



Eosinophilic esophagitis during sublingual and oral allergen immunotherapy

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Purpose of review

The aim of this review is to discuss the current evidence regarding the development of eosinophilic esophagitis (EoE) in individuals undergoing oral and sublingual immunotherapy (SLIT) for both food and environmental allergens. Cumulative incidence of EoE in patients on allergen immunotherapy for peanut, milk, and egg is estimated.

Recent findings

De novo development of EoE in patients undergoing oral and SLIT has been demonstrated on the scale of case reports and prospective randomized trials. However, few individuals with EoE-like symptoms during immunotherapy undergo endoscopy, and the long-term outcomes of immunotherapy-associated EoE are unknown.

Summary

Evidence exists to suggest that allergen immunotherapy could place individuals at risk for the development of EoE, the true incidence of which may vary depending on antigen exposure and methods used to define the condition.

Keywords

eosinophilic esophagitis, food allergy, oral immunotherapy, sublingual immunotherapy

INTRODUCTION

Food allergy is broadly characterized into two groups: IgE-mediated food allergy (IgE-FA) which causes anaphylaxis upon food exposure, and non-IgE-mediated forms such as eosinophilic esophagitis (EoE). Although these two groups have distinct pathophysiologic mechanisms, there is a high degree of comorbidity between them [1^{••}]. Further, it is generally appreciated that the prevalence of food allergy in the United States and other developed nations is on the rise, with 8–10% of the US population currently affected [2,3[•],4]. Although this rise is most commonly associated with classic IgE-FA, the rate of EoE has also seen a steady increase in prevalence since early case descriptions [5–7] and is now recognized as the leading cause of chronic dysphagia in children in the developed world [8,9^{••},10].

The current standard of care for IgE-FA is strict allergen avoidance, and the recommendation to carry injectable epinephrine in case of accidental allergen exposure and severe reaction [4,11]. At this time no US Food and Drug Administration (FDA)-approved treatments for IgE-FA exist, however, investigational therapies such as oral immunotherapy

(OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT) are in development. Although food avoidance practices are generally effective [12], patients and caregiver quality of life is often impacted as a result of anxiety associated with the potential for an accidental ingestion [13]. Thus, with the achievement of positive efficacy data for OIT and EPIT [14–18], the regular use of these therapies for IgE-FA is increasingly tangible and attractive alternative to avoidance alone.

When considering the introduction of these new therapies the adverse event profile of allergen

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KEY POINTS

- Significant evidence exists to suggest that both oral immunotherapy to foods and SLIT to aeroallergens may potentiate risk for the development of EoE.
- EoE poses a significant safety concern for patients undergoing allergen immunotherapy given lack of longitudinal data regarding patient outcomes.
- Onset of EoE can be seen both during dose escalation or during maintenance therapy.
- Given that adverse gastrointestinal symptoms are also common in patients undergoing immunotherapy, the true incidence of EoE may be underestimated given low rates of confirmatory testing.

immunotherapy must also be considered, and may present important limitations in clinical utility [14,19]. A relatively benign adverse event commonly associated with OIT and SLIT is localized and transient oral pruritis [15]. However, more serious gastrointestinal-related adverse events (GI-AEs) in OIT trials are also seen in trial participants, with varying severity [8,20]. Indeed, GI-AEs are the most common reason for treatment discontinuation in OIT trials [8,20–23]. Of particular concern is the development of EoE, which has been reported with both OIT and SLIT, and has been of significant clinical concern [8,9¹¹,10,24,25]. Here, we discuss the evidence surrounding immunotherapy-triggered EoE (IT-EoE) and the related clinical implications.

Eosinophilic esophagitis

EoE is a chronic, immune-mediated and allergen-triggered inflammation of the esophagus, that leads to progressive esophageal dysfunction [26,27]. EoE presents clinically with abdominal pain, reflux, vomiting, dysphagia, and food impaction [28]. If left untreated, long-term esophageal inflammation can lead to esophageal remodeling, narrowing, and stricture formation [26,27]. Diagnosis of EoE relies on esophageal biopsy demonstrating at least 15 eosinophils per high power field or 60 eosinophils/mm², with exclusion of other causes of esophageal eosinophilia, as outlined in recent changes to the EoE guidelines on diagnosis and management [29¹¹,30¹²]. In all patients undergoing endoscopy, EoE can be diagnosed in 2–7% of individuals, while rates may be as high as 12–23% in those with dysphagia.

On an epidemiologic scale, EoE is thought to affect 0.5–1 in 1000 individuals [31,32,33¹³,34], but in individuals with concurrent IgE-FA, the rate of EoE is markedly elevated to one in 20 individuals [1¹⁴,35]. Subsequent development of EoE following diagnosis

of IgE-FA can often be attributed to the same culprit food [1¹⁴,36], which has important implications regarding the potential immunologic mechanisms that may be responsible for the various food allergy phenotypes [1¹⁴,37,38¹⁵,39¹⁶]. Likewise, patients with EoE demonstrate higher rates of IgE-FA compared with the general population (10–60 vs. 8%) [40–42], with the most common food triggers (milk, egg, soy, wheat) implicated in both conditions [43]. Given the symptom overlap between EoE and GI-AEs from immunotherapy, diagnosis of IT-EoE is a potential challenge for allergists.

Notably too, while many patients experience GI-AEs secondary to OIT, a fewer number of patients actually undergo endoscopic evaluation, especially since discontinuation of OIT therapy usually results in symptom improvement [9¹¹,44]. Even fewer patients undergo endoscopy prior to OIT therapy. Thus, the actual rates of EoE during OIT may be higher than current estimates.

Allergen immunotherapy

OIT involves the controlled administration of increasing doses of a particular allergen over time, with the goal of inducing desensitization [8,22,45]. Desensitization is the temporary induction of a decreased reaction potential upon exposure to a specific amount of an allergic antigen [8]. Desensitization protocols for OIT involve mixing the allergenic food or equivalent protein powder into an inert medium with delivery in gradually increasing doses over time [8,21,22,45]. This typically involves an initial escalation phase performed under close physician supervision, followed by a build-up phase and maintenance in the home environment, with variations dependent on study protocol [8,21].

Other methods of desensitization are SLIT and EPIT, both of which offer alternative modes of allergen delivery but share the overall goal of allergen desensitization. SLIT therapy involves the placement of a tablet or liquid extract under the tongue on a daily basis [46,47], and several formulations have been FDA-approved for various environmental allergens for treatment of allergic rhinitis. No FDA-approved food SLIT therapies exist to date. EPIT utilizes an allergen containing patch to introduce controlled doses of allergen via the cutaneous immune system, though again, no current FDA-approved therapies either for aeroallergen or food-allergen therapies exist.

EOSINOPHILIC ESOPHAGITIS SECONDARY TO FOOD ORAL IMMUNOTHERAPY

A comprehensive review regarding IT-EoE was compiled in a meta-analysis by Petroni and Spergel in

Table 1. Rate of eosinophilic esophagitis in peanut, milk, and egg oral immunotherapy studies

Study	Number of patients	Discontinuation of OIT (%)	Symptomatic EoE (%)	Biopsy confirmed EoE (%)
Peanut				
Petroni <i>et al.</i> [9 [■]]	1624	16	6.7	5.2
Vickery <i>et al.</i> [48 [■]]	372	11.6	4.3	0.8
Wasserman <i>et al.</i> [49]	270	17.7	13.7	N/A
Recalculated incidence		15.5	7.1	4.4
Milk				
Petroni <i>et al.</i> [9 [■]]	2049	12	3.9	5.4
Mori <i>et al.</i> [50]	74	17.6	8.1	N/A
Gómez Torrijos <i>et al.</i> [52 [■]]	57	N/A	N/A	5.2
Recalculated incidence		12.2	4.1	5.4
Egg				
Petroni <i>et al.</i> [9 [■]]	959	11	2.7	3.1
Rodriguez Garcia <i>et al.</i> [53]	1	100	100	100
Recalculated incidence	960	11.1	2.8	3.2

EoE, eosinophilic esophagitis; N/A, not available; OIT, oral immunotherapy.

2017 [9[■]]. In this review, the authors sought to determine the incidence of EoE or symptoms possibly related to EoE, in patients undergoing OIT for milk, egg, or peanut allergies. Given the limited evidence surrounding EoE secondary to SLIT and EPIT therapies, this review focused solely on IT-EoE secondary to OIT. A total of 110 studies (including prospective studies, retrospective reports, case studies, and abstracts) were included in the review. Immunotherapy discontinuation rates, and rates of biopsy confirmed EoE per food were determined. Symptoms related to EoE were defined as general gastrointestinal symptoms and included abdominal pain, nausea, vomiting, anorexia, or reflux. Overall, the rate of patients with symptoms possibly related to EoE was as follows: 34% for those with general gastrointestinal symptoms, 32% for abdominal pain, and 12% for those with vomiting. Significantly, a higher rate of vomiting was seen in those undergoing peanut and egg OIT (20 and 17%, respectively), as compared with milk OIT (1%). Rates of reported abdominal pain, however, were similar among food allergies being treated (egg, 28%, milk 30%, peanut 40%). The overall rate of discontinuation of OIT was roughly 14%. Out of the 110 studies, 82 studies reported a reason for OIT discontinuation, 4.7% of which indicate symptoms possibly related to EoE. Notably, only 18 studies reported biopsies to confirm the diagnosis of EoE, which included 35 total cases, and an overall rate of biopsy-proven EoE in 5.3% of patients receiving OIT. Notably, a small subset of six patients with biopsy-confirmed EoE continued OIT therapy, though no long-term outcomes were reported.

Since this publication there has been a total of five additional reports reviewing adverse events related to food OIT (two involving peanut two involving milk, and one case report involving egg OIT). We summarize the findings of these five studies below and in Table 1.

Peanut oral immunotherapy

In the 2017 Petroni meta-analysis, peanut accounted for the most common food-related OIT leading to discontinuation of therapy secondary to symptoms of EoE [9[■]]. Data were compiled from 32 publications accounting for a total analysis of 1624 patients. Within this group, 16% discontinued OIT for any reason, with 6.7% of patients discontinuing treatment due to symptoms related to EoE. Of the patients on peanut OIT, 5.2% had biopsy confirmed EoE.

A subsequent phase 3 randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of immunotherapy in 555 children and adolescents (ages 4–17) with severe peanut allergy was recently conducted by Vickery *et al.* [48[■]]. Patients with any gastrointestinal symptoms, including EoE, were excluded at enrollment. The primary end point tolerance of a 600-mg peanut oral food challenge. There were 416 patients assigned to receive OIT, and 139 patients assigned to receive placebo. OIT was administered as a daily graduated dose (0.5, 1, 10, 20, 100, or 300 mg) with dose escalation every 2 weeks until participants reached 300 mg, the equivalent of one peanut. Maintenance dosing of 300 mg was continued for a 24-week period. After completion of the regimen, patients

underwent a double blind, placebo-controlled food challenge which included doses of 300, 600, and 1000 mg of peanut protein. In the active OIT treatment group, 16 patients (4.3%) discontinued the OIT due to chronic or recurrent dose limiting gastrointestinal symptoms. Of these, only three patients (2.4%) underwent endoscopy with one case (0.8%) of EoE confirmed by biopsy.

An additional retrospective review of 270 patients on peanut OIT at a single-center practice setting was also recently completed by Wasserman *et al.* [49]. In this study, 79% of enrolled patients were able to complete a peanut desensitization protocol with daily dosing. Notably, patients with a prior history of EoE or gastroenteritis were excluded. Of all participants, 37 patients (13.7%) experienced symptoms suggestive of EoE. A total of 21 patients discontinued treatment, however, confirmatory biopsies were not completed as part of this study (Table 1).

Milk oral immunotherapy

Petroni and Spergel reviewed 53 publication specific to cow's milk OIT, resulting in a total of 2046 patients [9^{***}]. Review of these data suggested that 12% of patients discontinued OIT for any reason with up to 3.9% of patients who may have discontinued treatment due to symptoms related to EOE. Of the patients on milk OIT, 5.4% had biopsy confirmed EoE.

There have been two subsequent studies reporting EoE in patients undergoing milk-specific OIT since the above meta-analysis. A retrospective study completed in a single-center practice setting described a cohort of 74 patient with milk allergy who underwent OIT therapy [50]. Each patient had a significant allergic history to milk, including previous episode of milk-associated anaphylaxis and concurrent positive skin prick test or serum detected milk-specific IgE. Administration of OIT was based on the Mori protocol [51]. This utilizes end point skin prick testing and seven progressive dilutions to determine the starting dose of OIT. Patients were followed for 10 years. Adverse events resulted in 17.6% of children discontinuing OIT. Of those who discontinued OIT, almost half (46.1%) reported chronic gastroenteric symptoms including abdominal pain, nausea, vomiting, anorexia, and dysphagia, possibly related to EoE onset. In this cohort, an 8.1% incidence of EoE was estimated based on symptomatology alone, however, confirmatory endoscopies were not preformed. Another retrospective review completed by Gómez Torrijos *et al.* [52^{*}] described outcomes for a smaller cohort of 57 children undergoing cow's milk immunotherapy. Within this cohort, three developed gastrointestinal symptoms possibly related to EoE.

Endoscopy was performed on all three symptomatic patients, and histological findings were consistent with a diagnosis of EoE in all cases. This accounted for an overall IT-EOE in the cohort of 5.2%. These patients demonstrated both clinical improvement and histologic remission of EoE after initiating a cow's milk free diet.

Egg oral immunotherapy

A total of 25 publications inclusive of 953 patients were reviewed related to egg OIT in the 2017 Petroni meta-analysis [9^{***}]. Within this group, 11% discontinued OIT for any reason with 2.7% of patients experiencing symptomatic EoE. Of the patients on egg OIT, 4.2% of patients has biopsy confirmed EoE.

Since then, only one case of EoE following baked egg has been reported [53]. This involved an egg-allergic adult patient on baked egg OIT at maintenance dosing. Symptom onset of EoE was notably 3 years after initiation of OIT therapy and positive endoscopy was performed in this case to confirm the diagnosis of EoE.

EOSINOPHILIC ESOPHAGITIS SECONDARY TO SUBLINGUAL IMMUNOTHERAPY

Although, EoE is associated with food allergy in the majority of patients, aeroallergens also appear to be significant antigenic triggers of EoE in a subset of patients. This is not entirely surprising, as a significant majority of patients with EoE have comorbid atopic conditions including allergic rhinitis, atopic dermatitis, and asthma. In fact, there is evidence to suggest that cross-reactivity to aeroallergen and food allergen may contribute to esophageal inflammation [54], though differentiating etiologic triggers in individual patients provides an additional challenge. Aeroallergen-sensitive EoE may therefore represent a distinct EoE endotype [39^{*},55–58]. There have been multiple reviews demonstrating distinct seasonal variability in EoE diagnosis. A retrospective review completed by Moawad *et al.* [59] identified 127 biopsy confirmed patients with EoE. Daily pollen counts for grass, trees, and weeds were obtained and correlated with each date of diagnosis. Thirty three percentage of patients were identified in the spring and 16% were diagnosed in the winter. Another retrospective study by Almansa *et al.* [60] also came to a similar conclusion. In this study, a total of 41 patients were reviewed, with EoE diagnoses found at higher rates during the months of April and May, as compared with other months. This observation was illustrated yet again by a retrospective review by Iwanczak *et al.* [61] which obtained

Table 2. Rate of eosinophilic esophagitis during sublingual immunotherapy to aeroallergens

	Age/Sex	Duration of treatment	Allergen	Biopsy confirmed?	Intervention	Outcome
Kawashima <i>et al.</i> [10]	53F	18 Days	Cedar pollen	Yes	Discontinued SLIT initiated a PPI	Repeat endoscopy negative at 8 weeks
Miehlke <i>et al.</i> [25]	44F	4 Weeks	Hazelnut, birch, alder	Yes	Discontinued SLIT	Repeat endoscopy negative at 4 weeks
Rokosz <i>et al.</i> [64]	9M	16 Months	Grass, tree, dust mite	Yes	Discontinued SLIT Initiated a PPI	Repeat endoscopy negative at 16 months
Antico <i>et al.</i> [66]	23M	1+ Year 2 Months	Dust mite Grass	Yes	Discontinued SLIT	Repeat endoscopy negative at 4 months
Béné <i>et al.</i> [67]	10F	8 Weeks	Dust mite	Yes	Discontinued SLIT Initiated a PPI	Repeat endoscopy negative at 3 months

EoE, eosinophilic esophagitis; PPI, proton pump inhibitor; SLIT, sublingual immunotherapy.

demographic data on 84 children with EoE. The diagnosis of EoE during the spring (45.2%) was significantly greater compared with the other seasons. This suggests that aeroallergens may affect esophageal eosinophil counts and overall symptoms in certain atopic EoE patients.

Notably, data have also demonstrated patients who experience a 'flare' in EoE symptoms with exposure to aeroallergens [56]. One retrospective study completed by Larsson *et al.* [62] even demonstrated a higher rate of food impaction in patients with EoE during allergy seasons. A total of 314 cases were identified in this study, with a statistically significant increased incidence of food impaction during the summer and fall. Finally, a retrospective review of 1180 patients with EoE completed by Ram *et al.* [63] was the largest cohort to demonstrate biopsy confirmed seasonal variability in EoE. Of all patients with EoE, 160 (14%) were suspected to have aeroallergen-induced EoE based on patient reported symptoms or changes in biopsy specimens during pollen season without changes made in diet. Of these, 32 (20%) demonstrated aeroallergen-associated EoE. Furthermore, within this subgroup, 13 of the 15 with positive skin testing to environmental allergens, demonstrated evidence of aeroallergen sensitization correlating with seasonal exacerbation of EoE symptoms.

To a similar regard, there have been six case reports documenting development of EoE in patients undergoing SLIT to aeroallergens, all of which were biopsy confirmed (Table 2). Of the six case reports, two cases report EoE onset during maintenance therapy [64]. The remaining case reports document diagnosis during up-dosing, which may have important clinical implications and considerations in terms of risk stratification based on SLIT dose and the potential for EoE development [10,25,65,66]. In each of the six cases, SLIT was discontinued and 50% (3/6) also

initiated proton pump inhibitor therapy. All cases documented clinical improvement with 83% reporting pathologic improvement as well. Of the biopsies that were pursued, improvement in EoE histopathology was shown within a time frame of 3–16 weeks. This suggests that SLIT-induced EoE may be a reversible process.

Finally, few studies regarding food-related SLIT have been performed. Currently, four randomized double-blind placebo-controlled trials exist, three studies of peanut SLIT and one study on hazelnut SLIT [67–70]. Reported adverse gastrointestinal symptoms are more specific to IgE mediated reactions and are not suggestive of EoE. There have been no case reports documenting the development of EoE following the initiation of SLIT for the management of food allergy.

To date, there has been no official GRADE analysis of the current evidence for OIT-induced EoE [71]. In a manner similar to the GRADE analysis, we find a moderate quality of evidence for the development of EoE during food OIT, as it was consistently witnessed during several double-blind studies. The evidence for SLIT and EoE is also moderate, as EoE development was seen in double blind trials. The evidence for subcutaneous immunotherapy and EoE is lacking as only case reports exist, suggesting a low quality of evidence.

CONCLUSION

IgE-FA is being increasingly seen as a relatively common and chronic condition in childhood. Accidental food exposure can result in a life-threatening allergic reaction. As such, our field has made considerable progress towards the development of novel therapeutic approaches for this condition. However, like many medical advances, there may be unforeseen consequences. In particular, evidence suggests

that immunotherapy could place individuals at risk for the development of EoE. Importantly, the true incidence of EoE during OIT and SLIT may vary, depending on the methods used to define EoE. In addition, the long-term effect of OIT and SLIT on EoE is unknown.

There are several potential immunologic mechanisms that could account for the clinical association between OIT and EoE. For example, OIT could act through IgE to cause inflammation of the esophagus. This mechanism is slightly different from the traditional model of EoE pathogenesis which is thought to be primarily IgE-independent. Alternatively, or in addition, there could be a rerouting of allergic manifestations away from those that are IgE-mediated (allergic rhinitis and IgE-FA) and towards one that is primarily T-cell-mediated (EoE) [39[■]]. One proposed mechanism of tolerance that could account for this phenomenon is the induction of IgG4 during OIT [72]. IgG4 has several noninflammatory properties including having a low affinity for activating antibody receptors, and forming bispecific and functionally monovalent antibodies that lack the ability to cross-link antigens. IgG4 may therefore competitively interfere with the ability of IgE to activate mast cells and basophils. Although elevations in allergen-specific IgG4 is a known feature of OIT [73], IgG4 is not known to alter allergen-specific T_H2-cell responses. Thus, IgG4 could provide an early and intermediate degree of tolerance to anaphylaxis (such as that seen during OIT to food allergens) while allergen-specific T_H2 cells are activated and can contribute to the development of EoE.

One question that should be addressed is the point at which patients are at highest risk for EoE development secondary to OIT or SLIT: during dose escalation or maintenance therapy. In cases where EoE is diagnosed during up-titration, it is not known whether EoE would persist on continued maintenance dosing or eventually resolve. Further, determining the risk of EoE with age stratification is paramount. At present, studies are underway to determine whether long-term tolerance can be obtained with OIT, and in such cases, we expect that OIT has altered allergen-specific T_H2 cells via other tolerogenic mechanisms such as regulatory T cells. In such cases, we would expect that EoE would also resolve. Regardless, providers should be aware of the potential for EoE during OIT. Further studies should be done to best determine who is most at risk for development of OIT-induced EoE and how should we manage these patients.

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Conflicts of interest

There are no conflicts of interest.

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