New York, NY (Protocol #1110011979). Inclusion criteria for the study included a clinical history of pruritis and/or edema in the oral cavity when consuming peanuts and age 18 years or greater. Patients with a history of allergy immunotherapy were excluded from the study. The actual allergic status of the patient to peanuts based on serum IgE testing was not known prior to enrollment. Patients were counseled about the research protocol and informed consent was obtained prior to enrollment. After enrollment, each patient was asked to fill out a questionnaire concerning the nature, frequency, and severity of their reactions when eating peanuts. Information about other food allergies and airborne allergies was also obtained. The first 10 patients underwent MBB of the dorsal tongue and the last 10 patients underwent MBB of the vestibule. All testing and data collection were performed at a single institution, Weill Cornell Medical College.

MBB

For the dorsal tongue MBB, a 7.75-inch cytology brush (Aeromed, Glastonbury, CT) was inserted along dorsal tongue, rotated, and moved back and forth approximately 10 times (Fig. 1A). For the vestibule MBB, 4 separate areas were biopsied in a similar fashion using 2 brushes, 1 for each side (Fig. 1B). After the procedure, the brushes were rinsed in phosphate buffered saline (PBS) to extract mucus and epithelial cells.

Measurement of total IgE, peanut-specific IgE, and total protein from MBB

The suspensions of epithelial cells were stored in a sterile, polypropylene tube and frozen immediately after harvest. After thawing, the cells were lysed using an ultrasonicator at 45% amplitude for 2 minutes at 15-second intervals (Branson Digital Sonifier, Danbury, CT). Up to 4 additional 15-second pulses were performed until the lysates appeared clear and Trypan Blue exclusion test demonstrated that no viable cells were present. Total protein concentration for the lysates was determined using a BCA assay (Thermo Fisher Scientific, Rockford, IL). One-milliliter (1-mL) samples of each lysate were then sent frozen to a reference laboratory (IBT Laboratories, Lenexa, KS) for ImmunoCAP analysis to determine total IgE levels as well as peanut-specific IgE levels (Thermo Fisher Scientific, Portage, MI). All IgE levels were standardized for total protein (corrected IgE). Positive values for peanut-specific IgE from MBB were defined as class 0/1 or higher.

Measurement of total IgE and peanut-specific IgE from serum

Venipuncture was performed on all subjects and collected in a serum separator tube (SST). These tubes were centrifuged at 3000 rpm (1077 g) for 15 minutes and serum was harvested. One-milliliter (1-mL) samples of serum were sent frozen to a reference laboratory (IBT Laboratories, Lenexa, KS) for ImmunoCAP analysis to determine total IgE levels as well as peanut-specific IgE levels (Thermo Fisher Scientific, Portage, MI).

Statistical analysis

Data are presented as mean values $\pm$ standard deviation (SD). The mean total IgE, mean total protein, mean corrected IgE, and mean peanut-specific IgE on MBB between the dorsal tongue and vestibule groups were each compared separately with Mann-Whitney U test using online statistical software.¹⁶ Mean serum total IgE, as well as peanut-specific IgE, between the MBB+ and MBB- groups was also compared in a similar fashion. Two-tailed *p* value was calculated for each comparison, with *p* < 0.05 considered statistically significant. Because of the small sample size, Fisher's exact probability testing was performed to examine the significance of the association between the presence of peanut-specific IgE on MBB vs serum, and a 2-tailed *p* value was calculated.

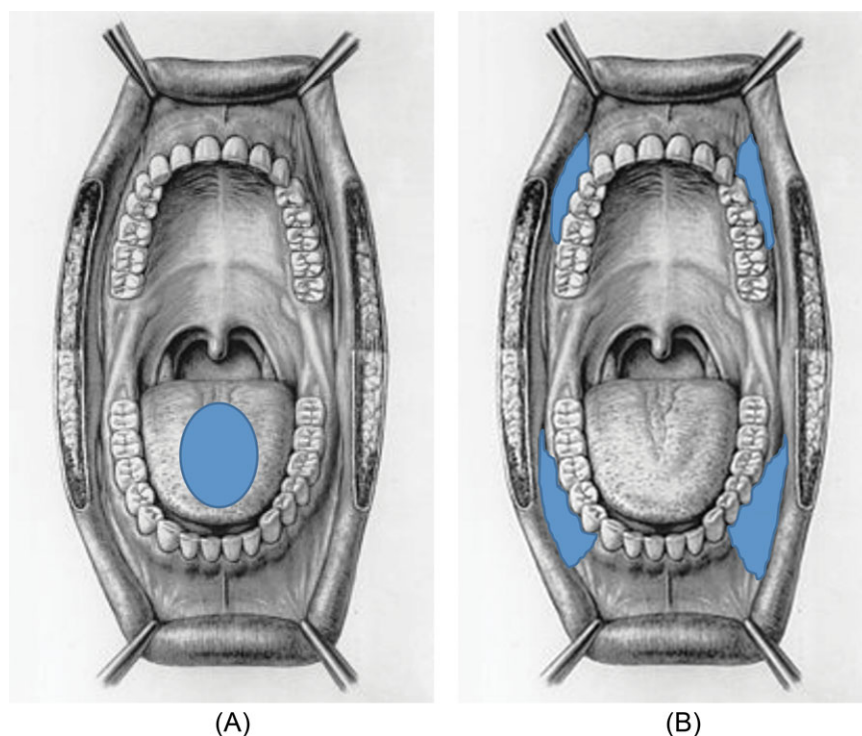


FIGURE 1. (A) Region of the dorsal tongue where MBB was performed. (B) Regions of the vestibule when MBB was performed. MBB = mucosal brush biopsy.

TABLE 1. Demographic and clinical features of study patients

Clinical feature	Tongue MBB (n = 10)	Vestibule MBB (n = 10)
Mean self-reported reactions to peanuts (range)	42.4 (1–200)	49.8 (3–300)
Positive peanut-specific IgE in serum	5 (50%)	5 (50%)
Oral cavity pruritis	9 (90%)	9 (90%)
Oral cavity edema	8 (80%)	8 (80%)
Nausea	3 (30%)	4 (40%)
Vomiting	3 (30%)	2 (20%)
Difficulty breathing	5 (50%)	3 (30%)
Pruritis in other areas besides the oral cavity	3 (30%)	7 (70%)
History of airborne allergies	8 (80%)	10 (100%)
History of other food allergies	8 (80%)	9 (90%)

IgE = immunoglobulin E; MBB = mucosal brush biopsy.

Results

A summary of the demographic and clinical data is shown in Table 1. Besides the higher prevalence of pruritis in areas of the body outside the oral cavity in the vestibule group, there were no significant differences in any of the other features between the dorsal tongue MBB group and the vestibule MBB group. Oral cavity itching and swelling were the most common symptoms reported. None of the patients reported any discomfort related to the biopsy, no complications occurred and no delayed adverse events were reported.

Serum testing

In both the groups, only 5 of 10 (50%) of the patients demonstrated positive peanut-specific IgE on serum testing (≥ 0.10 kU/L). In the dorsal tongue group, 4 patients had a class 2 IgE concentration (0.70–3.49 kU/L) and 1 patient had a class 0/1 IgE concentration (0.10–0.34 kU/L). In the vestibule group, 2 patients had a class 3 IgE concentration (3.50–17.49 kU/L) and 3 patients had a class 2 IgE concentration. Total serum IgE for the patients with positive peanut-specific IgE in serum (n = 10) ranged from 12 to 520 IU/mL, while those patients with negative specific IgE

TABLE 2. Mean total IgE, mean total protein, and mean corrected IgE (standardized for total protein) in MBB specimens from the dorsal tongue and vestibule

	Tongue MBB (n = 10)	Vestibule MBB (n = 10)	p
Mean total IgE (IU/mL)	4.90 ± 0.57 (4–6)	5.00 ± 0.67 (4–6)	0.8
Mean total protein (mg/mL)	0.24 ± 0.13 (0.07–0.48)	1.14 ± 0.27 (0.7–1.51)	0.0003
Mean corrected IgE (IU/mg)	27.87 ± 18.86 (10.42–71.43)	4.58 ± 1.10 (3.01–5.88)	0.0003

Values are mean ± SD (range). Values of *p* are based on Mann-Whitney U test. Statistically significant values are in bold.

IgE = immunoglobulin E; MBB = mucosal brush biopsy; SD = standard deviation.

in serum (n = 10) ranged from 16 to 365 IU/mL. There was no significant difference in total serum IgE (*p* = 0.90) or peanut-specific IgE (*p* = 0.56) between those patients who tested positive on MBB (n = 13) and those who tested negative on MBB (n = 7). The mean serum peanut-specific IgE in the dorsal tongue group was 0.72, compared to 2.10 in the vestibule group (*p* = 0.0002).

MBB testing

The results for total IgE, total protein, and corrected IgE concentrations are shown in Table 2. While the total IgE levels were the same for both oral cavity locations, the total protein was almost 5-fold higher in the vestibule group than in the dorsal tongue group, resulting in a significantly lower corrected IgE in the vestibule group (*p* = 0.0003). Of the 10 patients in the dorsal tongue group, 3 (30%) had positive peanut-specific IgE on MBB (≥ 0.10 kU/L). Of the 10 patients in the vestibule group, all 10 (100%) had positive peanut-specific IgE on MBB. All of the positive patients in both groups had class 0/1 concentrations of IgE. The mean, peanut-specific IgE (kU/L) on MBB for patients in the tongue group was 0.03 vs 0.17 in the vestibule group (*p* = 0.0002). There was no significant association noted between positive peanut-specific IgE on MBB with positive peanut-specific IgE on serum testing (*p* = 1.0).

Discussion

For at least the past 65 years, the importance of locally-present, antigen-specific IgE in the respiratory tract has been recognized. In 1947, Samter and Becker¹⁷ first demonstrated that nasal secretions from patients with ragweed allergy could passively transfer symptoms to nonallergic individuals. Antigen-specific IgE has been recovered from bronchoalveolar lavage fluid in atopic asthmatics after antigen challenge, and specific IgE is present in the nasal epithelium as well as in nasal secretions after antigen challenge.^{18,19}

For many years, it was believed that locally-present IgE was produced in the larger lymphoid structures of the body, such as the spleen or regional lymph nodes, and then transported to the respiratory mucosa. However, it is now known that locally-present, specific IgE is also able to be locally-produced. KleinJan et al.²⁰ demonstrated that

B cells in the nasal mucosa have the ability to undergo class switching to produce specific IgE in patients with seasonal and perennial AR, but not in nonallergic controls. Using in situ hybridization to analyze messenger RNA (mRNA) transcripts, Ghaffar et al.²¹ detected elevated isotype switching to IgE in B cells in both atopic and nonatopic chronic rhinosinusitis (CRS) patients compared to patients without CRS, though isotype switching was significantly higher in atopic patients. Gene transcripts indicative of IgE class switching are also present in the bronchial mucosa of both atopic and nonatopic asthmatics.²² Moreover, Vicario et al.²³ demonstrated local IgE class switching in the esophageal mucosa of eosinophilic esophagitis (EoE) patients, regardless of atopic status, but not in patients without EoE.

While local IgE in sinonasal tissue has been previously studied, this is the first known report of local, antigen-specific IgE harvested from the oral cavity using MBB in symptomatic patients. Previously, MBB has been used to harvest antigen-specific IgE to airborne allergens from the inferior turbinates in patients with AR who tested positive on SPT.¹¹ MBB was chosen for this study because it represents a less invasive method of sampling mucosal epithelium and secretions, compared to surgical biopsy, and no other test for local IgE in the oral cavity is clinically available. All patients in this study tolerated MBB well with no discomfort, and no immediate or delayed complications were reported.

Although local IgE has been detected in esophageal mucosa, it was unknown whether or not the increased keratinization of oral cavity mucosa would interfere with the detection of local IgE, particularly in the dorsal tongue group. The results of this study show that MBB is capable of detecting specific IgE to peanut within the oral cavity. Although the mean total IgE, corrected for total protein, was significantly higher in the dorsal tongue group, this can be explained by the significantly higher protein harvest in the vestibule group combined with the relatively small amounts of total IgE collected from each of the locations (Table 2). The larger protein harvest in the vestibule group may be further explained by the reduced keratinization and larger surface area of the vestibule biopsy, compared to the dorsal tongue, producing a greater harvest of epithelial cells (Fig. 1).

It has been demonstrated that local, specific IgE testing does not often correlate well with systemic testing, either through skin testing or in vitro methods.^{24,25} In a study by Rodon et al.,²⁶ 63% of patients who were symptomatic during the grass pollen season, but negative on systemic testing, had evidence of nasal IgE specific to grass pollen. Sabirov et al.²⁷ demonstrated that 60% of patients with CRS with nasal polyps had evidence of local, *Alternaria*-specific IgE in either sinonasal or polyp tissue without *Alternaria*-specific IgE present in the serum. Likewise, in this study, there was no significant association noted between the results of serum testing for the presence of peanut-specific IgE and those of local testing. It is not a surprising result, considering that serum testing is a measure of systemic sensitization, while oral mucosal testing, via MBB, is a measure of local sensitization.

Local IgE testing, on the other hand, has been found to correlate well with clinical symptoms. In 1985, Ohashi et al.²⁸ performed in vitro testing on nasal biopsy homogenates (tissue-radioallergosorbent test [t-RAST]) in patients with AR and those without. All 12 patients in the AR group were positive on t-RAST, while all patients in the control group were negative for local, specific IgE. Likewise, in this study, 100% of patients in the vestibule group had detectable, peanut-specific IgE on MBB, while only one-half of those patients tested positive in the serum. In the dorsal tongue group, which also had 50% positive testing in the serum, only 30% of patients tested positive on MBB. It is likely that this finding was due to the increased keratinization in that region, which led to significantly lower specific IgE harvest. The other alternative is that peanut-specific IgE is actually low in that region, but this seems unlikely given the high incidence of reported tongue pruritis and edema in the population studied.

Another possible reason behind the superior detection of specific IgE in the vestibule group is the presence of systemic sensitization. Merrett et al.²⁵ reported that 78% of RAST-negative patients with clinical AR had specific IgE to an airborne allergen on nasal lavage, more likely when total serum IgE was elevated. In 2012, Reisacher¹¹ reported that MBB of the inferior turbinates in patients with AR was more likely to be positive when the SPT grade was higher. In this study, patients with peanut-specific IgE on MBB did not have significantly higher total serum IgE than their negative counterparts. However, 70% of patients in the vestibule group reported pruritis in areas outside the oral cavity, compared to 30% in the dorsal tongue group, possibly indicating more systemic peanut sensitization in the vestibule group. Although there was no statistically significant difference in serum total IgE or peanut specific IgE between the MBB+ group vs MBB- group, the mean peanut-specific IgE on MBB in the vestibule group was 3 times higher than in the dorsal tongue group, which was statistically significant. While it is unknown at this time, the presence of systemic sensitization may signal a different route of sensitization, such as the skin or gastrointestinal (GI) tract. Alternatively, a “spillover” effect from local,

oral sensitization into the systemic circulation may take place after a critical threshold had been reached.

The results of this study not only confirm the feasibility of MBB for local IgE testing in the oral cavity, but also raise the question of whether or not this testing has any advantage over current diagnostic strategies, particularly when oral cavity symptoms are present. Given the limitations of systemic testing, which have already been discussed, it seems quite reasonable that testing should target the regions where the reaction takes place. In a study of Japanese cedar pollen, specific IgE in tears peaked sooner than serum IgE during the pollen season (March-June), while during the rest of the year, local IgE decreased while serum levels remained high.²⁹ This finding suggests that local IgE may be more reflective of clinically relevant allergens at the present time, compared to systemic testing, which may act as more of a “memory bank.”

MBB from the oral cavity mucosa is limited by the relatively small amount of IgE which can be harvested. Positive reactions were only in the 0/1 class, indicating a need to seek out methods of harvesting more IgE and improving the sensitivity of the assays used for MBB. While oral cavity MBB testing seems appropriate for food allergic patients with oral cavity symptoms, its utility needs to be determined for other food allergens and for patients with reactions manifesting in various locations, such as the skin or gastrointestinal tract. MBB testing in other regions of the oral cavity and GI tract should also be explored. Using microarray analysis of MBB samples from the inferior turbinate, species-specific IgE to shrimp was detected.³⁰ Future studies will also determine whether or not airborne allergens can be detected from oral cavity MBB testing. In addition, larger, controlled studies in both allergic and nonallergic populations will be necessary to help determine the sensitivity and specificity of oral cavity MBB testing.

Conclusion

MBB of the oral cavity is capable of harvesting antigen-specific IgE to peanut from both the tongue and vestibule in patients who report oral symptoms when ingesting peanuts. The vestibule is a superior biopsy site compared to the dorsal tongue, likely due to greater surface area available for biopsy, ease of access, and inherent mucosal qualities within that region. The presence of peanut-specific IgE on vestibule MBB did not correlate well with serum IgE testing for peanut allergen, but correlated very well with self-reported symptoms. Future studies will help determine the clinical utility of MBB with respect to guiding therapeutic approaches in patients with food allergy. 🌱

Acknowledgements

We gratefully acknowledge Karen Bunting, PhD, Ari Melnick, MD, Maria Bremberg, RN, and Teresa Valderrama, MPH for their valuable assistance in the completion of this study.

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