

Airborne and food sensitization patterns in children and adults with eosinophilic esophagitis

Yu Ting He, BS¹, Paul J. Christos, DrPH, MS² and William R. Reisacher, MD, FACS, FAAOA³

Background: The pathogenesis of eosinophilic esophagitis (EoE) is currently unknown, but evidence suggests that allergic sensitization to food and airborne allergens may play a key role. This retrospective study examines the rate of sensitization to both food and airborne allergens in EoE patients, and compares their sensitivity patterns to control groups.

Methods: We identified 103 patients with a diagnosis of EoE via esophageal eosinophilia (≥ 15 eosinophils/high-power field [hpf]), who had undergone comprehensive food and/or airborne allergen testing through either skin or in vitro methods. Food and airborne allergen sensitization was defined as positive testing in at least 1 food subgroup (milk, peanut, tree nut, seafood/fish, soy, grain, egg) or airborne subgroup (tree, grass, weed, mite/cockroach, animal, mold), respectively. The same sensitization criterion was applied to allergic rhinitis (AR) patients, with and without a clinical suspicion of food allergy (FA), in order to create control groups.

Results: Sensitization in the EoE group to at least 1 subgroup of food allergen and airborne allergen was seen in 77.1% (64/83) and 71.7% (38/53), respectively ($p = 0.82$).

There were significant differences in sensitization between EoE and control groups for tree nut, soy, grain, and egg, but no differences noted in any of the other food or airborne allergen subgroups, even after accounting for age and gender.

Conclusion: EoE and control groups had similar airborne allergen sensitization patterns, yet dissimilar food allergen sensitization patterns, suggesting that specific allergens may play a more prominent role in the pathogenesis of EoE. The EoE group had a more uniform distribution pattern for food allergens, compared to controls. © 2018 ARS-AAOA, LLC.

Key Words:

allergen; sensitization; airborne; food; eosinophilic esophagitis; EoE

How to Cite this Article:

He YT, Christos PJ, Reisacher WR. Airborne and food sensitization patterns in children and adults with eosinophilic esophagitis. *Int Forum Allergy Rhinol.* 2018;XX:1-6.

Eosinophilic esophagitis (EoE) is a chronic disease characterized by esophageal eosinophilia in the squamous

epithelium.¹ Its clinical features include failure to thrive and abdominal pain in children, and dysphagia with food impaction in older children and adults, often accompanied by esophageal remodeling such as thickening or furrowing.² It affects more males than females in both adult and children populations.

Its pathophysiology is yet unknown but emerging evidence indicates that airborne and food hypersensitivity may play a key role.³⁻⁶ Some reports show a seasonal variation of incidence of EoE, suggesting a role for airborne allergens in the clinical course of EoE, but the literature remains unclear on this point.⁷⁻⁹ Studies have shown that 68% of pediatric EoE patients have a history of allergic disorders such as allergic rhinitis (AR), asthma, atopic dermatitis, and food allergy (FA), and that allergy testing-directed diets in children with EoE achieved 69% resolution of the symptoms.¹⁰⁻¹² On the other hand, skin-prick testing (SPT)-directed diets in adult EoE patients only achieved a

¹Weill Cornell Medical College, New York, NY; ²Department of Healthcare Policy & Research, Weill Cornell Medical College, New York, NY; ³Department of Otolaryngology-Head and Neck Surgery, Weill 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, NewYork-Presbyterian Hospital, 1305 York Avenue, 5th Floor, New York, NY 10021; e-mail: wir2011@med.cornell.edu

Potential conflict of interest: W.R.R. is an advisor and shareholder for Alluvate Therapeutics. P.J.C. is supported by the following grant: Clinical and Translational Science Center at Weill Cornell Medical College (UL1-TR000457-06). Y.T.H. and P.J.C. have no conflicts of interest. Presented at the AAOA Annual Scientific Meeting on September 10, 2017 in Chicago, IL.

Received: 31 October 2017; Revised: 20 December 2017; Accepted: 10 January 2018

DOI: 10.1002/alr.22095

View this article online at wileyonlinelibrary.com.

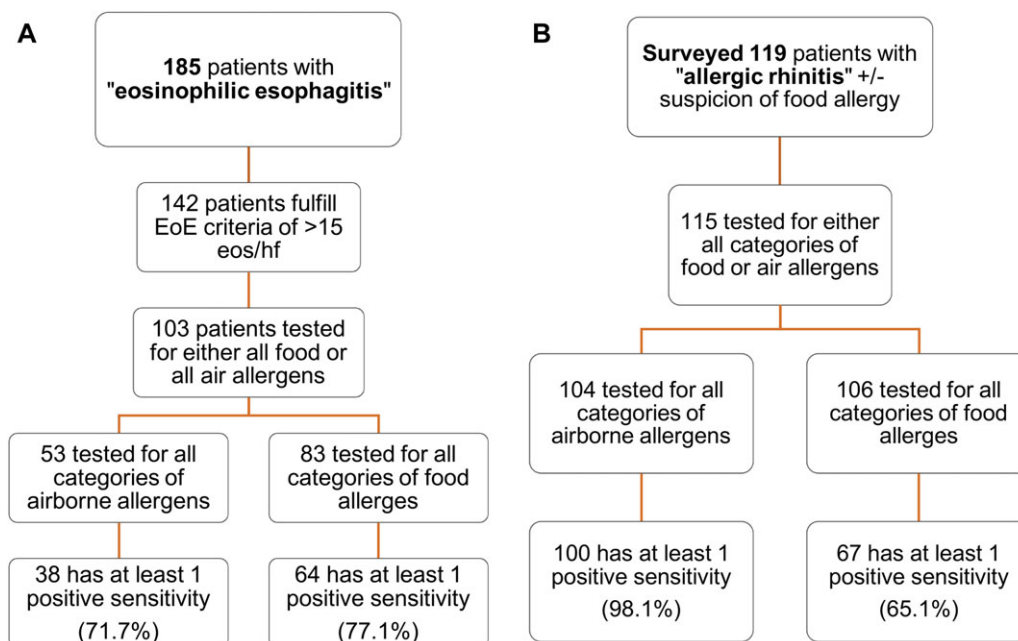


FIGURE 1. Selection of study participants for participants in study for the EoE and control groups. EoE = eosinophilic esophagitis.

13% to 26% response rate,^{13–15} though Penfield et al.¹⁵ reported that SPT-directed elimination diets were more effective than diets based on specific immunoglobulin E (IgE) testing. It is not known whether this is due to more severe, refractory disease in the adult population, or whether airborne allergens play a larger role in the adult population, compared to the pediatric population.

The purpose of this study is to compare the patterns of both airborne allergen and food allergen sensitization in people with EoE with AR and FA control groups, confirmed using skin testing and/or serum specific IgE testing. Because previous studies have indicated that the prevalence of food sensitivity in children and airborne allergen sensitivity in adults varies over time, the results are adjusted for both age and gender.³ The findings of this study are expected to strengthen our understanding of the pathophysiology behind this disease as future treatment strategies for EoE are developing.

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 #1605017271). Electronic medical records (EMRs) from 2010 to 2014 were searched for individuals with the clinical diagnosis of EoE who had undergone either SPT or serum specific IgE testing for airborne and/or food allergens (Fig.1). The diagnosis of EoE was confirmed in each case by esophageal biopsy demonstrating greater than 15 eosinophils per high powered field (hpf). Positive testing on SPT was defined as wheal diameter of greater than 3 mm at 15 minutes, compared to 50% glycerin

control and positive histamine control. Positive serum testing was defined as specific IgE level of 0.35 kU/L or greater.

The airborne control group (AR) included patients with a diagnosis of AR, without a known diagnosis of EoE, who tested positive to at least 1 of 6 subcategories of airborne allergens on serum specific IgE testing. The food allergy control group (FA) included those individuals with a diagnosis of AR, without a known diagnosis of EoE, plus a clinical suspicion of FA, who tested positive to at least 1 of 7 subcategories of food allergens on serum specific IgE testing. Clinical symptoms leading to suspicion of food allergy included swelling or itching in the oral cavity/oropharynx, gastritis, dermatitis, or anaphylaxis coinciding with the ingestion of food. Subcategories of airborne allergens included: tree, grass, weed, animal, mite/cockroach, and mold. Subcategories of food allergens included: milk, peanut, tree nut, seafood/fish, soy, grain, and egg. The grain category included mainly wheat, as well as rye, rice, oat, and barley.

Statistical analysis

Descriptive statistics (including mean, standard deviation, range, frequency, and percent) for demographic and air/food allergen characteristics were calculated for the EoE and AR groups, separately. The 2-sample *t* test was used to compare mean age and mean total number of allergies between the EoE and AR groups. The chi-square test was used to compare gender and airborne/food allergen status (ie, absent/present) between the EoE and AR groups. Univariate logistic regression was used to compute crude odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between air/food allergen status and type of diagnosis type (ie, EoE vs AR). Multivariable logistic regression models were performed to assess the independent

TABLE 1. Patient demographics

	Airborne allergens		<i>p</i>
	EoE	AR	
Age (years), mean (range)	22.79 (3–51)	43.54 (10–84)	<0.0001
Age group			<0.0001
Children, n (%)	19 (50)	15 (15)	
Adults, n (%)	19 (50)	85 (85)	
Gender			<0.0001
Males, n (%)	30 (78.9)	36 (36)	
Females, n (%)	8 (21.1)	64 (64)	
	Food allergens		<i>p</i>
	EoE	FA	
Age (years), mean (range)	17.92 (1–65)	41.52 (10–84)	<0.0001
Age group			<0.0001
Children, n (%)	42 (65.6)	12 (17.9)	
Adults, n (%)	22 (34.4)	55 (82.1)	
Gender			0.02
Males, n (%)	44 (68.8)	32 (47.8)	
Females, n (%)	20 (31.3)	35 (52.2)	

AR = allergic rhinitis; EoE = eosinophilic esophagitis; FA = food allergy.

effect of airborne/food allergen status on type of diagnosis (EoE vs AR), controlling for gender and age group (<18 years vs ≥18 years) (ie, separate models for each allergen sensitivity of interest). Adjusted ORs and 95% CIs from the multivariable models are presented. All *p* values are 2-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals (95% CIs) were calculated to assess the precision of the obtained estimates. All analyses were performed in SPSS version 24.0 (IBM Corp., Armonk, NY) and Stata version 14.0 (StataCorp, College Station, TX).

Results

Study population

The demographic characteristics of the study participants are presented in Table 1. Among the 103 EoE patients who had been tested for all subcategories of airborne allergens and/or food allergens, 38 of 53 (71.7%) were positive in at least 1 airborne subcategory and 64 of 83 (77.1%) were positive in at least 1 food allergy subcategory (*p* = 0.82). Thirty-one percent (31%) of EoE patients underwent SPT, 59% serum IgE, and 10% both. As expected, based on the typically high rate of atopy and allergies in those with EoE, 54% of the study group had a diagnosis of AR documented on their EMR.

Airborne allergen sensitization patterns

Among EoE patients, there was an approximately 50% to 60% rate of sensitization for each subcategory. Among the AR control group, there was an approximately 40% to 50% rate of sensitization for each category, except for mold (29.1%) and animals (61.2%). The airborne allergen sensitization patterns for EoE and control patients are shown in Figure 2A, demonstrating no significant difference in any subcategory.

Food allergen sensitization patterns

Among EoE patients, there was an approximately 50% to 60% rate of sensitization for each subcategory, except for seafood/fish (39.7%). Among the FA control group, the most common food sensitivities included peanut (47.9%) and seafood/fish (47.9%). The food allergen sensitization patterns for EoE and controls are shown in Figure 2B. There was a significant difference in sensitization rates between the EoE and FA control groups for tree nut, soy, grain, and egg.

Ranking of airborne allergen and food allergen sensitization frequencies

The frequencies of each allergen sensitization out of the total number of sensitivities found among the EoE vs AR/FA control groups were also examined. For airborne allergens, there was a relatively uniform distribution of sensitization frequencies among all the subcategories, especially among EoE patients (Table 2A). Tree, weed, animal, and mite/cockroach were among the most frequent allergen sensitivities, with grass and mold slightly lower in both the EoE and AR control groups.

For food allergens, there was a substantial difference between EoE and FA control groups in the ranking of allergen sensitization frequencies (Table 2B). For the EoE group, tree nut and soy were the most frequent sensitivities, while seafood/fish accounted for only 9.5% of the sensitivities. For the FA control group, seafood/fish and peanut were the most frequent sensitivities (21.9% and 21.3%, respectively).

Discussion

EoE is a chronic inflammatory condition, associated commonly with atopic individuals. Studies examining the pathophysiology of this disease in the mouse model have shown an association with a variety of circulating cytokines and chemokines that attract eosinophils to produce its classic appearance.¹⁶ In the broadest sense, individuals may produce an allergic inflammatory response to certain airborne and food allergens, and the first step to that response is the development of sensitization. Therefore, in this study we sought to compare EoE with 2 chronic allergic diseases, AR and FA, with respect to their patterns of allergen sensitization. However, while this study focused on type I, IgE-mediated hypersensitivity, it is understood that several

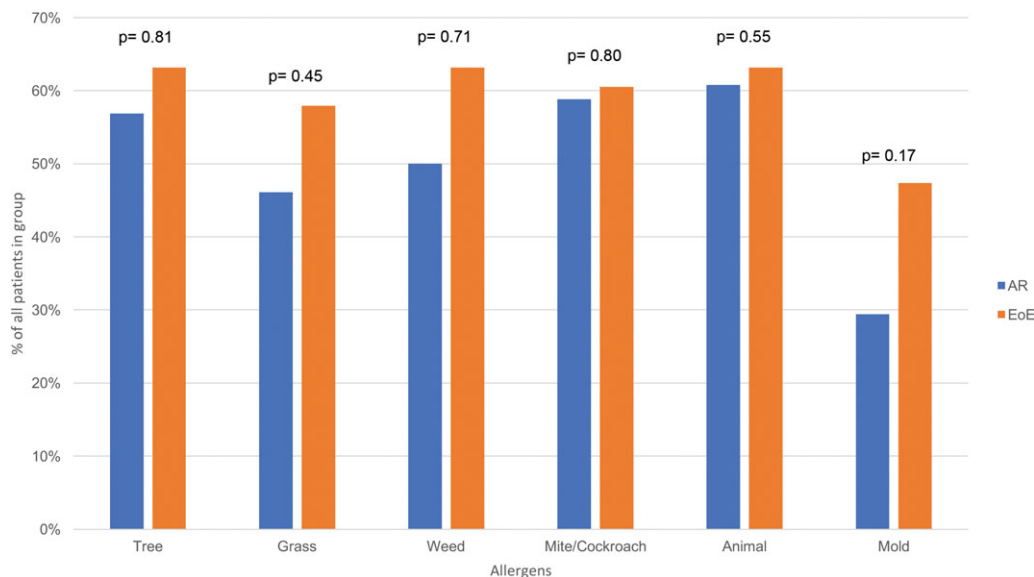


FIGURE 2A. (A) Airborne allergen sensitization patterns for EoE and AR control groups, p value adjusted for age and gender (significant values in bold).

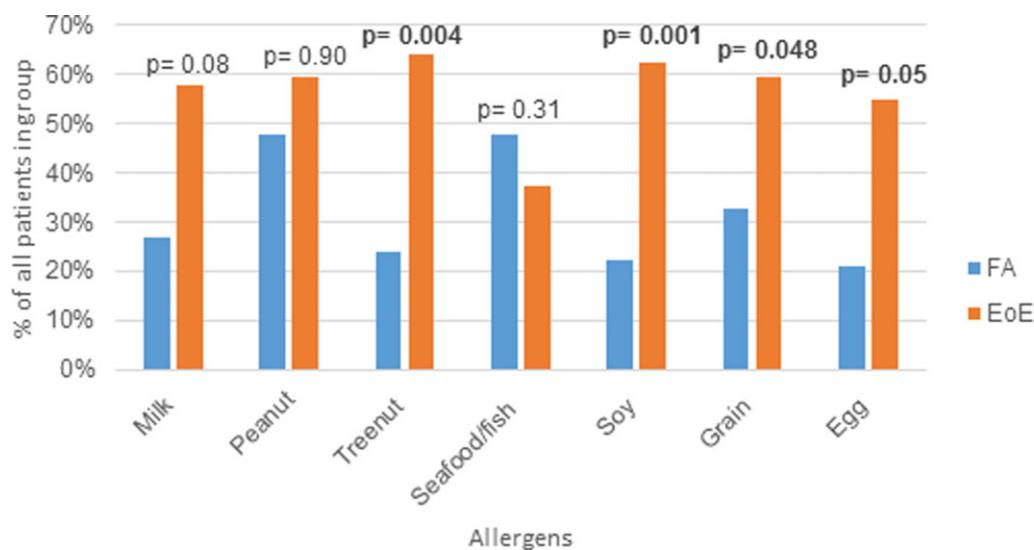


FIGURE 2B. (B) Food allergen sensitization patterns of EoE and FA control groups, p value adjusted for age and gender (significant values in bold). AR = allergic rhinitis; EoE = eosinophilic esophagitis; FA = food allergy.

other inflammatory pathways are likely contributing to the clinical entity of EoE.¹⁷

Our findings of sensitization rates of EoE patients in food and airborne allergens (77.1% and 71.7%, respectively) were consistent with previously published reports.^{10,18–20} Most of these studies included either pediatric or adult populations, but combining these populations did not impact the overall sensitization rates. Conversely, the heterogeneity of age groups and methods of testing used (serum specific IgE testing, SPT, atopy patch testing) likely contribute to the wide range of sensitivities to individual allergens cited

in the literature.^{15,18,20–22} For this study, the sensitivities for airborne allergens groups examined fell within the range of sensitivities found in the literature. For the food allergens subcategories, tree nut, seafood/fish, and grain exceeded the sensitivity ranges cited in other studies, perhaps because each subcategory included several allergens, with most other studies examined single allergens only.

This is the first study comparing airborne allergen sensitization patterns between patients with EoE and AR, demonstrating no significant difference. The ranking of the allergens from highest to lowest frequency was also similar

TABLE 2. Airborne allergen sensitivities as a percentage of total sensitivities in EoE and AR and FA control groups

(A) AR control group		
Rank order ^a	EoE (% of total)	AR (% of total)
1	Animal (17.8)	Animal (20.1)
2	Mite/Cockroach (17.8)	Mite/Cockroach (19.5)
3	Tree (17.8)	Tree (18.8)
4	Weed (17.8)	Weed (16.6)
5	Grass (16.3)	Grass (15.3)
6	Mold (13.3)	Mold (9.7)
(B) FA control group		
Rank order ^b	EoE (% of total)	FA (% of total)
1	Tree nut (16.2)	Seafood/fish (21.9)
2	Soy (15.8)	Peanut (21.3)
3	Peanut (15.0)	Grain (14.2)
4	Grain (15.0)	Milk (12.9)
5	Milk (14.6)	Tree nut (10.3)
6	Egg (13.8)	Soy (9.7)
7	Seafood/fish (9.5)	Egg (9.7)

^a1 = highest frequency; 6 = lowest frequency.
^b1 = highest frequency; 7 = lowest frequency.
AR = allergic rhinitis; EoE = eosinophilic esophagitis; FA = food allergies.

between EoE and AR groups. Moreover, the allergen sensitization rates were uniformly distributed in both the EoE and AR control groups. This may be because airborne allergen exposure tends to be similar in a given geographic region, while food allergen exposure may be influenced by cultural differences and dietary habits.

Tree nut, soy, grain, and egg sensitization rates were significantly higher in EoE patients than in FA patients. Similarly, when ranking each subcategory as a percentage of total sensitivities, seafood/fish sensitization shifted from having the highest sensitization frequency in the FA

control group to having the lowest sensitization frequency in the EoE group. In addition, the FA control group showed a higher prevalence of seafood and peanut allergen sensitivities, while the EoE group showed a nearly even distribution of sensitization rates for all the subcategories of food allergens. This may be due to the higher percentage of adults in the FA control group. However, it is also possible that persistent sensitization to food allergens which are typically outgrown past childhood, such as egg and wheat, may be an event leading to clinical EoE.

One limitation of this study is that a 2-month proton-pump inhibitor (PPI) trial was not part of the inclusion criteria, because this information was often not available in the medical record.²³ In addition, because EoE is associated with atopic diseases, it is possible that unrecognized EoE was present in both the AR and FA control groups.²⁴ The FA control group was also not ideal, as the participants were selected from the AR group and diagnosis did not include oral food challenge.

Further research will be required to advance our understanding of the pathophysiology of EoE. Since there are age-linked differences between food and airborne allergen sensitivities, a study comparing pediatric and adult populations would be helpful to further explore this variable. Moreover, IgE levels in the skin and circulatory systems may not be indicative of the level of IgE sensitization in the esophageal mucosa, and studies are currently underway to determine how local sensitization translates into the clinical manifestations of EoE.

Conclusion

Our study demonstrates that airborne allergen sensitization patterns are similar between individuals with EoE and those with AR, while food allergen sensitization patterns between individuals with EoE and FA differed. It was also determined that individuals with EoE have a highly uniform distribution of food allergen sensitizations. It is anticipated that this information will be useful as future investigations aim to determine which factors in sensitized individuals are associated with the development of clinical EoE. 

References

1. Furuta G, Liacouras C, Collins M, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology*. 2007;133:1342–1363.

2. Croese J, Fairley SK, Masson JW, et al. Clinical and endoscopic features of eosinophilic esophagitis in adults. *Gastrointest Endosc*. 2003;58:516–522.

3. Sugnanam K, Collins J, Smith P, et al. Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. *Allergy*. 2007;62:1257–1260.

4. Mishra A, Hogan S, Brandt E, Rothenberg M. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest*. 2001;107:83–90.

5. Stone K, Prussin C. Immunomodulatory therapy of eosinophil-associated gastrointestinal diseases. *Clin Exp Allergy*. 2008;38:1858–1865.

6. Chehade M, Sampson H. Epidemiology and etiology of eosinophilic esophagitis. *Gastrointest Endosc Clin North Am*. 2008;18:33–44.

7. Almansa C, Krishna M, Buchner A, et al. Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. *Am J Gastroenterol*. 2009;104:828–833.

8. Frederickson N, Bayman L, Valestin J, et al. Lack of seasonal variation in the incidence of eosinophilic esophagitis in adolescent and adult non-PPI-responsive oesophageal eosinophilia midwestern US populations. *United European Gastroenterol J*. 2014;2:69–76.

9. Lucendo A, Arias Á, Redondo-González O, González-Cervera J. Seasonal distribution of initial diagnosis and clinical recrudescence of eosinophilic esophagitis: a systematic review and meta-analysis. *Allergy*. 2015;70:1640–1650.

10. Simon D, Marti H, Heer P, et al. Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. *J Allergy Clin Immunol*. 2005;115:1090–1092.

11. Spergel J, Brown-Whitehorn T, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol*. 2012;130:461–467.e5.

12. Orenstein S, Shalaby T, Lorenzo C, et al. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am J Gastroenterol*. 2000;95:1422–1430.

13. Gonsalves N, Yang G, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology*. 2012;142:1451–1459.e1.

14. Molina-Infante J, Martín-Noguerol E, Alvarado-Arenas M, et al. Selective elimination diet based on skin testing has suboptimal efficacy for adult eosinophilic esophagitis. *J Allergy Clin Immunol*. 2012;130:1200–1202.

15. Penfield J, Lang D, Goldblum J, Lopez R, Falk G. The role of allergy evaluation in adults with eosinophilic esophagitis. *J Clin Gastroenterol*. 2010;44:22–27.

16. Leung J, Koen RB, Shen AH. Allergic mechanisms of eosinophilic oesophagitis. *Best Pract Res Clin Gastroenterol.* 2015;29:709–720.
17. D'Alessandro A, Esposito D, Pesce M, et al. Eosinophilic esophagitis: from pathophysiology to treatment. *World J Gastrointest Pathophysiol.* 2015;6:150.
18. Baxi S, Gupta S, Swigonski N, Fitzgerald J. Clinical presentation of patients with eosinophilic inflammation of the esophagus. *Gastrointest Endosc.* 2006;64:473–478.
19. Simon D, Cianferoni A, Spergel J, et al. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. *Allergy.* 2016;71:611–620.
20. Roy-Ghanta S, Larosa D, Katzka D. Atopic characteristics of adult patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol.* 2008;6:531–535.
21. Olson A, Evans M, Johansson M, et al. Role of food and aeroallergen sensitization in eosinophilic esophagitis in adults. *Ann Allergy Asthma Immunol.* 2016;117:387–393.e2.
22. Pham H, Chad Z, Sussman G, et al. Aeroallergen and food sensitization patterns in adults with eosinophilic esophagitis. *J Allergy Clin Immunol.* 2016;137:AB230.
23. Dellon E, Gonsalves N, Hirano I, et al. ACG Clinical Guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol.* 2013;108:679–692.
24. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol.* 2011;128:3–20.