Risk factors for reactions and adverse effects during oral immunotherapy

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ABSTRACT

Oral immunotherapy (OIT) involves the potential for a variety of adverse events, which range from serious systemic reactions that require epinephrine to minimal oral reactions that require no treatment. This chapter describes common types of reactions seen in the course of OIT, reviews the frequency of and risk factors for different types of events as reported in recent literature (with a focus on real-world reports from private practice), and discusses treatment strategies for these adverse events. As the availability of OIT expands, it is paramount to ensure that allergists who offer OIT have a robust understanding of these reactions and mechanisms, with the overarching goal being the safety and tolerability of the therapy for the individual patient.

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EPINEPHRINE-TREATED REACTIONS

Severe systemic reactions and the need for autoinjectable epinephrine treatment of such reactions cause great anxiety for patients in OIT, caregivers, and providers alike. As with any desensitization therapy, the process itself carries a low but measurable risk of serious, immediate hypersensitivity reactions. Fortunately, such reactions are rare overall, and the frequency diminishes with increased duration at maintenance dosing. There also are several well-recognized cofactors that increase the likelihood of such a reaction and, as such, can generally be avoided to reduce this risk.

In general, the frequency of epinephrine-treated reaction (ETR) during OIT is <1 ETR per 1000 doses delivered. In a large survey of 352 patients with > 240,000 OIT doses delivered for peanut OIT, Wasserman *et al.*[1] reported a rate of 0.7 ETRs per 1000 doses delivered during dose escalation and a rate of 0.2 ETRs per 1000 doses delivered during the maintenance-phase OIT. In another large study, Afinogenova *et al.*[2] noted a dose escalation ETR rate of 0.6 per 1000 doses and a maintenance-phase ETR rate at 0.5 per 1000 doses. Also, Soller *et al.*[3] described a combined dose escalation and maintenance rate of ETR at 0.3 per 1000 doses delivered during peanut OIT in both academic and community settings, although this study was limited to children ≤ 5 years old, who tend to have an overall better safety profile.

It should be noted that all of the above data refer explicitly to peanut OIT, which may not be generalizable to all allergens. For instance, Keet *et al.*[4] note a combined rate of ETR for milk OIT at ~0.2 ETR per 1000 doses delivered, combining escalation and maintenance phases, similar to the peanut literature. However, in a large Israeli cohort of >1000 patients with OIT, milk OIT was associated with a significantly higher rate of ETR versus OIT with other foods.[5] It should also be noted that, although ETRs are more common during the escalation phase, they can occur even after years on maintenance dosing. Also, the Peanut Allergen immunotherapy, Clarifying the Evidence study[6] provides insight from a meta-analysis of nine included randomized peanut OIT trials, which included epinephrine usage data. In this study, the investigators report a risk ratio of 2.21 for ETRs during OIT (combining build and maintenance phase) versus the avoidance groups.[6]

Given that one of the primary motivations for pursuing OIT is avoidance of accidental reactions (as well as the fear associated with potential reactions), avoidance of ETRs during OIT treatment is highly desirable, both from a safety and a patient anxiety standpoint during OIT. There are several recognized risk factors that contribute to the propensity for an ETR during OIT. These include the following: immediate exertion after dosing; dosing on an empty stomach; poorly controlled asthma; and dosing when ill, particularly with a febrile illness.[2,7] Higher peanut specific immunoglobulin E (IgE) levels before starting OIT and a history of systemic reaction during the buildup phase were the best predictors of systemic reaction during the maintenance phase.[2]

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Overall, ETRs during OIT remain relatively rare events, and many of these are potentially avoidable by adherence to good dosing practice and avoidance of known risk factors. For patients with high food-specific IgE levels, OIT can still be successful, but care should be given over to counseling with regard to a potentially higher risk of ETR. More gradual buildup protocols or the use of adjunctive therapies, *e.g.*, omalizumab, to enhance OIT safety should also be considered in patients who are highly sensitized. Of note, a report that used a gradual OIT protocol for peanut desensitization (keeping the maximum percent increase to 25% and achieving 250 mg of peanut protein maintenance across 33 steps compared with one-third or fewer steps for typical protocols) resulted in no ETRs.[8]

EOSINOPHILIC ESOPHAGITIS AND EOSINOPHILIC ESOPHAGITIS–LIKE OIT-RELATED SYNDROME

Both eosinophilic esophagitis (EoE) and eosinophilic esophagitis-like OIT-related syndrome (ELORS) are non-IgE adverse events associated with peripheral and tissue eosinophilia. Prototypical EoE implies upper gastrointestinal (GI) symptoms, including dysphagia, reflux, food regurgitation, and food impaction, whereas ELORS, as noted by Wasserman *et al.*,[9] is a characteristic pattern of vomiting after OIT dosing, which typically occurs between 2 and 8 hours after dosing.[9] Essentially, the same phenomenon has been identified by Goldberg *et al.*,[10] which they termed OIT-induced GI and eosinophilic responses. Because OIT can also induce frequent GI symptoms related to immediate hypersensitivity, it is important to distinguish abdominal pain, nausea, and emesis, which occurs immediately after OIT dosing (*i.e.*, within 30 minutes), which is more characteristic of GI mast cell activation, versus the typical delayed GI symptoms of ELORs.[11]

Earlier data with regard to EoE frequency induced by OIT has been reported at a rate of 2.7%.[12] However, this report considered only biopsy-proven EoE, and, because most patients with symptoms suggestive of EoE or ELORS while on OIT do not actually undergo biopsy, this is almost certainly a significant underestimate.[12] A more recent large retrospective review, including symptoms suggestive of EoE or ELORS, such as abdominal pain and emesis (but not biopsy proven), supports an incidence between 8% and 14% of this phenomenon.[13] A similar incidence of ELORS was noted at 14% in a large private practice setting of 270 patients on peanut OIT.[14]

It should be noted that it can be difficult, if not impossible, to distinguish unmasking of latent primary EoE versus truly iatrogenic EoE due solely to the OIT process because there can be a significantly elevated rate of asymptomatic or minimally symptomatic esophageal eosinophilia in patients undergoing OIT.[11] EoE or ELORS typically arises early during dose escalation (weeks to months) at relatively low doses, although it can be recognized less frequently during long-term maintenance.[11,14] ELORS is associated with a significantly slower progression to a target maintenance dose, more than doubling the time to achieve maintenance in a large peanut OIT study from 31 weeks to 69 weeks.[14] Risk factors that may be associated with EoE or ELORS include baseline absolute eosinophil count > 600 cells/uL, higher starting OIT dose, and more rapid dose escalation.[10]

The development of EoE or ELORS secondary to OIT is concerning but does not necessarily warrant immediate cessation of therapy. Many patients and parents are committed to OIT, irrespective of adverse effects or complications, so a shared decision-making process with a clear discussion of risks and benefits is necessary before a decision to proceed or stop therapy is made. A reasonable first-line treatment is a short course of proton pump inhibitor, which might vary in length from 1 to 4 weeks.[14] Furthermore, there is promising evidence that reducing the allergen load by reducing the dose and/or increasing the dosing interval may result in clinical remission of EoE or ELORs and the therapy may be continued at a decelerated rate or, indeed, temporarily paused.[10] During such a dose deceleration (or dosing pause) strategy, monitoring the AEC may be helpful, although it should be noted that peripheral and tissue eosinophilia are poorly correlated.

Because it is impractical in most community OIT practices to obtain a biopsy specimen to prove EoE, a clinical diagnosis is needed based on symptoms and perhaps AEC elevation. However, if there is no improvement in apparent EoE or ELORs symptoms despite PPI and/or dosing deceleration, obtaining an Esophagogastroduodenoscopy with biopsy may be warranted to prove the suspected etiology. In the future, less-invasive methods that provide a direct measurement of GI tissue eosinophilia (esophageal string test, cytosponge) may become more commonplace.[11] Also, it should be noted that many consider preexisting EoE to be an absolute contraindication to initiating OIT, but there may be unique circumstances in which OIT can be considered in a patient with known EoE.

NON-ELORS GI ADVERSE EVENTS

Mild or moderate GI symptoms, such as dyspepsia or abdominal pain, are highly prevalent in OIT but are not generally limiting in terms of progression to a maintenance level. In a large retrospective review in private practice OIT, 68% of the patients had abdominal symptoms during dose escalation, but this was decreased dramatically, to only 13% of the patients at maintenance dosing.[2] It is important to distinguish such mild, non–dose-related GI adverse effects from

Table 1 **Risk Factors for Reactions in OIT**

Risk Factor	Suggested Intervention
Exercise and/or overheating*	Avoiding strenuous exertion 1 hr before and 2 hr after dosing
Dosing on an empty stomach*	Ensure that the dose is taken with a meal or snack
Febrile illness*	Avoiding dosing within 24 hr of febrile illness
Unstable asthma*	Ensure asthma is well controlled before starting OIT and routinely monitored during OIT
Oral wounds	Avoid dosing with any oral surgery wound while healing (typically 1–2 days after a procedure)
Menses	Consider dose reduction during the menstrual cycle in some females (does not affect all)
NSAID usage	Consider using acetaminophen for fever and/or pain during OIT
Dehydration	Ensure that patients on OIT are adequately hydrated
Sleep deprivation	Ensure that patients on OIT have adequate age-appropriate sleep and follow a scheduled dosing pattern

OIT = Oral food challenge; NSAID = nonsteroidal anti-inflammatory drug.
**A major factor.*

either immediate and severe abdominal pain and vomiting (within 1 hour of dosing, which is highly likely to be an IgE-mediated reaction) or ELORS, which is reviewed above. Mild GI symptoms often occur entirely separate from dosing (≥12 hours separation) and are often insignificant enough that they are not always remarked on by patients or parents.

However, because they can be uncomfortable, a dose reduction–interval increase strategy (similar to that used in ELORS) may be helpful. Some providers and patients may elect to dose through such symptoms, so long as they are not severe, but a reasonable metric would be to target at least 7–14 days symptom-free before a dose increase is attempted.[15] Many OIT physicians have used probiotics for such symptoms, although there is relatively little published evidence for this practice. Also, gastroesophageal reflux disease medications such as H2 blockers or PPIs may be considered but, because these symptoms are often mild, a medication approach is often not necessary. Again, it is highly relevant to ensure that either a GI manifestation of an immediate IgE-mediated reaction or that EoE or ELORS is not being missed. However, both of these phenomena should be fairly easy to distinguish based on timing and clinical presentation (the former occurring within 60 minutes and often associated with respiratory or cutaneous symptoms, the latter being typified by vomiting 2–8 hours after dosing).

CONTACT REACTIONS AND ORAL ADVERSE REACTIONS

Contact reactions such as perioral hives or mucosal reactions, including mouth and/or throat itching, are fairly common but not worrisome in isolation. A large retrospective analysis noted that 48% of the patients experienced oral itching and 28% of the patients had at least one episode of hives during dose escalation.[2] It is important to educate parents and patients that such reactions are common, and, although they should be monitored, do not typically indicate a more serious reaction to come but rather are part of the desensitization process. It is not necessary to treat all such symptoms because they are typically self-limited. However, treatment with a rapid-acting but nonsedating H1 antihistamine, *e.g.*, cetirizine, is reasonable if these symptoms are uncomfortable or noted several days in a row. If frequent antihistamine is required, then consideration should be made for dose reduction or delay in updosing because persistent mild symptoms suggest a lack of adequate desensitization.[15]

PATIENT CONTACT STRATEGIES

It is of crucial importance that parents have a ready mechanism to contact providers outside of office hours in the event of a serious reaction or adverse event during OIT. Although mild and transient adverse effect issues can be reported at the time of updosing, any severe reaction should be reported immediately so that reaction management advice can be offered and any necessary dosing adjustments made. Traditional after-hours telephone messaging systems may suffice, but providers may wish to consider a dedicated OIT cellphone to facilitate more rapid text or video messaging. However, parents should be instructed that a severe, multisystem reaction should always be treated with autoinjectable epinephrine, identical to any other food reaction.

Parents should also be educated that administration of epinephrine should not be delayed while awaiting provider contact. Although it remains an area of some

controversy, in the era of the coronavirus disease 2019 pandemic, it is acceptable to administer epinephrine and then monitor at home, assuming immediate improvement and the ability to contact the OIT provider, who ideally may be able to conduct a virtual survey of the patient *via* a video call. Epinephrine is not a fundamentally dangerous medication, and, in the context of an OIT reaction, even one that requires epinephrine, the need for emergency department observation and/or emergency medical services activation should be judged by the clinical response of the patient, the need for additional medical care, and any evidence of biphasic or prolonged anaphylaxis.[16] Fundamental to this assessment is the ability of the parent and/or patient to reach the OIT provider in a timely manner during such a reaction.

PATIENT DOSING PRECAUTIONS

There are several dosing precautions that are foundational in OIT, which have been long advised to enhance the safety of OIT. Several of these practices are universal in OIT practices, and there are, as well, a number of situational or procedural dosing risks (Table 1). The most important precautions are the following:

a. No vigorous exercise around the time of the dose (typically 1 hour before and 2 hours after dosing but some patients may require as long as a 4-hour postdose rest period)
b. Ensure dosing at the time of a snack or meal and/or avoid dosing on an empty stomach
c. Avoid dosing if ill, in particular, with febrile illness

All three of the above precautions can potentiate immediate reactions, in some cases, requiring epinephrine.[2,7,15] There are a number of other considerations that can be risk factors for reactions, which can include nonsteroidal anti-inflammatory drug use, a recent dental procedure or oral surgery, menses, or unstable asthma, among others.[15] Sleep deprivation and dehydration have also been identified as risk factors for food anaphylaxis, and, although not specific to OIT, providers should be cognizant of these potential reaction cofactors.[17,18] All of these require consideration of individual patient circumstances; a history of a certain trigger may require extra precautions for a given patient.

CLINICAL PEARLS

- ETRs due to OIT are relatively rare events that occur at a frequency of generally < 1 ETR per 1000 doses delivered.
- A significant number of these reactions occur due to cofactors, such as immediate exertion, dosing on an empty stomach, or febrile illness, which are avoidable with diligent adherence to good dosing practices.
- ELORS is a fairly common GI reaction, characterized by vomiting 2–8 hours after dosing; this should be distinguished from both an immediate IgE-mediated reaction as well as nonspecific GI symptoms that are also common in OIT; risk factors for ELORS include an elevated baseline eosinophil count and more rapid dose escalation protocols.
- A robust communication strategy for after-hours concerns is essential in OIT; this may involve text messaging or video calling for rapid information exchange, patient assessment, and treatment advice.

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