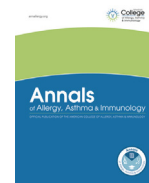




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Eosinophilic esophagitis and symptoms possibly related to eosinophilic esophagitis in oral immunotherapy

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Clinical Problem

Food allergy is seen in 2% to 8% of the US population and continues to increase.^{1–3} Patients with food allergy often have an impaired quality of life and may experience nutritional deficiencies.^{4,5} Currently, there are no US Food and Drug Administration–approved treatments for food allergy, and it is recommended that patients practice allergen avoidance and carry epinephrine for use in case of severe reaction to unintentional allergen exposure.⁶ The lifestyle of allergen avoidance presents a challenge and often causes anxiety for patients and caregivers.^{4,7} Oral immunotherapy (OIT) is currently being investigated as a treatment for food allergy. OIT involves consuming the food allergen in gradually increasing doses.^{8,9} Although protocols vary, OIT generally begins with an initial escalation phase, which is conducted under observation in a controlled setting (eg, a clinic or hospital). This is followed by a build-up phase of several weeks or months, during which doses given at home are interspersed with incremental escalation doses given under supervision at a clinic. The final phase is a maintenance phase.^{8,9}

The efficacy of OIT depends on individual treatment goals, but a commonly reported end point is desensitization, a temporary state in which the patient can safely consume a prespecified amount of antigen without reaction as assessed by oral food challenge.¹⁰

Successful desensitization, as defined by the individual study protocols, has been reported at rates ranging from approximately 40% to 90%.¹⁰ To maintain a state of desensitization, patients must continue to regularly consume the food allergen. The capacity of OIT to produce long-lasting efficacy after treatment cessation, an outcome clinically termed *sustained unresponsiveness*, is currently unclear. Sustained unresponsiveness after a period of avoidance lasting 1 to several months has been reported by several studies, but at rates generally lower (27%–50%) than those for desensitization after therapy of varying durations.^{11–14} However, a recent study of peanut OIT in children 9 to 36 months of age reported 91% of patients achieved sustained unresponsiveness 1 month after treatment, suggesting that a more durable response may be achievable in younger patients.¹⁵

Although efficacy data are promising, adverse events (AEs) may limit the use of OIT in routine clinical practice.¹⁶ Approximately 90% of participants in clinical trials of OIT for food allergy experience AEs, with local symptoms, such as abdominal pain or oral pruritus, being the most common.^{5,16} Abdominal pain and gastrointestinal (GI) symptoms are often cited as the reason for treatment discontinuation in studies of OIT.^{5,8,17} Eosinophilic esophagitis (EoE) has also been reported in several studies of OIT.⁵

EoE is a chronic, immune-mediated disease characterized by eosinophil infiltration of the esophagus and symptoms that include abdominal pain, vomiting, reflux, anorexia, dysphagia, food impaction, and chest pain.¹⁸ However, clinical presentation varies by age. Infants present mainly with feeding dysfunction, school-aged children with vomiting and abdominal pain, and adolescents with dysphagia and food impaction.¹⁹ In adults, dysphagia is the most common symptom.²⁰ A diagnosis of EoE requires confirmation by biopsy, with specimens showing at least 15 eosinophils per high-power field and the exclusion of proton pump inhibitor–responsive esophageal eosinophilia.¹⁸ Untreated EoE is a risk factor for

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esophageal stricture, narrow-caliber esophagus, food impaction, and esophageal perforation.¹⁸

The clinical presentation of EoE is similar in symptoms to the known GI AEs of OIT. Furthermore, EoE is frequently associated with food allergy; the prevalence of EoE is significantly higher in patients with IgE-mediated food allergy than the general population (1 in 20 vs 1 in 2,500).²¹ In a 2014 meta-analysis of 12 OIT studies for food allergy, biopsy-confirmed EoE occurred in 2.7% of patients.²² An additional recent prospective study of 128 patients undergoing OIT reported a prevalence of biopsy-confirmed EoE of 4.69%.²³

Although many patients undergoing food immunotherapy have GI symptoms that are possibly related to EoE, relatively few patients undergo endoscopy, so the actual rate of EoE is unknown. In addition, OIT-associated symptoms possibly related to EoE often abate once OIT is discontinued.²⁴ We sought to better characterize the incidence of EoE and symptoms possibly related to EoE in patients undergoing OIT for common food allergies (milk, egg, and peanut) and to provide guidance on how to monitor and treat these patients.

Strategies and Evidence

Methods

To assess the incidence of symptoms possibly related to EoE during OIT, we performed a search of the MEDLINE and Cochrane databases using the following terms on May 10, 2017: (*oral OR sublingual*) AND (*immunotherapy OR tolerance OR desensiti**) AND (*peanut OR milk OR egg*). No time limit was imposed on the search. Articles were filtered to exclude duplicates and include only English-language, human studies with full text available online, either freely or for purchase. Included studies were of patients with IgE-mediated egg, milk, or peanut allergy undergoing OIT. Prospective, retrospective, and case studies were included. Studies that focused exclusively on sublingual immunotherapy were excluded, as were studies that did not describe AEs. References reporting on the same study population were combined. Abstract books from the annual meetings of the American Association of Allergy, Asthma & Immunology (AAAAI), European Academy of Allergy and Clinical Immunology (EAACI), and American College of Allergy, Asthma & Immunology (ACAAI) were manually searched for relevant abstracts that contained data yet to be published in manuscript form for the years 2015 to 2016 for EAACI and ACAAI and 2015 to 2017 for AAAAI.

The article search yielded 282 citations from the Cochrane database and 1,309 from MEDLINE, for a total of 1,591 references (eFig 1). From these, 99 studies met the inclusion criteria and are reviewed in eTable 1. Several studies reported overall AE rates but did not describe these events by organ system affected or specific symptoms and were excluded from the review. The abstract search resulted in the identification of 16 eligible abstracts. Six references provided additional data on a previously published study

population and were combined with the original report, resulting in 110 total studies.

Data extracted from each study where available included overall discontinuation rate, overall rate of symptoms possibly related to EoE (general GI symptoms or, depending on how data were collected, abdominal pain, nausea, vomiting, anorexia, or reflux), rate of discontinuation attributable to symptoms possibly related to EoE, and rate of biopsy-confirmed EoE. Each rate was determined separately from only those studies that reported each end point of interest (eg, only patients from studies outlining reasons for discontinuation were included in the denominator for the determination of rate of discontinuation attributable to symptoms possibly related to EoE). Rates of specific AEs were assessed on a per-patient basis. Data from studies that reported AEs as a percentage of total OIT doses were not included in the estimate of AE rates. Studies with similar AE reporting methods were combined to estimate overall rates of AEs. Data from studies that reported AEs by organ system (general GI symptoms) were not combined with those from studies that reported specific symptoms (eg, abdominal pain, vomiting).

Results

AE reporting was inconsistent, with 72 studies (N = 3,084) reporting AEs per patient, 25 (N = 994) reporting AEs as a percentage of total OIT doses, and 14 (N = 803) describing AEs that led to discontinuation or cases of EoE without providing overall specific AE rates. Of the studies that reported AEs per patient, 20 described AEs by organ system (N = 2,239), 42 by specific symptom (N = 738), and 10 reported no AEs with OIT (N = 107). Of the specific AEs of interest, only abdominal pain and vomiting were reported consistently, so rates were estimated only for these events. The overall rates per patient for symptoms possibly related to EoE were 34% for general GI symptoms, 32% for abdominal pain, and 12% for vomiting (Table 1). Rates of abdominal pain were similar among food allergies treated (egg, 28%; milk, 30%; peanut, 40%), but vomiting occurred more frequently with egg and peanut (17% and 20%, respectively) than with milk (1%) (Table 1).

A discontinuation rate was reported in 107 (N = 3,734) of the included studies and was approximately 14.1% overall. Reasons for discontinuation were provided in 82 studies (N = 2,424), which indicated that symptoms possibly related to EoE (abdominal pain, nausea, and/or vomiting, or general GI symptoms) led to discontinuation in approximately 4.7% of patients. In 18 studies (N = 663) biopsies were conducted to confirm a diagnosis of EoE. EoE was confirmed in 35 cases total, for a combined rate of approximately 5.3% of patients undergoing OIT. Not every patient diagnosed with EoE discontinued treatment (29 of 35 patients [83%] with confirmed EoE discontinued treatment). The rate of discontinuation attributable to a diagnosis of EoE or symptoms possibly related to EoE was 5.6% (Table 1).

Table 1
Summary of Safety Data From OIT Studies of Patients With Egg, Milk, or Peanut Allergy^a

Rate	Discontinuation (any reason), %	SPR-EoE, %			EoE (biopsy), %	Discontinuation cause, %	
		Organ system		Specific symptom		SPR-EoE	EoE or SPR-EoE
		GI symptoms	Abdominal pain	Vomiting			
Overall	14	34	32	12	5.3	4.7	5.6
Egg	11	ND ^b	28	17	4.2	2.7	3.1
Milk	12	18	30	1	5.4	3.9	4.6
Peanut	16	56	40	20	5.2	6.7	8.5

Abbreviations: AE, adverse event; EoE, eosinophilic esophagitis; GI, gastrointestinal; ND, not determined; OIT, oral immunotherapy; SPR-EoE, symptoms possibly related to EoE.

^aRates were derived from separate sample populations based on data availability and AE reporting.

^bRate of GI symptoms could not be determined for egg OIT because no studies of egg OIT reported AEs per patient by organ system.

Discussion

For most patients with symptoms possibly related to EoE, an endoscopy with biopsy is not performed; therefore, a confirmed diagnosis of EoE cannot be made, complicating estimates of true prevalence. The number of patients discontinuing study participation because of symptoms possibly related to EoE without a confirmed diagnosis is also unknown because studies frequently do not report the reason for discontinuation. In addition, many patients have symptoms that are not reported in studies because they may occur after long-term allergen exposure, potentially beyond the follow-up period.²⁵ For those patients who are diagnosed with EoE during or after OIT, identifying a clear association between EoE and OIT treatment may not be possible. Endoscopies are not routinely performed before OIT, so the presence of EoE at baseline cannot be ruled out. However, regardless of whether these symptoms are truly attributable to EoE, they tend to resolve on their own after termination of OIT.²⁴

To better understand the prevalence of EoE and symptoms possibly related to EoE during studies of OIT, a broad literature search was conducted. This analysis has several limitations. The rates reported here are estimates from a large and heterogeneous segment of the literature and did not take into consideration differences in OIT dosing, study design or duration, concomitant medication, baseline demographics or comorbid conditions of the individual study populations, or the severity of the AEs reported. In addition, the chronicity of the symptoms examined here is not known because the number of events per patient is not frequently reported. This information would be useful in estimating the prevalence of EoE because, as a chronic disease, EoE may be indicated by persistent symptoms.¹⁸ Discontinuations because of symptoms possibly associated with EoE may be informative, with the assumption that symptom persistence ultimately led to discontinuation, but the full clinical picture for each patient is unknown and results should be interpreted with caution.

Currently, there is no approved option for the treatment or prevention of food allergy.^{6,16} Because of the risk of severe reactions, US and European guidelines note traditional immunotherapy should only be used in highly controlled settings.^{6,16} There are no guidelines for the management of symptoms possibly related to EoE during OIT. A high percentage (approximately 30%) of patients experience GI symptoms during OIT, limiting its efficacy. Patients should be monitored closely. EoE treatment can involve removal of the offending food from the patient's diet and treatment with topical steroids.¹⁸ If symptoms possibly related to EoE develop or if EoE is confirmed by biopsy, stopping OIT should be considered, thus removing the possible trigger. Prompt diagnosis and management are important because untreated EoE is a risk factor for esophageal strictures.¹⁸

Conclusions and Recommendations

OIT can lead to desensitization in patients with food allergy but is associated with tolerability issues and a risk of serious AEs, including anaphylaxis.⁵ Symptoms possibly related to EoE present a safety concern because OIT is a risk factor for the development of EoE. Clinical symptoms of EoE may occur at any time during OIT dosing and up to more than a year after protocol completion.²³ This analysis focused on the incidence of general GI symptoms, abdominal pain, and vomiting because these were the most consistently reported symptoms that could be possibly related to EoE. Because most OIT studies are conducted in children, available AE data on the incidence of abdominal pain and vomiting, the most common symptoms associated with EoE in this age group, are of particular interest.¹⁹ On the basis of this analysis, the rate of EoE or symptoms possibly related to EoE can vary from a low of 5.1% based on

confirmed cases to a high of 34% based on symptoms possibly related to EoE experienced by patients receiving OIT. Delays in the appearance of symptoms and protocol discontinuations because of GI symptoms without diagnostic endoscopy likely result in EoE being underreported in studies of OIT. It is important to note, however, that symptoms described here as possibly related to EoE may not in fact be caused by EoE and that patients may experience GI symptoms during OIT that are not associated with EoE. In addition, several studies do not report patient reasons for discontinuation, so the true rate of discontinuation attributable to symptoms possibly related to EoE is difficult to determine. More specific and consistent reporting of AEs during studies of OIT and the inclusion of long-term follow-up are warranted to better understand the prevalence of EoE. However, on the basis of this review of the literature, the rate of symptoms possibly related to EoE is high. A study directly comparing OIT and sublingual immunotherapy reported a higher rate of GI symptoms with OIT during escalation and maintenance than with sublingual immunotherapy.¹⁴ Patients should be notified of this potential AE of therapy as part of the informed consent process and monitored closely during and in the years after OIT. If symptoms are present, clinicians should collaborate with patients and caregivers regarding options, including a diagnostic endoscopy to confirm EoE and/or elimination of the food allergen, considering the severity of the symptoms, the response to treatment, and the patient/caregiver goals for food allergy management.

Supplementary Data

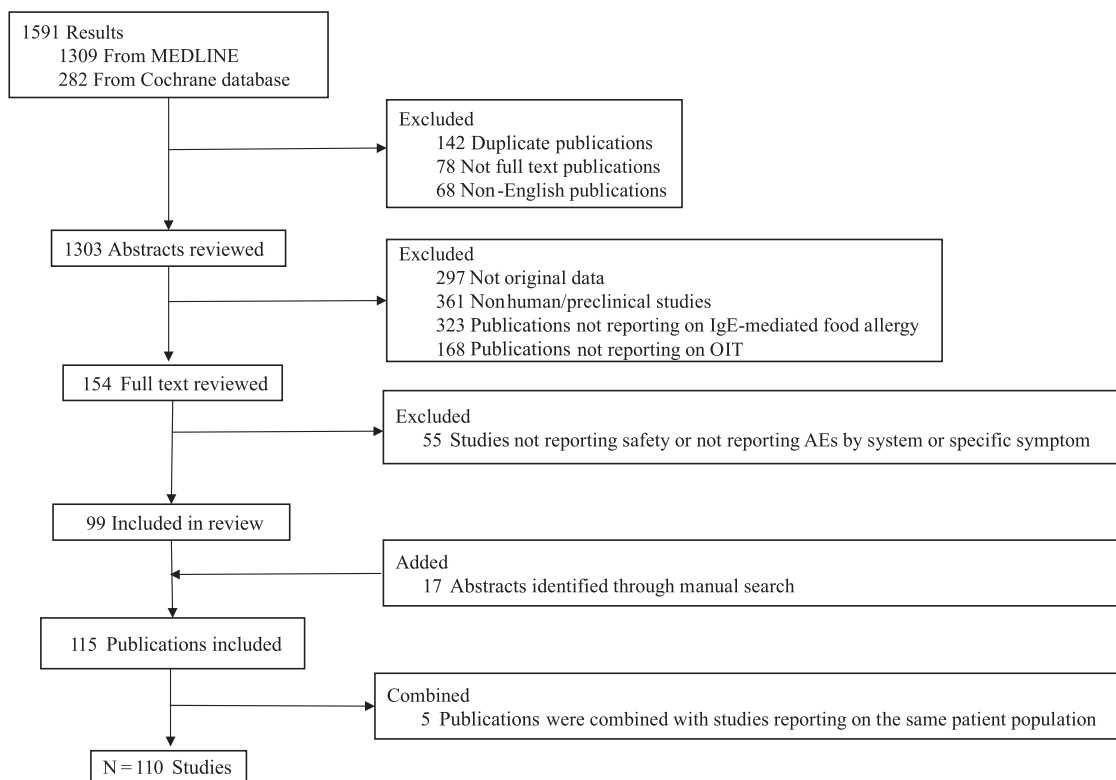
Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jana.2017.11.016>.

References

- [1] Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128:e9–e17.
- [2] Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol*. 2010;125:1322–1326.
- [3] Chafen JJ, Newberry SJ, Riedl MA, et al. Diagnosing and managing common food allergies: a systematic review. *JAMA*. 2010;303:1848–1856.
- [4] Walkner M, Warren C, Gupta RS. Quality of life in food allergy patients and their families. *Pediatr Clin North Am*. 2015;62:1453–1461.
- [5] Wood RA. Food allergen immunotherapy: current status and prospects for the future. *J Allergy Clin Immunol*. 2016;137:973–982.
- [6] Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored Expert Panel Report. *J Allergy Clin Immunol*. 2010;126:1105–1118.
- [7] Marchisotto MJ, Harada L, Blumenstock JA, et al. Global perceptions of food allergy thresholds in 16 countries. *Allergy*. 2016;71:1081–1085.
- [8] Burbank AJ, Burks W. Food specific oral immunotherapy: a potential treatment for food allergy. *Expert Rev Gastroenterol Hepatol*. 2015;9:1147–1159.
- [9] Hofmann AM, Scurlock AM, Jones SM, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J Allergy Clin Immunol*. 2009;124:286–291, e281–286.
- [10] Wood RA. Oral immunotherapy for food allergy. *J Invest Allergol Clin Immunol*. 2017;27:151–159.
- [11] Narisety SD, Frischmeyer-Guerrero PA, Keet CA, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol*. 2015;135:1275–1282, e1271–1276.
- [12] Buchanan AD, Green TD, Jones SM, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol*. 2007;119:199–205.
- [13] Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med*. 2012;367:233–243.
- [14] Keet CA, Frischmeyer-Guerrero PA, Thyagarajan A, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. *J Allergy Clin Immunol*. 2012;129:448–455, e441–445.
- [15] Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol*. 2017;139:173–181, e178.
- [16] Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy*. 2014;69:1008–1025.
- [17] Keet CA, Wood RA. Emerging therapies for food allergy. *J Clin Invest*. 2014;124:1880–1886.

- [18] 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, e26; quiz 21–22.
- [19] Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med*. 2004; 351:940–941.
- [20] Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology*. 2003;125:1660–1669.
- [21] Hill DA, Dudley JW, Spergel JM. The prevalence of eosinophilic esophagitis in pediatric patients with IgE-mediated food allergy. *J Allergy Clin Immunol Pract*. 2017;5:369–375.
- [22] Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol*. 2014;113:624–629.
- [23] Echeverria-Zudaire LA, Fernandez-Fernandez S, Rayo-Fernandez A, Munoz-Archidona C, Checa-Rodriguez R. Primary eosinophilic gastrointestinal disorders in children who have received food oral immunotherapy. *Allergol Immunopathol (Madr)*. 2016;44:531–536.
- [24] Hsieh FH. Oral food immunotherapy and iatrogenic eosinophilic esophagitis: an acceptable level of risk? *Ann Allergy Asthma Immunol*. 2014;113:581–582.
- [25] Maggadottir SM, Hill DA, Ruymann K, et al. Resolution of acute IgE-mediated allergy with development of eosinophilic esophagitis triggered by the same food. *J Allergy Clin Immunol*. 2014;133:1487–1489, e1481.

Supplementary Data



eFigure 1. Flow diagram of search results and included publications. AE, adverse event; OIT, oral immunotherapy.

eTable 1
Safety Data for Patients Receiving Immunotherapy During OIT Clinical Studies

Food	No. of patients	EoE-PRS, No. (%)	Discontinued, No. (%)	No. of patients with EoE	Discontinuation reason, No.	
					EoE-PRS	EoE or EoE-PRS
Egg ¹	18	AP: 6 (33); V: 4 (22)	3 (17)		0	0
Peanut ²	22	AP: 11 (50); N: V: 4 (18)	1 (5)		1	1
Peanut ³	94	AP: 54 (57); N: 31 (33); V: 31 (33)	8 (9)			
Milk ⁴	18	AP: 5 (28); V: 4 (22)	1 (6)	1	0	1
Peanut ⁵	11	NR	2 (18)		1	1
Egg ⁶	7	AP: 5 (71); V: 2 (29)	0 (0)		0	0
Peanut ⁷	13	NR		2	2	4
Egg ⁸	17	V: 1 (6); AP: 2 (12)	1 (6)		0	0
Milk ⁹	10	AP: 3 (43)	2 (20)		0	0
Peanut ¹⁰	4	AP: 2 (50); N: 1 (25); V: 1 (25)	0 (0)		0	0
Egg ¹¹	10	AP: 2 (20)	0 (0)		0	0
Milk ¹²	14	V, AP: 1 (7)	1 (7)		1	1
Egg/Milk ¹³	128	NR	NR	6		
Milk ¹⁴	195	GI: 17 (9)	14 (7)			
Milk ¹⁵	112	GI: 8 (7)	13 (12)			
Peanut ¹⁶	100	GI: 40 (40)	7 (7)		4	4
Egg ¹⁷	40	AP: 12 (30); V: 6 (15)	3 (8)	1	2	3
Egg ¹⁸	23	AP: 10 (43); N: 1 (4); V: 6 (26)	1 (4)		1	1
Milk ¹⁹	36	GI: 14 (39)	3 (8)		2	2
Egg ²⁰	15	V: 1 (7)	4 (27)		0	0
Milk ²¹	15	GI: 5 (33)	11 (73)		3	3
Milk ^{22, 23}	57	NR		3		
Egg ²⁴	6	AP, V: 4 (67)	0 (0)		0	0
Milk ²⁵	10	GI: 0	2 (20)		0	0
Milk ²⁶	32	GI: 8 (25)	5 (16)			
Milk ²⁷	74	AP: 49 (66); N: 28 (38)	13 (18)			
Milk ²⁸	76	GI: 20 (26)	12 (16)			
Peanut ²⁹	39	Build-up: AP: 16 (41); N: 5 (13); V: 4 (10) Maintenance: AP: 6 (18); N: 2 (6); V: 2 (6)	11 (28)			
Egg ³⁰	17	AP: 12 (71); N: 2 (12); V: 10 (59)	3 (18)		1	1
Milk ³¹	280	NR	39 (14)		8	8
Milk ³²	30	Escalation: AP: 23 (77) Maintenance: AP: 14 (47)	3 (10)			
Milk ³³	50	GI: 11 (22)	18 (36)		4	4
Peanut ³⁴	37	NR	3 (8)	2	1	3
Peanut ³⁵	1	GI: 0	0 (0)		0	0
Milk ³⁶	30	GI: 9 (30)	1 (3)			
Milk ³⁷	4	AP: 1 (25)	0 (0)		0	0
Egg	9	AP: 1 (11)	0 (0)			
Milk ³⁸	5					
Milk ³⁹	21	AP: 3 (14); V: 1 (5)	3 (14)		1	1
Egg ⁴⁰	10	AP, V: 2 (20)	1 (10)		0	0
Egg/Milk ⁴¹	4	AP: 3 (75)	0 (0)		0	0
Milk ⁴²	20	V: 0 (0)	6 (0)			
Milk ⁴³	1	V: 1 (100)	1 (100)	1	0	1
Milk ⁴⁴	82	GI: 21 (26)	13 (16)		6	6
Milk ⁴⁵	30	GI: 6 (16)	0 (0)		0	0
Egg	49	NR				
Milk ⁴⁶	27		3 (11)		2	2
Milk ⁴⁷	11	NR	1 (9)		1	1
Milk ⁴⁸	3	GI: 0	0 (0)		0	0
Milk ⁴⁹	1	GI: 0	0 (0)		0	0
Milk ⁵⁰	1	N: 1 (100)	0 (0)		0	0
Peanut ⁵¹	1	AP, N, V: 1 (100)	0		0	0
Milk ⁵²	20	GI, 3 years: 4 (20), N = 20 GI, 4 years: 3 (18), N = 17 GI, 5 years: 1 (8), N = 13 GI, 7 years: 2 (13), N = 16	2 (10)		0	0
Milk ⁵³	15	AP: 5 (33)	5 (33)		0	0
Milk ⁵⁴	45	AP, viral: 1 (25)	0 (0)		0	0
Milk ⁵⁵	4	GI: 0	0 (0)		0	0
Peanut ⁵⁶	1	GI: 0	0 (0)		0	0
Milk	5	AP: 1 (20)	2 (33)		0	0
Egg ⁵⁷	6	AP: 1 (17)				
Milk ⁵⁸	1	N: 1 (100)	0 (0)		0	0
Egg ⁵⁹	1	R: 1 (100)	0 (0)	1	0	0
Egg ⁶⁰	17	AP: 9 (53); V: 3 (18)	3 (18)			
Milk ⁶¹	24	GI: 16 (67)	2 (8)		2	2
Milk ⁶²	3	AP: 2 (67); A: 1 (33)	3 (100)	3	0	
Milk ⁶³	40	NR	8 (20)		3	3
Milk ⁶⁴	26	NR	6 (23)		2	2
Peanut ⁶⁵	13	NR	1 (8)		1	1

(continued on next page)

eTable 1 (continued)

Food	No. of patients	EoE-PRS, No. (%)	Discontinued, No. (%)	No. of patients with EoE	Discontinuation reason, No.	
					EoE-PRS	EoE or EoE-PRS
Peanut ⁶⁶	3	AP: 1 (33); V: 1 (33)	3 (100)	3	0	3
Egg/Milk ⁶⁷	25	N: 6 (24); V: 6 (24)	9 (36)			
Egg/Wheat/Milk ⁶⁸	5	GI: 5 (100)	0 (0)		0	0
Peanut ⁶⁹	31	AP: 3 (9); V: 1 (17)	3 (10)		0	0
Egg ⁷⁰	8	AP: 4 (50); V: 2 (25)	2 (25)		0	0
Peanut ⁷¹	4	V: 1 (100)	1 (100)		0	0
Peanut ⁷²⁻⁷⁴	104	GI: 51 (49)	21 (20)	2	8	10
Milk ⁷⁵	18	AP: 2 (11); N: 1 (6); V: 1 (6)	1 (6)		0	0
Milk ⁷⁶	1	N: 1 (100)	1 (100)	1	0	1
Peanut ⁷⁷	29	GI: 21 (72)	6 (21)		6	6
Peanut ⁷⁸	49	NR	5 (10)		4	4
Egg/Milk ^{79, 80}	63	NR	7 (11)	3		
Peanut ⁸¹	177	GI: ~120 (68)	NR			
Egg	427	V, eosinophilia:	98 (23)		29	29
Milk		Milk: 7 (7.7)				
Peanut		Peanut: 29 (12.5)				
Cashew ^{82, 83}		Cashew: 1 (5.6)				
Egg	45	GI: 0	0 (0)			
Milk ⁸⁴	32		1 (3)			
Peanut ⁸⁵	33	GI: 4 (12)				
Peanut ⁸⁶	21	AP: 1 (5)	10 (48)			
Milk ^{87, 88}	4	GI: 0	0 (0)		0	0
Peanut ⁸⁹	662	GI: 382 (58)	NR			
Peanut ⁹⁰	4	GI: 0	0 (0)		0	0
Milk ⁹¹	2	GI: 0	0 (0)		0	0
Milk ⁹²	132	GI: 28.8	4 (3)			
Milk ⁹³	209	% of reactions: Mild: 43% GI Mod: 40% GI Severe: 20% GI				
Peanut	15	AP/V: ~2%	3 (20)		0	0
Multiple ⁹⁴	25	AP/V: ~2%	3 (25)			
Peanut ⁹⁵	23	GI: ~1	8 (35)			
Egg ⁹⁶	40	GI: 5.5	6 (15)		4	
Egg ⁹⁷	30	GI: 4	2 (7)		2	2
Peanut ⁹⁸	28	GI: ~1.2	5 (18)	1		
Peanut ⁹⁹	6	GI: 16	2 (33)		0	0
Egg ¹⁰⁰	34	GI: 0.3	9 (26)		0	0
Milk (OIT Phase ^a) ¹⁰¹	20	GI: ~4.2	2 (7)		1	1
Milk ¹⁰²	25	GI: 33	0		0	0
Peanut (OIT/SLIT ^b) ¹⁰³	20	GI: ~6	4 (36)		3	3
Milk ¹⁰⁴	15	GI: 3.7	1 (7)		1	1
Peanut ¹⁰⁵	18	N: 13; V: 13	2 (11)		2	2
Egg ¹⁰⁶	31	GI: 55.1	0 (0)		0	0
Egg ¹⁰⁷	19	GI: 23	2 (11)		1	1
Milk ¹⁰⁸	13	GI: 19	1 (8)		0	0
Egg ¹⁰⁹	30	GI: 0.29	1 (3)		0	0
Egg ¹¹⁰	50	GI: 2.9	18 (36)			
Milk ¹¹¹	81	AP: 1.2; V: 0.97	6 (7)	1		
Peanut ¹¹²	37	AP: 0.17; N/V: 0.08	5 (14)	1	1	2
Milk ¹¹³	57	GI: 1.7	7 (12)	1	1	2
Milk ¹¹⁴	12	GI: 4.2	0 (0)		0	0
Peanut ¹¹⁵	24	AP: 5.2; N/V: 0.15	1 (4)		1	1

Abbreviations: A, anorexia; AP, abdominal pain; EoE, eosinophilic esophagitis; GI, gastrointestinal symptoms; N, nausea; NR, not reported; OIT, oral immunotherapy; PRS, potentially related symptoms; SLIT, sublingual immunotherapy; V, vomiting.

^aIncludes only patients receiving OIT doses (patients receiving sublingual immunotherapy excluded).

^bIncludes only patients receiving OIT or OIT in combination with sublingual immunotherapy (patients receiving sublingual immunotherapy alone excluded).

eReferences

- [1] Akashi M, Yasudo H, et al. *Pediatr Int*. 2017;59:534–539.
- [2] Anagnostou K, Clark A, et al. *Clin Exp Allergy*. 2011;41:1273–1281.
- [3] Anagnostou K, Islam S, et al. *Efficacy Mech Eval*. 2014;1.
- [4] Babaie D, Nabavi M, et al. *Iran J Allergy Asthma Immunol*. 2017;16:45–52.
- [5] Bird JA, Feldman M, et al. *J Allergy Clin Immunol Pract*. 2015;3:433–435 e431–433.
- [6] Buchanan AD, Green TD, et al. *J Allergy Clin Immunol*. 2007;119:199–205.
- [7] Burk CM, Dellon ES, et al. *J Allergy Clin Immunol Pract*. 2017;5:498–501.
- [8] Caminiti L, Pajno GB, et al. *J Allergy Clin Immunol Pract*. 2015;3:532–539.
- [9] Caminiti L, Passalacqua G, et al. *Allergy Asthma Proc*. 2009;30:443–448.
- [10] Clark AT, Islam S, et al. *Allergy*. 2009;64:1218–1220.
- [11] Dello Iacono I, Tripodi S, et al. *Pediatr Allergy Immunol*. 2013;24:66–74.
- [12] Ebrahimi M, Gharagozlou M, et al. *J Investig Allergol Clin Immunol*. 2016;26:341–343.
- [13] Echeverria-Zudaire LA, Fernandez-Fernandez S, et al. *Allergol Immunopathol (Madr)*. 2016;44:531–536.
- [14] Elizur A, Appel MY, et al. *Allergy*. 2016;71:275–278.
- [15] Elizur A, Goldberg MR, et al. *Ann Allergy Asthma Immunol*. 2015;114:240–244 e241.
- [16] Factor JM, Mendelson L, et al. *Ann Allergy Asthma Immunol*. 2012;109:348–352 e342.
- [17] Fuentes-Aparicio V, Alonso-Lebrero E, et al. *Pediatr Allergy Immunol*. 2012;23:648–653.
- [18] Garcia Rodriguez R, Urrea JM, et al. *Clin Exp Allergy*. 2011;41:1289–1296.
- [19] Garcia-Ara C, Pedrosa M, et al. *Ann Allergy Asthma Immunol*. 2013;110:290–294.
- [20] Giavi S, Vissers YM, et al. *Allergy*. 2016;71:1575–1584.
- [21] Goldberg MR, Nachshon L, et al. *J Allergy Clin Immunol*. 2015;136:1601–1606.
- [22] Gomez F, Bogas G, et al. *Clin Exp Allergy*. 2017;47:339–350.
- [23] García Rodriguez C, Torrijos EG, et al. *J Investig Allergol Clin Immunol*. 2014;24:363–365.
- [24] Itoh N, Itagaki Y, et al. *Allergology Int*. 2010;59:43–51.
- [25] Kaneko H, Teramoto T, et al. *J Investig Allergol Clin Immunol*. 2010;20:538–539.
- [26] Keet CA, Seopaul S, et al. *J Allergy Clin Immunol*. 2013;132:737–739 e736.
- [27] Kivisto JE, Korppi M, et al. *Acta Paediatr*. 2015;104:1164–1168.
- [28] Kuitunen M, Englund H, et al. *Allergy*. 2015;70:955–962.
- [29] Kukkonen AK, Uotila R, et al. *Acta Paediatr*. 2017;106:274–281.
- [30] Letran A, Espinazo M, et al. *J Investig Allergol Clin Immunol*. 2012;22:147–149.
- [31] Levy MB, Elizur A, et al. *Ann Allergy Asthma Immunol*. 2014;112:58–63 e51.
- [32] Longo G, Barbi E, et al. *S J Allergy Clin Immunol*. 2008;121:343–347.
- [33] Luyt D, Bravin K, et al. *J Asthma Allergy*. 2014;7:1–9.
- [34] MacGinnitie AJ, Rachid R, et al. *J Allergy Clin Immunol*. 2017;139:873–881 e878.
- [35] Macfield L. *Ann Allergy Asthma Immunol*. 2006;97:266–267.
- [36] Martorell A, De la Hoz B, et al. *Clin Exp Allergy*. 2011;41:1297–1304.
- [37] Martorell Aragones A, Felix Toledo R, et al. *Allergol Immunopathol (Madr)*. 2007;35:174–176.
- [38] Martorell-Calatayud C, Michavila-Gomez A, et al. *Pediatr Allergy Immunol*. 2016;27:544–546.
- [39] Meglio P, Bartone E, et al. *Allergy*. 2004;59:980–987.
- [40] Meglio P, Giampietro PG, et al. *Pediatr Allergy Immunol*. 2013;24:75–83.
- [41] Meglio P, Giampietro PG, et al. *Int J Immunopathol Pharmacol*. 2011;24:803–811.
- [42] Meglio P, Giampietro PG, et al. *Pediatr Allergy Immunol*. 2008;19:412–419.
- [43] Moraes Silva P, Antunes J, et al. *Eur Ann Allergy Clin Immunol*. 2014;46:154–156.
- [44] Mori F, Cianferoni A, et al. *Int J Immunopathol Pharmacol*. 2017;30:182–187.
- [45] Mori F, Pucci N, et al. *Pediatr Allergy Immunol*. 2010;21:e450–e453.
- [46] Morisset M, Moneret-Vautrin DA, et al. *Eur Ann Allergy Clin Immunol*. 2007;39:12–19.
- [47] Nadeau KC, Schneider LC, et al. *J Allergy Clin Immunol*. 2011;127:1622–1624.
- [48] Nucera E, Pecora V, et al. *United European Gastroenterol J*. 2015;3:272–276.
- [49] Nucera E, Schiavino D, et al. *J Investig Allergol Clin Immunol*. 2008;18:219–222.
- [50] Nucera E, Schiavino D, et al. *Dig Dis Sci*. 2000;45:637–641.
- [51] Ojeda P, Ojeda I, et al. *J Investig Allergol Clin Immunol*. 2010;20:524–528.
- [52] Paasilta M, Salmivesi S, et al. *Acta Paediatr*. 2016;105:215–219.
- [53] Pajno GB, Caminiti L, et al. *Ann Allergy Asthma Immunol*. 2010;105:376–381.
- [54] Pajno GB, Caminiti L, et al. *Pediatr Allergy Immunol*. 2013;24:376–381.
- [55] Patriarca G, Buonomo A, et al. *Int J Immunopathol Pharmacol*. 2002;15:53–58.
- [56] Patriarca G, Nucera E, et al. *Dig Dis Sci*. 2006;51:471–473.
- [57] Patriarca G, Schiavino D, et al. *Hepatogastroenterology*. 1998;45:52–58.
- [58] Peraita-Adrados R, Lopez-Esteban P, et al. *Sleep Med*. 2011;12:730–731.
- [59] Ridolo E, De Angelis GL, et al. *Ann Allergy Asthma Immunol*. 2011;106:73–74.
- [60] Ruiz Garcia M, Haroun E, et al. *J Investig Allergol Clin Immunol*. 2012;22:529–531.
- [61] Salmivesi S, Korppi M, et al. *Acta Paediatr*. 2013;102:172–176.
- [62] Sanchez-Garcia S, Rodriguez Del Rio P, et al. *J Allergy Clin Immunol*. 2012;129:1155–1157.
- [63] Savilahti EM, Kuitunen M, et al. *Int Arch Allergy Immunol*. 2014;164:32–39.
- [64] Savilahti EM, Kuitunen M, et al. *Pediatr Allergy Immunol*. 2014;25:227–235.
- [65] Schneider LC, Rachid R, et al. *J Allergy Clin Immunol*. 2013;132:1368–1374.
- [66] Semancik E, Saye WN. *Pediatr Allergy Immunol*. 2016;27:539–541.
- [67] Staden U, Rolinck-Werninghaus C, et al. *Allergy*. 2007;62:1261–1269.
- [68] Takahashi M, Taniuchi S, et al. *Allergy Asthma Clin Immunol*. 2014;10:3.
- [69] Tang ML, Ponsonby AL, et al. *J Allergy Clin Immunol*. 2015;135:737–744 e738.
- [70] Vickery BP, Pons L, et al. *Ann Allergy Asthma Immunol*. 2010;105:444–450.
- [71] Vila L, Amado A. *J Investig Allergol Clin Immunol*. 2016;26:207–209.
- [72] Virkud YV, Burks AW, et al. *J Allergy Clin Immunol*. 2017;139:882–888, e885.
- [73] Jones SM, Pons L, et al. *J Allergy Clin Immunol*. 2009;124:292–300, 300 e291–297.
- [74] Varshney P, Jones SM, et al. *J Allergy Clin Immunol*. 2011;127:654–660.
- [75] Zapatero L, Alonso E, et al. *J Investig Allergol Clin Immunol*. 2008;18:389–396.
- [76] Brosseron L, Reis Ferreira A, et al. *Allergy*. 2015;70:1–649:Abstract 1725.
- [77] Bird J, Spergel J, et al. *Allergy*. 2015;70:1–649:Abstract 1522.
- [78] Bird JA, Spergel JM, et al. *J Allergy Clin Immunol*. 2016;137:AB408.
- [79] Cortes J, Gil J, et al. *Allergy*. 2015;70:1–649:Abstract 684.
- [80] Colom M, Gil J, et al. *Allergy*. 2015;70:1–649:Abstract 687.
- [81] Factor JM, Mendelson LM, et al. *J Allergy Clin Immunol*. 2015;135:AB23.
- [82] Hague AR, Silvers SK, et al. *J Allergy Clin Immunol*. 2017;139:AB134:Abstract 428.
- [83] Silvers SK, Hague AR, et al. *J Allergy Clin Immunol*. 2017;139:AB134:Abstract 429.
- [84] Hirayama J, Nagao M, et al. *Allergy*. 2016;71:3–633:Abstract 1146.
- [85] Lewis MO, Brown-Whitehorn TF, et al. *J Allergy Clin Immunol*. 2017;139:AB387.
- [86] Mudd K, Seopaul S, et al. *J Allergy Clin Immunol*. 2016;137:AB85.
- [87] Pajno G, Caminiti L, et al. *Allergy*. 2015;70:1–649:Abstract 398.
- [88] Pajno GB, Caminiti L, et al. *J Allergy Clin Immunol*. 2015;135:AB259.
- [89] Rubin TN, Patel S, et al. *J Allergy Clin Immunol*. 2017;139:AB134.
- [90] Turner P, Mehr S, et al. *Allergy*. 2015;70:1–649:Abstract 1521.
- [91] Zande M, Psarros F, et al. *Allergy*. 2015;70:1–649:Abstract 955.
- [92] Barbi E, Longo G, et al. *Allergol Immunopathol (Madr)*. 2012;40:41–50.
- [93] Barbi E, Longo G, et al. *Eur Ann Allergy Clin Immunol*. 2012;44:18–25.
- [94] Begin P, Winterroth LC, et al. *Allergy Asthma Clin Immunol*. 2014;10:1.
- [95] Blumchen K, Ulbricht H, et al. *J Allergy Clin Immunol*. 2010;126:83–91 e81.
- [96] Burks AW, Jones SM, et al. *N Engl J Med*. 2012;367:233–243.
- [97] Escudero C, Rodriguez Del Rio P, et al. *Clin Exp Allergy*. 2015;45:1833–1843.
- [98] Hofmann AM, Scurllock AM, et al. *J Allergy Clin Immunol*. 2009;124:286–291, 291 e281–286.
- [99] Jagdis A, Berlin N, et al. *Allergy Asthma Clin Immunol*. 2014;10:36.
- [100] Jones SM, Burks AW, et al. *J Allergy Clin Immunol*. 2016;137:1117–1127 e1111–1110.
- [101] Keet CA, Frischmeyer-Guerrero PA, et al. *J Allergy Clin Immunol*. 2012;129:448–455, 455 e441–445.
- [102] Martinez-Botas J, Rodriguez-Alvarez M, et al. *Clin Exp Allergy*. 2015;45:1071–1084.
- [103] Narisety SD, Frischmeyer-Guerrero PA, et al. *J Allergy Clin Immunol*. 2015;135:1275–1282 e1271–1276.
- [104] Narisety SD, Skripak JM, et al. *J Allergy Clin Immunol*. 2009;124:610–612.
- [105] Nozawa A, Okamoto Y, et al. *Pediatr Allergy Immunol*. 2014;25:323–328.
- [106] Ojeda P, Ojeda I, et al. *Isr Med Assoc J*. 2012;14:34–39.
- [107] Perez-Rangel I, Rodriguez Del Rio P, et al. *Ann Allergy Asthma Immunol*. 2017;118:356–364 e353.
- [108] Skripak JM, Nash SD, et al. *J Allergy Clin Immunol*. 2008;122:1154–1160.
- [109] Sudo K, Taniuchi S, et al. *Allergy Asthma Clin Immunol*. 2014;10:11.
- [110] Vazquez-Ortiz M, Alvaro-Lozano M, et al. *Clin Exp Allergy*. 2013;43:92–102.
- [111] Vazquez-Ortiz M, Alvaro M, et al. *Clin Exp Allergy*. 2014;44:130–141.
- [112] Vickery BP, Berglund JP, et al. *J Allergy Clin Immunol*. 2017;139:173–181 e178.
- [113] Wood RA, Kim JS, et al. *J Allergy Clin Immunol*. 2016;137:1103–1110 e1101–1111.
- [114] Yanagida N, Sato S, et al. *Int Arch Allergy Immunol*. 2015;168:131–137.
- [115] Yu GP, Weldon B, et al. *Int Arch Allergy Immunol*. 2012;159:179–182.