

Grand Rounds Review

Management of Eosinophilic Esophagitis During Oral Immunotherapy

Derek K. Chu, MD, PhD^a, Jonathan M. Spergel, MD, PhD^b, and Brian P. Vickery, MD^c *Hamilton, ON, Canada; Philadelphia, Pa; and Atlanta, Ga*

Food allergies are antigen-driven diseases that can lead to IgE-mediated reactions of immediate hypersensitivity (eg, anaphylaxis triggered by a single food) or non-IgE reactions of delayed hypersensitivity such as eosinophilic esophagitis (eg, inability to eat multiple foods manifesting as abdominal pain, choking, dysphagia, vomiting, reflux, food impaction). Although both types of disease have their own unique set of challenges in diagnosis and management, it is a particularly vexing problem when a patient is afflicted by both conditions. This situation can happen when individuals with IgE-mediated food allergy undergo desensitization using currently available forms of oral immunotherapy. In this Grand Rounds Review, we review diagnostic approaches to oral immunotherapy—associated eosinophilic esophagitis, potential relationships between primary and secondary eosinophilic esophagitis, potential management approaches, areas of uncertainty, and upcoming research. Optimally supporting patients in their journey with food allergy requires shared decision making regarding alternative management strategies and the stimulation of robust research. © 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2021;■:■-■)

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CASE PRESENTATION

D.J.B. is a 7-year-old boy with mild perennial allergic rhinitis with spring seasonal exacerbation, a history of resolved infantile gastroesophageal reflux that at one point required proton pump inhibitor (PPI) treatment, and peanut allergy. His peanut allergy

was diagnosed at age 18 months after he had a reaction with diffuse urticaria and vomiting with first oral exposure. His sensitization measured by skin prick test during an allergy consultation showed a 12-mm mean wheal diameter and specific IgE to peanut of 28.5 kUA/L. Over the next 5 years, he had 5 reactions including 2 episodes of anaphylaxis leading to emergency visits with the use of epinephrine autoinjector. These repeated reactions resulted in significant parental anxiety over possible future accidental exposures. Through shared decision making, the family preferred a therapy that entailed him eating small quantities of peanut in controlled settings to potentially relieve anxiety related to reactions from possible future accidental exposures. They evaluated the increased rate of reactions from currently available forms of oral immunotherapy (OIT) versus unintended real-world exposure, increased cost of therapy of OIT, following a strict regimen, and additional engagement with the medical system (including need for Risk Evaluation and Mitigation Strategy if a commercial product is used).¹ After initiating peanut OIT and completing a third of up dosing, approximately 40 mg out of a target 4000 mg daily dosing of peanut protein, D.J.B. began to have recurrent abdominal pain and intermittent vomiting (typically within an hour, sometimes delayed by 2-3 hours) associated with ingesting his peanut OIT doses. The symptoms persisted despite the addition of non-sedating second-generation H1 antihistamines and ensuring that the dose was taken with a full meal. Therefore, the joint decision to try to improve peanut OIT tolerability was to lower the dose to 10 mg and extend the interval at that dose for a month instead of the usual 2 weeks. Abdominal symptoms nevertheless continued and lansoprazole 30 mg twice a day was added. There was no improvement in abdominal symptoms on lansoprazole. Instead, the family reported vomiting and regurgitation occurring with meals despite no other food ingestion for the 12 hours after the daily peanut OIT dose. An esophagogastroduodenoscopy was arranged a week later, and the patient discontinued OIT. Endoscopy showed mild to moderate esophageal

^aDepartment of Medicine, Dept HEI, McMaster and SJHRI, Hamilton, ON, Canada

^bDivision of Allergy and Immunology, Children's Hospital of Philadelphia, Department of Pediatrics, Perelman School of Medicine at University of Pennsylvania, Philadelphia, Pa

^cEmory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, Ga

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Corresponding author: Derek K. Chu, MD, PhD, McMaster Children's Hospital HSC-3V41, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada. E-mail: chudk@mcmaster.ca. Or: Jonathan M. Spergel, MD, PhD, Children's Hospital of Philadelphia, 3550 Market St, Philadelphia, PA 19104. E-mail: spergel@email.chop.edu. Or: Brian P. Vickery, MD, Emory University School of Medicine, 2015 Uppergate Dr, NE, Atlanta, GA 30322. E-mail: bpvick@emory.edu.

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*Abbreviations used**EoE- Eosinophilic esophagitis**GI- Gastrointestinal**OIT- Oral immunotherapy**PPI- Proton pump inhibitor**RCT- Randomized controlled trial*

edema, furrows, mild gastritis, and an unremarkable duodenal bulb. Multiple esophageal biopsies were taken from at least 2 esophageal levels: 2 at the lower esophagus and 2 at the upper esophagus following recent American College of Allergy Asthma and Immunology and American Academy of Allergy Asthma and Immunology Joint Task Force for Practice Parameters and American Gastroenterology Association guidance and general consensus guidelines.^{2,3} While awaiting the biopsy results, the patient's family shared that in retrospect, before starting OIT, D.J.B. frequently would eat meals slowly and only after chewing them extensively, and often drank liquid with meals to "wash down any leftover food into my belly."

The approach to abdominal pain associated with nausea and vomiting is broad, especially in school-age children. In this case, the association of the onset of abdominal pain and vomiting with OIT along with temporal worsening of symptoms after dosing, at least initially, is suggestive of OIT as causing eosinophilic esophagitis (EoE). The differential diagnosis, however, includes other common causes of childhood abdominal pain such as constipation, gastroesophageal reflux, infectious disease, inflammatory bowel disease, irritable bowel syndrome, celiac disease, esophageal dysphagia (ring, stricture, dysmotility disorder, etc), and other inflammatory, infiltrative, or structural causes including other eosinophilic gastrointestinal (GI) disorders. In this case, other causes including immediate IgE-mediated GI reactions from OIT, anxiety from previous food reactions, and/or adhering to the OIT regimen also needed to be considered.

If EoE is confirmed in a patient undergoing OIT, the second question is its etiology. Is this a primary process, a condition with approximately 0.026% prevalence (1 in 3846),^{4,5} occurring coincidentally with or unmasked/exacerbated because of OIT, or is it a secondary, iatrogenic process that would not have occurred had the patient not attempted OIT (risk estimates discussed below)? Although we are learning more about subtypes of EoE and their underlying immunobiology,⁶ in this Grand Rounds Review, we review diagnostic approaches to OIT-associated EoE, potential relationships between primary and secondary EoE, potential management approaches, areas of uncertainty, and upcoming research (Table 1).

WHEN SHOULD I WORRY THAT IT IS EoE?

Abdominal pain and vomiting, among other adverse events, are common during conventional peanut OIT,^{1,7} but the available randomized controlled trials (RCTs) have detected only a few events of EoE.^{1,8-10} In addition to the usual diagnostic challenges facing EoE including the patchy nature of biopsy findings, estimates of the incidence of OIT-induced EoE cases are limited and are at risk of a large underestimation because (1) RCTs did not systematically evaluate all research participants with GI symptoms for EoE; (2) patients with food allergy, and perhaps other conditions, may have eosinophilia (tissue level and/or peripheral blood) at baseline; (3) endoscopy provides a

single (snapshot) assessment as to the current presence or absence of EoE; and (4) the sample size and duration of individual RCTs may have not been large enough or long enough to reliably estimate OIT-associated EoE incidence, analogous to the uncommon but important safety signals undetected in pivotal RCTs addressing coronavirus disease 2019 vaccines but that were estimated more clearly only after the general public vaccine rollout. In addition, patients with IgE-mediated food allergy are at increased risk for EoE,¹¹ which would also increase the occurrence of EoE from OIT.

Estimating EoE risk precisely is difficult because endoscopies are required but they are an invasive procedure that is not routinely done before, during, and after OIT build-up or maintenance. Furthermore, patients developing abdominal symptoms with OIT may first experience immediate hypersensitivity symptoms to their dosing, due to the rich presence of mast cells lining the GI tract, before developing OIT-associated EoE. For example, initial vomiting episodes may be due to activation of mast cells in the GI tract and be mistaken as EoE. If an upper endoscopy is done, then the biopsy may be normal and misleading (false negative for EoE features), because chronic exposure to the allergens may then cause EoE to subsequently develop.

Estimates of OIT-induced EoE or EoE-like symptoms range from 5% to 20% if just based on abdominal symptoms, leading to discontinuation.^{9,12} Other studies have tried to measure esophageal eosinophilia: Wright et al¹³ examined esophageal eosinophilia associated with peanut OIT in 21 adult patients at baseline. They found that 3 patients (14%) had evidence of EoE with greater than 15 eosinophils per hpf and classic findings of edema and furrowing on the endoscopy, suggesting that many patients undergoing peanut OIT may have asymptomatic esophageal eosinophilia at baseline. In a follow-up study, 10 subjects (7 active/3 placebo) had endoscopy at 52 weeks and 12 subjects had endoscopies at 104 weeks.¹⁴ Six participants (57%) had worsening or new-onset esophageal eosinophilia (>15 eosinophils/hpf) at week 52. However, 4 of 6 patients had resolution of esophageal eosinophilia at week 104. One patient developed EoE within the study and was treated with PPI, and the rate of spontaneous resolution of the study population is otherwise is unknown. These findings suggest a very high rate of baseline esophageal eosinophilia before starting OIT in adults, and higher than previously estimated, but resolution in some patients with either natural history or medication. There are no data on children, but it is an area that should be actively explored.

Patients with IgE-mediated food allergy are approximately one hundred times more likely to develop EoE compared with the general population (which would bring the rate to 2.6%),¹⁵ which is similar to the rate found in a recent review of OIT-induced EoE⁹ of 5%. Patients who spontaneously outgrow their IgE-mediated food allergy can also develop EoE to the same food.¹⁶ These findings suggest that patients may have both IgE and EoE reactions to the same food. It is thus possible that OIT is simply uncovering EoE that might have occurred regardless.

Although OIT-associated EoE can develop at any point in therapy, there are, conceptually, 2 time points for developing EoE or EoE-like symptoms during OIT. Most seem to appear early in the course of treatment as in our representative patient case. But, there are also reports that slower to develop cases can occur, with symptoms developing 2 to 3 years after starting OIT.¹⁷⁻²⁰ Early onset OIT-induced EoE often manifests as

TABLE I. OIT-associated EoE, key points

Definition	Development of new diagnosis of EoE after starting OIT
Epidemiology	Symptoms suggestive of EoE have been reported to occur in 14%-57% of individuals, but obtaining precise estimates has been challenging for multiple reasons Approximately 5% of food-allergic patients develop EoE, even in the absence of OIT, but potential range is 0.5%-30% depending on definition
Etiology	Food-induced non-IgE disease assuming through T-cell–dependent mechanisms; possible contribution of impairment in esophageal barrier
Prognosis	Very low quality evidence suggests patients can improve when the food is eliminated and that some develop persistent EoE despite cessation. Most studies have been retrospective, with only 1 prospective study to date
Investigations	Consideration of differential diagnoses and endoscopy is common for suspected EoE. EoE-specific questionnaires are often used in research. Noninvasive diagnostic approaches for EoE are in development
Clinical presentations	Increased symptoms of esophageal dysfunction: - o Dysphagia - o Food impaction - o Food refusal - o Heartburn - o Regurgitation - o Vomiting - o Chest pain - o Odynophagia - o Abdominal pain - o Malnutrition Several reports suggest that OIT-induced EoE tends to present early during up dosing, but cases have been reported well into maintenance phase
Treatment	Removal of culprit food (cessation of OIT) and support for allergen avoidance Addition of PPI Topical steroids Enrollment into a randomized trial Future: Biologics or safer desensitization approaches

vomiting and/or abdominal pain with OIT. But if the symptoms resolve with just non-PPI treatment, OIT-induced EoE is less likely. However, if the symptoms persist on PPI, the diagnosis of EoE is more likely. For the late developing patients with general GI symptoms, the workup would be similar to that for regular patients with EoE.³

For the case presented in the vignette, at least 3 scenarios exist to explain his EoE: (1) He could have had it at baseline as indicated by his underlying symptoms of dysphagia and esophageal dysfunction, and increasing symptoms with OIT reflected the natural course of his underlying EoE; (2) the peanut OIT exacerbated his underlying EoE with worsening symptoms; and (3) peanut OIT-induced new-onset EoE and previous symptoms of dysphagia were not related to EoE.

HYPOTHESIZED PATHOGENESIS OF OIT-INDUCED EoE

The uncertain pathogenesis and pathophysiology of OIT-induced adverse reactions has led to the hypothesis that GI symptoms are analogous to the immediate (minutes), early (hours), and delayed-onset (eg, 12-24 hours) reactions seen in subcutaneous inhalant allergen immunotherapy. It follows that the immediate symptoms would be predicted to be IgE- and mast cell–mediated and hence, H1 antihistamines and mast cell stabilizers would be beneficial. But, there are no robust randomized trials to inform if this is accurate. RCTs comparing OIT with versus without omalizumab suggest that OIT-induced abdominal symptoms are not IgE-mediated because the use of omalizumab did not reduce the occurrence of prolonged GI side effects due to OIT.²¹⁻²⁴ Therefore, there appear to be 2 types of GI reactions to

OIT: (1) IgE-mediated, which occur within minutes of the start of symptoms, and (2) delayed non-IgE-mediated reactions, which appear to be more like EoE in nature based on symptoms because IgE-mediated are immediate and those like EoE are more delayed. The delayed symptoms or late-onset symptoms from OIT appear to follow the classic pathogenesis of EoE with barrier dysfunction and involvement of T cells, mast cells, and basophils. Indeed, repetitive food allergen ingestion has been used as an experimental mouse model of EoE and shown to induce thymic stromal lymphopoietin to drive eosinophilic and basophilic inflammation, fibrosis, stenosis, and food impaction,²⁵ independent of IgE. More study is needed to understand the pathophysiology of EoE within and outside of the context of OIT.

MANAGEMENT OPTIONS

For the treatment of OIT-induced EoE, the options include stopping OIT or continuing OIT (perhaps with a modification to the dosing regimen) while attempting to treat the EoE. Indeed, EoE is exclusionary for the Food and Drug Administration–approved form of peanut OIT. Baseline EoE has generally been exclusionary in clinical trials of OIT, and little is known about how best to manage EoE once it occurs during OIT. Because EoE is an antigen-driven disease, many providers and patients choose to stop OIT in an attempt to resolve the EoE. The concern with continuing OIT is possible development of stricture if you do not treat the EoE and persistence of EoE even after discontinuation of OIT.¹⁷ However, the treatment decision also depends on how patients and families weigh the choices of the risk of reaction (including potentially anaphylaxis) from an accidental exposure to their allergenic food, versus the

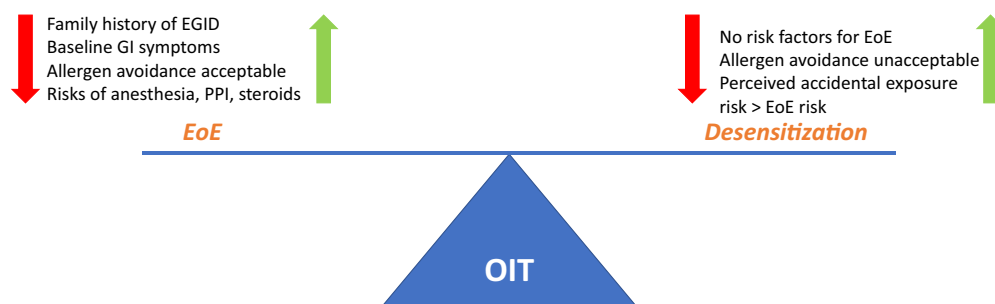


FIGURE 1. Balancing potential benefits and harm for currently available food allergen OIT and complications of associated EoE. *EGID*, eosinophilic gastrointestinal disorders.

benefits and harms of ongoing dysphagia and the additional medication burden to try to relieve it. Many patients and their caregivers would likely place a high value on being able to eat routine meals, and hence, dysphagia is an appropriate reason for discontinuation of OIT. Other families might place a high value on avoiding a reaction from an accidental exposure and less of a value on added medication burden, and therefore wish to continue OIT.

Supporting patients who discontinue OIT is paramount. Advocating through shared decision making is the best management strategy for the patient at the time of evaluation to avoid sunk cost fallacy—the common mistaken reasoning that further investments or commitments are justified because the resources already invested will be lost otherwise. Although beyond the scope of this review, alternative strategies include understanding and enhancing avoidance practices, novel therapies, and enrolling in randomized trials.

For the patients who want to continue OIT and develop EoE, the first approach is the initiation of a PPI. The 2018 AGREE (A working Group on ppi-REE [PPI-responsive esophageal eosinophilia]) changed the diagnostic criteria for EoE and eliminated the need for a PPI trial to diagnose EoE.³ PPI was reframed as a treatment for EoE rather than a lack of response to be a diagnostic criteria. It is additionally confusing with the use of PPI because patients can also develop gastroesophageal reflux disease and general GI symptoms that resolve with PPI. If a patient is already on PPI for gastroesophageal reflux disease, stopping the medication to diagnose EoE is not required. Therefore, in some cases, it may be unclear if the PPI is treating EoE or gastroesophageal reflux disease. Other treatment measures include swallowed steroids such as fluticasone²⁶ or budesonide (eg, 1 mg/4 mL sucralose slurry twice a day, or a not-yet-available orodispersible tablet).^{27–29} Other treatment options, including mechanical and systemic therapies, have a rapidly changing evidence base with latest guidance from the recent practice parameter and their associated systematic reviews.²

Another possibility is that the OIT-induced EoE is temporary and can be treated. The study by Wright et al¹³ found that 57% had worsening or new-onset esophageal eosinophilia after starting peanut OIT. But, 4 of 6 patients had resolution of esophageal eosinophilia at week 104, so the exact rate of spontaneous resolution is unknown. Two independent groups looking at peripheral blood eosinophils in patients experiencing abdominal pain on OIT proposed new terms to describe incident gastrointestinal symptoms during OIT: OIT-induced gastrointestinal symptoms and eosinophilic response¹⁹ and EoE-like OIT-related

syndrome.¹² In the first study, a series of 65 patients, the authors slowed the dosing interval or reduced the total daily dose on the basis of the peripheral eosinophil count and the onset of GI symptoms and reported this being associated with improvement in symptoms and resolution of eosinophilia.¹⁹ Similarly, in a series of 270 patients undergoing peanut OIT, 14% (37 of 262 patients) developed EoE-like OIT-related syndrome, with vomiting or abdominal pain occurring 2 hours after the dosing. In this group, 21 of 37 (57%) who developed EoE-like OIT-related syndrome discontinued OIT. Thirteen of 37 (35%) reached maintenance associated with dosing reductions or the use of medications.^{12,30} However, 40 of 270 who began the study discontinued OIT and 16 were not followed; of the 214 who reached maintenance dosing, 25 stopped and 33 were lost to follow-up (in total, 68% stopped or did not report outcome data). Taken together, these 3 case-series studies suggest that OIT-related EoE can occur in 14% to 57% of the patients, some of whom may have had tissue eosinophilia at baseline, and that early, very low-certainty evidence (noncomparative designs at high risk of bias) shows that dose reductions, slowing the interval of dosing, and adding a PPI are potential management strategies that need rigorous study.

In the future management of patients with food allergy who want to pursue conventional forms of OIT, screening for previous or existing EoE symptoms in advance of starting OIT might be enabled by noninvasive EoE biomarker or symptom tools and help identify those in whom OIT would be contraindicated. Similarly, these noninvasive biomarkers could monitor patients during OIT build-up and maintenance. However, there are as of yet no noninvasive and reliable biomarkers for the diagnosis of EoE or OIT-induced adverse effects. A number of promising approaches to biomarkers or other less-invasive methods are being developed (such as esophageal string test,³¹ cytosponge,³² peripheral blood eosinophil progenitors,²² or food-specific T-cell activation³³), and the availability of such techniques may help answer these critical questions by overcoming a key problem in diagnosis, which is the dependence on esophagogastroduodenoscopy. It should be noted that in general, peripheral blood eosinophil counts are not helpful to diagnose or monitor EoE because they may be normal in affected patients.³⁴

FUTURE DIRECTIONS

In these types of scenarios, shared decision making^{35,36} needs to take place balancing the potential reduction of anxiety of future immediate hypersensitivity reactions from accidental

allergen exposure if OIT is stopped versus the need for additional medications to treat their EoE, and the potential for long-term sequelae if the EoE is not controlled (Figure 1). Complicating this decision-making process is the possibility that a patient might have underlying EoE before starting OIT and simply stopping OIT will not stop the symptoms. Without robust evidence on the values and preferences of patients, decision making around current forms of OIT requires transparent discussion about multiple competing risks and uncertainties: (1) the potential undesirable consequences of OIT or (2) the associated adverse events and their consequences, including EoE and the uncertain treatment strategies reviewed above, (3) a potential for OIT to reduce risks of immediate hypersensitivity reactions from accidental exposure and therefore, family anxiety, and (4) a potential for other current and future treatment options, including avoidance and enrollment into an RCT, to fulfill their goals. Each family may have different values, and shared decision making is critical to determine what might best match the individual patient's goals.

In the future, before starting OIT, it would be logical to screen patients for EoE either by questionnaire or by possible noninvasive biomarkers.³⁷ The use of noninvasive tests (eg, cytosponge and esophageal string test) can help monitor patients with abdominal symptoms for development of EoE. Future tests such as peripheral food-specific T-cell activation might also predict which patients are at risk for developing EoE to the food.

Additional therapies to treat EoE or OIT-induced EoE are under development. Multiple biologics (anti-Siglec 8, anti-IL-13, or anti-IL-4 receptor- α)^{32,38} are in clinical trials for the treatment of EoE³⁹ and could be used in the future to treat OIT-induced EoE in addition to the current PPI and swallowed steroids, if supported by evidence. Families will have to weigh the benefits of OIT versus the cost and benefits/risks of additional medical therapies. Another option would be to use immunotherapeutic approaches that either do not appear to induce EoE or are associated with a lower rate. Several novel forms of immunotherapy using modified antigens and/or different doses and routes of administration for the treatment of food allergy are currently under study. For example, epicutaneous immunotherapy has been shown to treat milk-induced EoE, suggesting that it may lead to a lower rate of food-immunotherapy-induced EoE.^{40,41} Similarly, sublingual immunotherapy appears to have a lower rate of EoE compared with OIT.⁴² Each individual and their family would have to evaluate the benefits and risks of each therapy and treatment to help guide their decisions.

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