

Esophageal IgE, IgG4, and mucosal eosinophilia in individuals with dysphagia

Apoorva T. Ramaswamy, MD¹, Jae Seong No, BS⁴, Lillye Anderson, BS⁴, Aliza Solomon, DO², Thomas Ciecierrega, MD², Elaine Barfield, MD², Kimberly Chien, MD², Felice Schnoll-Sussman, MD³ and William R. Reisacher, MD, FACS, FAAOA¹

Background: Eosinophilic esophagitis (EoE) is an inflammatory disease of the esophagus, producing failure to thrive in infants and dysphagia with food impaction in older children and adults. Although most people with EoE manifest atopic/allergic disease, the specific allergens to which immunoglobulin E (IgE) is directed, if any, have not yet been characterized.

Methods: Mucosal brush biopsy (MBB) and solid tissue biopsy (STB) specimens were prospectively obtained from 25 individuals with dysphagia and suspicion of EoE. Specific IgE (sIgE) against 112 epitopes from airborne and food proteins, antigens known to cause a polyclonal IgE response and IgG4 to food allergens, were measured.

Results: There was no difference in total IgE harvested between the 2 biopsy methods ($p > 0.05$) or between the EoE-positive ($N = 12$) and EoE-negative ($N = 13$) groups ($p > 0.05$). None of the samples in either group contained measurable serum IgE to any of the airborne or food proteins tested, but low levels of IgE specific to *Candida* and *Staphylococcus enterotoxins* were detected. Low levels of

IgG4 specific to wheat, soy, peanut, and egg were also detected.

Conclusions: Both MBB and STB are able to harvest measureable levels of IgE and IgG4 from the esophageal mucosa. Low levels of serum-specific IgE suggest that other inflammatory mechanisms, besides type I, IgE-mediated, allergen-specific hypersensitivity, may act as the primary catalyst for mucosal eosinophilia. Clarifying the role of both IgE-mediated and non-IgE-mediated inflammatory mechanisms will help identify more targeted diagnostic and treatment strategies for individuals who present with dysphagia and esophageal eosinophilia. © 2019 ARS-AAOA, LLC.

Key Words:

eosinophilic esophagitis; inflammation; dysphagia; allergen; IgE; sensitization; airborne; EoE; IgG4

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Eosinophilic esophagitis (EoE), first described in the 1970s, often manifests with dysphagia, chest pain, and food impaction in adults, whereas children typically

present with failure to thrive, difficulty feeding, nausea, and vomiting.¹ This predominantly male disorder has a prevalence of 0.05-0.1% in the United States, although rates appear to be increasing.^{2,3} Considering the rising importance of EoE, an understanding of its pathophysiology is critical to guide improvements in diagnosis and treatment.

Individuals with EoE often have a personal or family history of atopy, with asthma, eczema, rhinitis, or food allergy being common comorbidities.^{3,4} Previous studies reported a personal atopic history in 50-60% of individuals with EoE.^{5,6} Because of this association and the eosinophilic nature of the inflammatory response, EoE has been hypothesized by many to be a type I, immunoglobulin E (IgE)-mediated allergic process to either food or airborne allergens, both of which are swallowed.⁷ This hypothesis has been strengthened by evidence of clinical improvement of EoE with elimination diets, such as amino acid elemental diets and the six-food elimination diet (SFED).⁸ However,

¹Department of Otolaryngology-Head and Neck Surgery, Weill Cornell Medical College, New York, NY; ²Department of Pediatric Gastroenterology, Weill Cornell Medical College, New York, NY;

³Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, NY; ⁴Weill Cornell Medical College, New York, NY

Correspondence to: William R. Reisacher, MD, FACS, FAAOA, Department of Otolaryngology-Head and Neck Surgery, Weill Cornell Medical College, New York-Presbyterian Hospital, 1305 York Avenue, 5th Floor, New York, NY 10021; e-mail: wir2011@med.cornell.edu

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elimination diets based on the results of allergy testing, through either skin prick testing (SPT) or serum-specific IgE (sIgE) measurement, only demonstrate a 50-60% response rate, compared with a 90-96% response rates for elemental diets.⁹ Spergel reported that, among people who improved on elimination diets, only 13% tested positive to the eliminated food on SPT.⁴

The limited success from testing-based elimination diets could be an indication that type I, IgE-mediated hypersensitivity is not playing a pivotal role in the etiology of EoE. However, it is also possible that evidence for allergen sensitization may be present in the locally symptomatic esophageal tissue, but not in the skin or serum. Previous studies using both mucosal brush biopsy (MBB) and solid tissue biopsy (STB) demonstrated that specific IgE to airborne and food allergens may be present in locally symptomatic nasal and oral cavity mucosa, even when SPT and sIgE testing to those allergens is negative.¹⁰⁻¹³ Moreover, Rodon and colleagues determined that individuals who demonstrated only local sensitization to grass pollen had similar subjective and objective improvements from subcutaneous immunotherapy as individuals with evidence of atopy on skin or serum testing.¹⁴

The primary goal of this study is to assess the feasibility of collecting and measuring sIgE harvested directly from the esophageal mucosa using both MBB and STB. Vicario and colleagues demonstrated local class switching to IgE and IgE production in the esophageal mucosa of individuals with EoE, regardless of their atopic status, along with increased density of B cells and mast cells, but they were not able to determine which proteins the antibodies were directed against.¹⁵ Therefore, the secondary goal of this study was to compare the levels of total IgE, sIgE, and IgG4 to various antigens in the esophageal mucosa of individuals with and without EoE who present with dysphagia. The levels of antibodies harvested by MBB were compared with those harvested by STB.

Patients and methods

Study population

Approval for this study was obtained from the institutional review board of Weill Cornell Medical College, New York City (Protocol #1603017056). The inclusion criteria included individuals over the age of 1 year who were recommended to undergo esophagogastroduodenoscopy (EGD) for suspicion of EoE based on the presence of dysphagia with suspected esophageal cause, reflux, vomiting, failure to thrive, food impaction, or a combination of these symptoms. All participants were recruited from the adult and pediatric divisions of the Gastroenterology Department at Weill Cornell Medical College. Electronic health records were used to characterize demographic data, past medical history, medication history, allergic history, and pathologic data regarding the included participants.

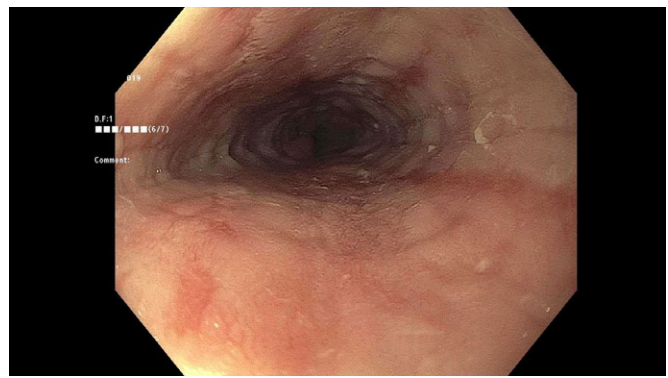


FIGURE 1. Endoscopic view of the esophagus demonstrating a region of high clinical suspicion for eosinophilic esophagitis.

Tissue sampling

All participants underwent EGD by a board-certified adult or pediatric gastroenterologist in accordance with their clinical plan and standard of care. Sedation and intubation, when indicated, were performed by the anesthesiology team, either in the operating room or endoscopy suite. A transoral flexible EGD scope was used for diagnostic examination, according to clinical plan, and for the biopsies. Multiple STBs were taken of the esophagus at the regions of highest clinical suspicion for EoE, as determined by the operating surgeon, using micro cup forceps (Fig. 1). If no particular site was inflamed, random biopsies of the esophageal mucosa were taken. These samples were placed in formalin and sent to the Pathology Department at Weill Cornell Medicine for examination. The pathologic diagnosis of EoE was made when the concentration of eosinophils in one high-powered field was ≥ 15 .

As directed by the study protocol, one of the STB specimens was set aside for use in this study and placed in phosphate-buffered saline (PBS). After this, MBB was obtained by passing an endoscopic brush along an area of the esophageal mucosa where suspicion for pathology was present (Cellebri™ Single-Use Cytology Brush; Boston Scientific, Marlborough, MA). After rinsing all saliva and cellular debris from the brush, both biopsy samples were isolated in polypropylene tubes containing PBS, frozen immediately after harvest, and then stored at -27°C .

Immunologic testing

After thawing and homogenization of each of the biopsy samples, the cells were lysed using an ultrasonicator (Branson Digital Sonifier, Branson Ultrasonics, Danbury, CT) at 45% amplitude for 2 minutes at 15-second intervals. Up to 4 additional 15-second pulses were performed until the lysates appeared clear and no viable cells were present.

Samples of each lysate were then sent frozen to a reference laboratory (PiRL Laboratories, Portage, MI) for total IgE and solid-phase immunoassay (Immuno Solid-phase Allergen Chip) to measure sIgE against 112 allergenic

TABLE 1. Study population demographics for the EoE-positive and EoE-negative groups

	EoE-positive	EoE-negative	p value
Number	12	13	NA
Mean age (range)	11.8 (2-27)	6.6 (2-13)	>0.05
Female:male	1:1	1.6:1	>0.05
Prior PPI therapy	83.3%	30.8%	0.015 ^a
Prior allergy testing	50%	23.1%	>0.05

^aStatistically significant ($p < 0.05$).

EoE = eosinophilic esophagitis; NA = not applicable; PPI = proton pump inhibitor.

epitopes from airborne and food proteins. These included 53 species-specific airborne components, 29 species-specific food components, and 30 cross-reactive components. Lysate samples from 10 participants in the EoE-positive group and 10 participants in the EoE-negative group were also tested for sIgE against *Candida* and *Staphylococcus* enterotoxins A, B, and C, and toxic shock syndrome toxin using ImmunoCAP analysis (PiRL Laboratories). In addition, IgG4 specific for milk, wheat, egg, beef, soy, peanut, and chicken was measured using the same assay.

Statistical analysis

Total IgE data are expressed as mean $\pm$ standard error of the mean (SEM), whereas sIgE, IgG4 specific to food, and age data are expressed as mean values only. The nonparametric Mann-Whitney *U* test was used to compare total IgE, sIgE, and specific IgG4 levels between the EoE-positive and EoE-negative groups, as well as between the MBB and STB groups. Fisher's exact probability test was used to test the associations between a positive pathologic diagnosis of EoE and gender, previous proton pump inhibitor (PPI) therapy, and previous allergy testing. Two-tailed *p* values were calculated using online statistical software, and $p < 0.05$ was considered statistically significant.¹⁶

Results

Recruitment and pathologic testing

Twenty-five participants were successfully enrolled in the study and completed EGD with all biopsies performed without any complications. Of these individuals, 12 (48%) had a prior history of EoE, whereas the remaining 13 (52%) had another or unknown cause of dysphagia, 9 (36%) had previously undergone allergy testing, and 14 (56%) had prior PPI therapy. From pathologic examination of the study biopsies, 12 (48%) were positive for EoE, whereas 13 (52%) were negative for EoE. Demographic information for the study population, comparing the EoE-positive and EoE-negative groups, is shown in Table 1.

In the EoE-positive group, 9 (75%) had a prior diagnosis of EoE, refractory to PPI therapy, whereas 3 (25%)

TABLE 2. Total and antigen-specific IgE levels for EoE-positive and EoE-negative groups according to method of biopsy

	EoE-positive (kU/L)	EoE-negative (kU/L)	p value
Total IgE			
MBB	3.91 $\pm$ 1.13	4.12 $\pm$ 1.14	>0.05
STB	3.76 $\pm$ 1.08	4.48 $\pm$ 1.24	>0.05
Airborne/food allergens			
MBB	None detected	None detected	NA
STB	None detected	None detected	NA
<i>Candida</i>			
MBB	0.08	0.09	>0.05
STB	0.08	0.11	>0.05
<i>Staphylococcus</i> enterotoxins ^a			
MBB	0.06-0.09	0.06-0.09	>0.05
STB	0.06-0.08	0.08-0.10	>0.05

^a*Staphylococcus* enterotoxins include A, B, and C, and toxic shock syndrome toxin.

EoE = eosinophilic esophagitis; MBB = mucosal brush biopsy; IgE = immunoglobulin E; NA = not applicable; STB = solid tissue biopsy.

received a new diagnosis of EoE. In the EoE-negative group, 11 (85%) biopsies demonstrated no abnormalities, whereas 2 (15%) biopsies had findings consistent with acid reflux disease. Three (23%) participants had a prior diagnosis of EoE, but only 2 of them had PPI therapy, putting them in the PPI-responsive esophageal eosinophilia (PPI-REE) category. Two other participants in the EoE-negative group had prior PPI therapy, but no prior EoE diagnosis, whereas 1 participant had eosinophilia noted on a prior esophageal biopsy, but did not meet the criteria for EoE.

Immunologic testing

Measureable levels of IgE were harvested from the esophageal mucosa of all 25 participants using both MBB and STB. The mean total IgE detected from all the biopsies in the study was 4.1 $\pm$ 0.58 kU/L. There was no significant difference between the amounts of IgE harvested using MBB or STB methods, nor was there any significant difference between the EoE-positive and EoE-negative groups, taken together or when stratified by biopsy method (Table 2). Although there was no sIgE against food, airborne, or cross-reacting allergen components, low levels of sIgE against *Candida* and *Staphylococcus* enterotoxins were detected in both groups.

ImmunoCAP testing for specific IgG4 against food allergens is presented in Table 3. As with IgE, there were no significant differences between biopsy methods for a given allergen, when comparing the EoE-positive with the

TABLE 3. Food allergen-specific IgG4 levels for EoE-positive and EoE-negative groups according to method of biopsy

	EoE-positive (kU/L)	EoE-negative (kU/L)	p value
Wheat			
MBB	0.09	0.07	>0.05
STB	0.05	0.05	>0.05
Soy			
MBB	0.02	0.02	>0.05
STB	0.01	0.01	>0.05
Chicken			
MBB	None detected	None detected	NA
STB	None detected	None detected	NA
Beef			
MBB	0.30	0.31	>0.05
STB	0.28	0.29	>0.05
Peanut			
MBB	0.01	0.01	>0.05
STB	0.01	0.01	>0.05
Egg			
MBB	0.02	None detected	>0.05
STB	None detected	None detected	NA
Milk			
MBB	10.95	10.96	>0.05
STB	11.37	10.72	>0.05

EoE = eosinophilic esophagitis; MBB = mucosal brush biopsy; NA = not applicable; STB = solid tissue biopsy.

EoE-negative group. However, for MBB, IgG4 against egg was detected in the EoE-positive group, but not in the EoE-negative group. Very low to undetectable levels of IgG4 were found for wheat, soy, chicken, and peanut. Low levels of IgG4 against beef and high levels against milk were detected in all samples tested.

Discussion

This is the first report of successfully harvesting measurable amounts of IgE from the esophageal mucosa using MBB. Although there was no significant difference in the amount of IgE harvested compared with STB, MBB offers several potential advantages over STB, including the ability to sample a wider region, with less mucosal damage, and the ability to harvest antibodies in the mucus as well as from epithelial tissue. In addition, MBB eliminates the risk of penetration into the muscular layer or potential perforation of the esophagus. However, MBB

does not have the ability to harvest tissue from layers deeper than the superficial epithelium and samples may not retain the tissue architecture required for pathologic diagnosis.

This is also the first attempt at characterizing the specific antigens to which IgE are directed against in the esophageal mucosa by direct tissue sampling coupled with antibody assay, although this has been accomplished in other regions of the aerodigestive tract, such as the nose, oral vestibule, and Waldeyer's ring.^{10,12,17} In 2013, Zhang and colleagues detected airborne- and food allergen-specific IgE from hyperplastic adenotonsillar tissue in 62% of children with obstructive sleep apnea, without a history of allergic rhinitis, even when allergen-specific IgE was not detected in the serum.¹⁷ Endoscopic intramucosal provocation testing, through injection of 6 diluted food allergen extracts, was attempted by Warners and colleagues on 8 individuals with symptomatic EoE. Although positive reactions 24 hours later (defined by luminal obstruction or mucosal blanching) were noted in 5 of 8 participants and 0 of 3 controls, correlation with positive skin and serum IgE testing was only seen in 3 of 8 participants.¹⁸

There is substantial evidence supporting the central role of IgE in the pathophysiology of EoE, beyond the high prevalence of this condition in atopic individuals. The mucosal inflammation produced by EoE features T-cell and mast-cell infiltration, as well as a distinctly T-helper 2 (Th2)-dominated cytokine pattern and elevated mRNA levels of eotaxin-3, interleukin (IL)-5, tumor necrosis factor- α , IL-5 receptor α chain, and IL-13.^{19–21} The upper portion of the gastrointestinal tract seems to be particularly vulnerable to IgE-mediated inflammation. Bannert and colleagues reported high expression of the high-affinity IgE receptor, Fc- ϵ RI, primarily in the esophagus, stomach, and duodenum, correlating well with clinical mucosal inflammation, but not with total IgE levels in the serum.²² This makes sense from a clinical standpoint, as the proximal regions of the gastrointestinal tract play the primary role in defense against hazardous ingestion.

Although the association of EoE with total IgE levels, as well as with IgE sensitization to food, airborne, and cross-reacting allergens is clear, the causation between type 1-mediated hypersensitivity and EoE is still unclear.^{23,24} The seasonal incidence of EoE helps support causation, but additional evidence can also be found in the immunotherapy literature.²⁵ There are reports for oral immunotherapy with food allergens and sublingual immunotherapy with aeroallergens triggering endoscopically and pathologically confirmed EoE, which resolved after withdrawal of therapy.^{26–28}

There are also robust data that call the causation between IgE-mediated food allergy and EoE into question. Clayton and colleagues reported that omalizumab, a monoclonal antibody that blocks the binding of IgE to basophils and mast cells, failed to improve EoE clinically or pathologically in a 16-week, double blind placebo controlled (DBPC) trial

in adults.²⁹ Another piece of evidence against causation is the poor outcome from food testing-directed elimination diets mentioned earlier, and this reinforces the need to explore local sensitization directly at the site of inflammation. It is also possible that the improvements in EoE with elemental diets and elimination diets, such as the SFED, may be due to bowel rest and changes in the microbiome, as demonstrated with inflammatory bowel disease, rather than by the removal of a triggering food allergen.^{30,31}

IgG4 specific to food antigens has also been suspected to play a role in EoE. Clayton and colleagues reported that IgG4 was increased by 45-fold in individuals with EoE, compared with controls, largely present as extracellular granular deposits and within plasma cells within the deep lamina propria.²⁹ In 2016, Wright and colleagues reported that total and food-specific IgG4 decreased in the esophageal mucosa of adults with EoE who responded clinically to elimination diets.³² In our study, only low levels of IgG4 antibodies to wheat, soy, and peanut were detected, but no differences were seen between the EoE-positive and EoE-negative groups. Only egg IgG4 collected using MBB was positive in the EoE-positive group, but negative in the EoE-negative group. The higher levels of IgG4 to milk and beef in both groups are likely due to nonspecific binding of the antibody conjugates used in the ImmunoCAP assay.

Because of its association with Castleman disease, eosinophilic granulomatosis with polyangiitis, and sarcoidosis, elevated IgG4 is thought to represent a marker of mucosal barrier breakdown, rather than a direct trigger. Genomewide association studies have identified several genes associated with epithelial barrier abnormalities through genetic and epigenetic mechanisms.³³ Tissue eosinophilia has also been reported in other diseases, such as chronic rhinosinusitis with nasal polyps and nonallergic rhinitis with eosinophilia syndrome, where nonspecific inflammation has been suggested to result from antigen exposure in the setting of a primary epithelial barrier abnormality.^{34–36}

If an epithelial barrier abnormality is pivotal in the etiology and pathogenesis of EoE, then the inflammatory cascade may come from multiple sources and be represented by several types of hypersensitivity, including a delayed T-cell response.³⁷ Certain antigens known to produce a brisk, polyclonal IgE response, such as *Candida* and *Staphylococcus* enterotoxins, were both detected in our study, and IgE sensitization to *Candida* has been reported in both pediatric and adults with EoE.^{38–40} The lack of specific IgE against any of the food, aeroallergen, or cross-reacting components detected in any of our study samples also supports the role of polyclonal IgE production in the pathophysiology of EoE.

Current evidence suggests that epithelial barrier disruption is an important factor in the pathogenesis of EoE. It has also been implicated as an underlying cause of atopic dermatitis, which is seen in >50% of individuals with EoE.³⁷ Specifically, the expression of epidermal

differentiation complex genes, which code for important epithelial integrity proteins such as filaggrin and keratin, are downregulated in the esophageal epithelium in response to IL-13.⁴¹ In addition, decreased expression of protease inhibitors with active EoE leads to further disruption of the epithelial barrier.⁴² This mechanical damage to the epithelium, combined with increased toll-like receptor stimulation and microbe colonization, leads to deeper penetration of allergens. This, in turn, elicits a strong Th2 response and recruitment of eosinophils under the influence of thymic stromal lymphopoietin (TSLP).⁴³ TSLP has been shown to mediate barrier defects in other sites of the intestinal and respiratory tracts, supporting the “skin-gut-lung” model of disease pathogenesis.⁴⁴

Limitations of our study include the relatively small amount of mucosal material from which to measure antibody levels and the difficulties in identifying the ideal sites for biopsy. The mean total IgE level in our samples was 4.1 kU/L, and the endoscopic brush used for MBB in this study was smaller than the standard cytology brush used in previous studies. Reisacher reported that positive nasal MBB samples had a mean total IgE of 13.6 kU/L in individuals with allergic rhinitis, whereas negative MBB samples had a mean total IgE of 4.6 kU/L.¹⁰ However, other MBB samples from both the nose and oral cavity yielded detectable sIgE when the total IgE levels were 4.75 kU/L and 4.9 kU/L, respectively.^{11,12} The development of more sensitive assays, mucosal stains to better identify pathologic tissue, and standardized, systematic biopsy protocols will all help to optimize mucosal antibody detection in the future.

Another limitation of this study was the absence of an absolutely healthy control group, which is difficult to obtain within the context of ethical investigation. All participants were experiencing dysphagia, as well as other gastrointestinally related symptoms, and the underlying pathology in the EoE-negative group could have resulted in the same antibody profiles as seen in the EoE-positive group. Also, most of the participants in our study were children. Although EoE has a biphasic age distribution in the population, adults should be adequately represented in future studies. In the future, larger study populations will be necessary to help differentiate EoE from PPI-REE, and the feasibility of office-based esophageal MBB should be studied to facilitate future investigation.

Conclusion

This study has established the feasibility of esophageal MBB to harvest mucosal tissue and measure IgE and IgG4 antibodies within that tissue using commercially available immunoassays. Although no IgE against food, aeroallergen or cross-reacting allergens was detected, IgE against *Candida* and *Staphylococcus* enterotoxins and IgG4 against certain food allergens were detected in both groups. The detection of significant levels of total IgE, however, supports the idea that other mechanisms, besides

allergen-specific inflammation, are contributing to symptoms in individuals with dysphagia, with or without esophageal eosinophilia, and continued investigation in this direction is warranted. 

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