

Triggers for Home Epinephrine-Treated Reactions During Oral Immunotherapy for Food Allergy



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What is already known about this topic? Severe home reactions to previously tolerated doses are a main safety limitation of oral immunotherapy (OIT). Previous descriptions of potential triggers for such reactions are limited by their small sample sizes.

What does this article add to our knowledge? We identified triggers (physical exercise, fatigue, and concurrent infectious disease) and protocol-dependent (dose size, dosing interval) and -independent factors (seasonality) associated with home epinephrine-treated reactions in a large group of patients undergoing OIT for various foods.

How does this study impact current management guidelines? The identification of triggers and various factors associated with home epinephrine-treated reactions during OIT may assist both caregivers and patients in minimizing the risk for such reactions and improving treatment safety.

BACKGROUND: Home reactions requiring epinephrine treatment represent a significant obstacle to oral immunotherapy (OIT) and impair treatment outcome.

OBJECTIVE: To identify potential triggers for such reactions for improvement of patient safety.

METHODS: All patients aged older than 3.7 years who began an open-label OIT treatment program to milk, peanut, egg, sesame, or tree nuts in the Institute of Allergy, Immunology, and Pediatric Pulmonology at Shamir Medical Center between April 2010 and March 2018 were enrolled. Information on home epinephrine-treated reactions (HETRs) during the up-dosing phase of OIT was collected from the documentation in patients' files and the reports were transmitted by email and via a web reporting system.

RESULTS: A total 1,270 OIT treatments were included (milk 780; peanut 256; egg 63; sesame 72; and tree nuts 99). Home epinephrine was administered in 200 treatments (15.7%) and in 70 of them a second epinephrine-treated reaction occurred. The

leading identified triggers for HETRs were physical exercise temporally associated with administration of home dose (20%), and dose consumption during infectious disease (16.7%), or when fatigued (13.8%). The rate of first HETRs was highest (10.1%) to doses of 500 mg protein or less and particularly to 300 mg or less. The occurrence of first HETRs was highest (35.5%) during the first and decreased to 13.8% by the last of the 4-week home-treatment phase. Second HETRs occurred in a similar rate throughout these 4 weeks. The incidence of HETRs was highest during pollen season and vacation months.

CONCLUSIONS: The identification of factors, some protocol-dependent, that trigger HETRs should assist in improving OIT safety. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:1070-6)

Key words: Adverse reactions; Epinephrine; Food allergy; Oral immunotherapy; Triggers

INTRODUCTION

Oral Immunotherapy (OIT) is effective in desensitizing patients with a variety of food allergies.¹⁻⁴ Among its benefits, OIT minimizes the risk for anaphylactic reactions to unintentional consumption of allergenic foods,⁵ reduces dietary limitations,⁶ and improves patients' quality of life.^{7,8} For this reason, the practice of OIT has widely spread in recent years, and it is currently being performed in an increasing number of medical centers as well as office-based practices.^{9,10} However, the safety of OIT is hampered by an increased risk for allergic reactions to the treatment doses,^{11,12} mainly during the up-dosing phase.¹³ Therefore, the U.S. Food and Drug Administration approval for a peanut OIT product in children¹⁴ was given under the request of a Risk Evaluation and Mitigation Strategy to mitigate the risk of anaphylaxis associated with this treatment.

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Abbreviations used

HETR-Home epinephrine-treated reaction

OIT-Oral immunotherapy

SHTD-Single highest tolerated dose

Whereas dose escalation during OIT is performed in the clinic and under medical supervision, home doses are given away from medical care, and treatment of reactions might be delayed and inadequate. Most home reactions are mild, and many involve local symptoms that resolve either spontaneously or with administration of antihistamines.^{4,13,15} However, home reactions may be severe and even life-threatening.¹⁶ Therefore, such severe reactions comprise the main safety limitation of OIT. Although the characterization of home reactions during OIT is of paramount importance, their study is limited by the lack of objective and accurate classification, given that they occur in the absence of medical supervision.

Epinephrine administration represents an objective marker for reaction severity, at least as experienced by the patients, and is also associated with increased treatment failure.¹⁷ It can, therefore, provide a tool to study severe reactions at home during OIT.¹⁷ We previously reported on patient intrinsic risk factors (milk OIT, concomitant asthma, and the severity of food allergy) for home epinephrine-treated reactions (HETRs) in 1,100 OIT treatments.¹⁷ Interestingly, however, we recently observed a significant reduction in the incidence of HETRs during the extensive coronavirus disease 2019 (COVID-19) lockdown in Israel, even among patients with such risk factors.¹⁸ This finding suggests that certain potentially avoidable factors might trigger home reactions. Indeed, certain triggers, such as infections, physical exertion, and menses, that might affect the reaction threshold to the allergenic food and lead to reactions to previously tolerated doses were described.^{19,20} Utilizing this information, instructions for the prevention and avoidance of such potential triggers are typically included in OIT protocols.³ However, the information regarding the variety of these associated factors and their relative impact on severe home reactions during OIT is limited and based on small sample sizes.²¹ The current study aimed to identify and characterize the triggers associated with severe home reactions during OIT.

METHODS

Patients

All patients aged older than 3.5 years who began an open-label OIT treatment program to milk, peanut, egg, sesame, or tree nuts (walnut, cashew, hazelnut, or almond) at the Institute of Allergy, Immunology, and Pediatric Pulmonology at Shamir (formerly Assaf-Harofeh) Medical Center, Zerifin, Israel, between April 2010 and March 2018 were enrolled. The program is designated for patients who have passed the age of 3.5 years to allow for spontaneous recovery. Eligibility for OIT was based on evidence of immunoglobulin E to the target food together with a history of a recent (within the last year) reaction, including objective symptoms, to the specific food, or a positive oral food challenge.²²⁻²⁵ A minimal tolerated dose of 5 mg protein for milk and of 1 mg in the case of all other foods was required to initiate OIT. Patients with stable asthma and those previously hospitalized for severe anaphylactic reactions were included. Informed parental or patient (for those aged >18 years) written consent for treatment was obtained from all participants. Approval for the documentation and publication of all patient data

was obtained from the Helsinki Institutional Review Board Committee.

Pre-OIT assessment

A comprehensive medical history was obtained from each patient/parent and skin prick tests were performed to the treated food and to house dust mite (as a surrogate marker for allergic rhinitis in Israel).²⁶ All patients who were able to perform pulmonary function tests (typically patients aged ≥ 5 years) underwent spirometry, with or without a bronchodilator before OIT (Minispir, Mir; Rafamedical, Yavne, Israel). Uncontrolled asthma was first stabilized for 2 to 3 weeks before OIT initiation. Patients diagnosed with asthma were asked about their current asthma symptoms and performed spirometry at each clinic visit prior to up-dosing.

OIT protocol

The OIT treatment protocols for milk, egg, peanut, sesame, and tree nuts were previously published.²²⁻²⁵ Briefly, the treatment began with an initial 4-day dose-escalation phase aimed to determine each patient's individualized single highest tolerated dose (SHTD), which is the highest dose that did not elicit any objective symptoms, and to confirm the diagnosis of food allergy. The SHTD then served as the starting home dose for each patient. Subsequent dose escalations visits were performed every 4 weeks in an ambulatory care setting, followed by home treatment periods. The initial goal of treatment was to reach a target maintenance dose, in grams of protein, that would provide partial desensitization and protection in the case of accidental exposure: milk, 180 mg milk protein (6 mL); peanut, 300 mg protein (1 g peanut); tree nuts 300 mg protein (2 g of walnut and hazelnut, 1.7 g of cashew); egg, 1500 mg protein (one-quarter omelet from 1 egg); and sesame, 240 mg protein (1 g of Tahini). Patients wishing to consume *ad lib* continued to a full dose of milk, 7,200 mg protein; peanut, 3,000 mg protein; tree nuts, 3,900 mg protein; egg, 12,000 mg protein; or sesame, 4,000 mg protein. Patients unable to reach full or partial desensitization at the end of up-dosing were considered treatment failures.

Home treatment guidelines

Patients were instructed to consume their daily dose at home under the supervision of an adult family member for 1.5 hours and to take the precautions listed in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). In general, other than the limitation surrounding the timing of home doses, patients were allowed to continue their daily routine, including leisure activities and family vacations away from home and abroad. A staff physician was on call 24 hours a day, 7 days a week for consultation. Each patient was prescribed with antihistamines, bronchodilators, and 2 epinephrine autoinjectors. For reactions consisting of either a severe abdominal pain, shortness of breath, or lethargy, or whenever in doubt, patients were advised to administer epinephrine auto-injector and to go to a local emergency room (Table E2; available in this article's Online Repository at www.jaci-inpractice.org). Following such reactions, patients were contacted and asked to send the report from the local emergency room. Based on the circumstances leading to the reaction, staff physicians would then make a joint decision about permanent or temporary protocol modification or discontinuation of treatment.

Home treatment report

Patients were asked to report daily on their home dose consumption, initially (2010-2012) by email, and subsequently using an electronic web reporting system to minimize recall bias.^{27,28} Delayed

TABLE I. Characteristics of patients with HETRs

Characteristics	Parameter	Result
Demographics	Age (y), median (IQR)	7.9 (5.6–11.8)
	Male sex, n (%)	122 (61)
	HDM sensitivity, n (%)	139 (69.5)
	Asthma, n (%)	137 (68.5)
	SPT (mm)	8 (6–10)
Pre-OIT	Anaphylaxis, n (%)	159 (79.5)
	Epinephrine, n (%)	117 (58.5)
	Emergency room, n (%)	142 (71.0)
	Hospitalization, n (%)	58 (29)
Food treated	Milk OIT, n (%)	147 (73.5)
	Egg OIT, n (%)	5 (2.5)
	Peanut OIT, n (%)	26 (13.0)
	Sesame OIT, n (%)	6 (3)
	Tree nuts OIT, n (%)	16 (8)
OIT	SHTD (mg)	22 (12–45)
	Epinephrine-I, n (%)	96 (48)

HDM, House dust mite; IQR, interquartile range; SPT, skin prick test.

entries were allowed to account for temporary technical limitations. Patients were asked to report the details of their reactions, including signs, symptoms, and organ systems involved. In addition, patients could either choose a potential trigger for their reaction out of a list of previously described triggers or report their own perceived triggers for each reaction.²⁸ If no identifiable cause was noted, the patients reported as such.

Patients' reports were continuously monitored and instructions were adjusted as needed by the treating staff.

Data collection and statistical analysis

The information was collected from the documentation in patients' files and the reports transmitted by email and via the reporting web site. Statistical analysis was done using SPSS-20 software. Categorical variables were described with numbers and percentages. Continuous variables were described by means $\pm$ SD (if normally distributed) or medians and interquartile range (non-normally distributed). Rate of HETRs experienced for ranges of home treatment doses are presented with 95% CIs. The Cochran-Armitage trend test was used to explore the trend of HETR rate along the dosages.

RESULTS

Efficacy and safety of OIT treatment

A total of 1,288 OIT treatments began during the study period. Eighteen treatments were discontinued before any home doses were given and were, therefore, excluded (9 milk OIT treatments owing to a SHTD $<$ 5 mg protein, and 9 treatments owing to lack of cooperation). Of the total 1,270 treatments included, OIT was administered to milk in 780 treatments (61.4%); peanut in 256 (20.2%); egg in 63 (5%); sesame in 72 (5.7%); and tree nuts in 99 treatments (7.7%). Patients' characteristics are detailed in Table E3 (available in this article's Online Repository at www.jaci-inpractice.org). By March 2018, 31 of the patients were still in the up-dosing phase and did not achieve a final disposition. Of the remaining 1,239 patients, 889 (71.8%) achieved full desensitization to the treated food, 220 (17.8%) were partially desensitized, and the remaining 130 (10.5%) patients failed OIT.

Home epinephrine was administered in 200 of the 1,270 treatments (15.7%). Patients who experienced HETRs were at a median age of 7.9 years and 61% were males (Table I). Most patients (68.5%) had asthma and most (58.5%) had anaphylactic reactions to the treated foods requiring injectable epinephrine treatment, prior to starting OIT. The proportion of HETRs varied between the treated foods, from 7.9% of the treatments in egg to 18.8% in milk OIT (Table I). A total of 142 of the 200 patients (71%) who experienced HETRs were either fully ($n = 68$) or partially ($n = 74$) desensitized at the end of OIT, 48 patients (24%) failed, and 10 patients were still in treatment. In 70 of these 200 OIT treatments (35%), 2 epinephrine-treated reactions were experienced, resulting in a total of 270 HETRs that were analyzed together. Twenty-seven patients experienced more than 2 HETRs during a single OIT treatment and, overall, 38 HETRs were added. These reactions comprise a separate set with distinct features and were, therefore, analyzed separately, given the finding of a high rate of reports of epinephrine administration due to nonmedical reasons (Table E4; available in this article's Online Repository at www.jaci-inpractice.org), and the team impression that some of the patients had learned to appreciate the rapid relief of symptoms obtained with epinephrine treatment and used it too liberally. Overall, a total of 270 HETRs were included for further analysis in this study (Figure 1).

Characteristics of HETRs

Of the 270 HETRs analyzed, information regarding symptoms experienced and organ systems involved was missing in 44 reactions (11 of those were the second HETR in that patient) (Table II). Of the 226 HETRs with available information, the respiratory system was the organ system most commonly affected ($>90\%$), and 175 (77.4%) of HETRs involved more than a single organ system. In cases of HETRs with a single organ involvement, the respiratory system was involved in 37 cases, whereas the skin and gastrointestinal systems were involved in 7 cases each. The cardiovascular system was involved in 2 multi-system reactions, with a significant decrease in blood pressure. Symptoms and organ systems involved in first and second HETRs were comparable (Table II).

Monthly variability was observed in the rate of HETRs during the year (Figure 2). The highest number of HETRs were experienced in April (the peak pollen season) and August (the peak vacation season), with more than 25 such reactions in each of these months. In contrast, only 14 such reactions were reported in February and 18 in September; in all other months, 20 to 25 HETRs were reported.

Protocol-associated factors for HETRs

The doses eliciting HETRs are presented in Figures 3, 4, and E1 (available in this article's Online Repository at www.jaci-inpractice.org). The rate of first HETRs was highest 10.1% (95% CI, 8.4–11.98), at doses of 500 mg protein or less (Figure 3). This rate decreased substantially to 3.3% (95% CI 2.31–4.56) at doses of 501 to 1,000 mg, with further decrease to less than 1% at doses greater than 1,500 mg. This finding was also true for the second HETRs, which naturally occurred for higher doses, with 3.25% (95% CI 2.3–4.45) at doses of 500 mg protein or less and less than 0.5% at higher doses (Cochran-Armitage trend test P value $<$.0001 for first HETR and $P = .0008$ for second HETRs. Whereas the occurrence of HETRs

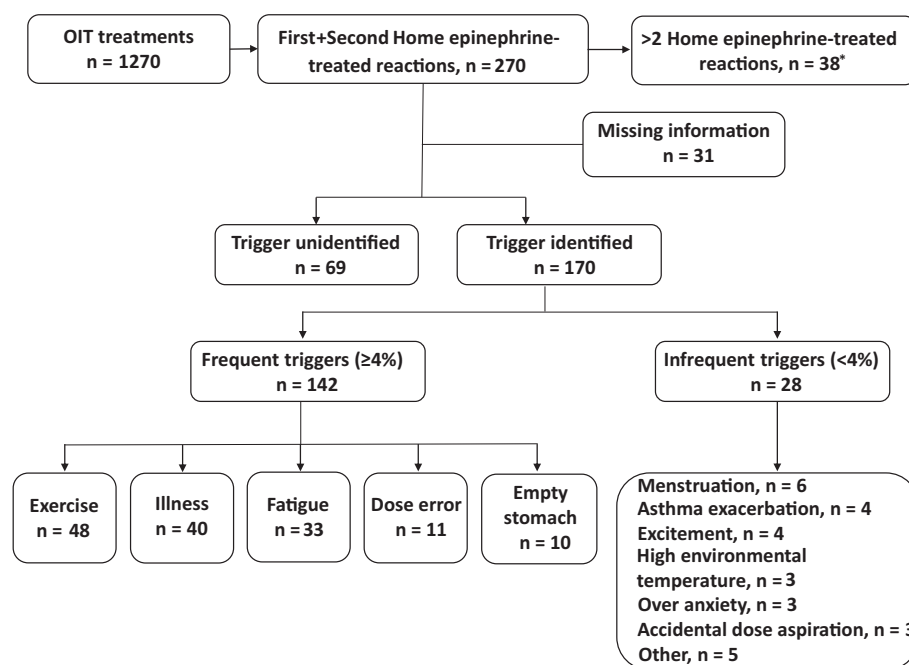


FIGURE 1. A consort diagram shows HETRs included in this study and their reported triggers. *Information in Table E4.

TABLE II. Organ systems involved in adverse reactions treated with epinephrine at home

Organ system	All (n = 270)	First home epinephrine (n = 200)	Second home epinephrine (n = 70)
Sufficient information	226 (83.7%)	167 (83.5%)	59 (84.3%)
Multisystem	175 (77.4%)	126 (75.5%)	49 (83%)
Skin	152 (67.2%)	110 (65.9%)	42 (71.2%)
Respiratory	210 (92.9%)	153 (91.6%)	57 (96.6%)
Gastrointestinal	71 (31.4%)	57 (34.1%)	14 (23.7%)
Cardiovascular	2 (0.9%)	2 (1.2%)	0

continued to decrease with increasing doses, such reactions still occurred even at doses greater than 2,500 mg protein. Within the 0- to 500-mg highest occurrence range, the rate of first HETRs was 5.75% (95% CI 4.33–7.48) at 100 mg or less, decreased to approximately 2% at doses up to 300 mg, with further decrease to approximately 1% at higher doses (Cochran-Armitage trend test P value < .0001 for first HETR and P = .0045 for second HETR) (Figure 4). Overall, most HETRs (152 of 270 = 56.3%) occurred in response to doses of less than 500 mg protein and most (n = 124) of these 152 reactions (81.6%) occurred to doses of 300 mg protein or less (Figure E1).

We next looked at the time interval between the last dose escalation and the occurrence of HETRs. In-clinic dose escalation rounds were performed routinely every 4 weeks. Patients whose up-dosing was delayed beyond 28 days, because of either technical limitations, concurrent illnesses (any acute unusual symptoms, typically upper respiratory infection, gastrointestinal symptoms, or fever), or a severe or recurrent reaction at home represent a specific subset. The HETRs occurring beyond the 28th day in these patients did not represent the effect of the protocol interval, but rather the patients themselves, and were therefore excluded from this specific analysis. Of the 270 HETRs studied, 152 first HETRs and 51 second HETRs were analyzed.

The rate of HETRs was highest (35% of HETRs) during the first week of the 4-week home treatment interval and decreased gradually in the following weeks (second week 24.6%, third week 24.1%, fourth week 16.3%) with a significant difference only between weeks 1 and 4 (P < .001). That was primarily driven by the first HETRs and by the decrease in their rate from the first 3 weeks to the fourth week, with a significant difference between the first week (P < .001), the second week (P = .037), and the third week (P = .028), and between the fourth week (P < .001). In contrast, a nonsignificant mild reduction was observed in cases of a second HETR (first week 33.3%, second week 23.5%, third week 19.6%, and fourth week 23.5%) (Figure 5).

Protocol-independent factors for HETRs

Information regarding possible triggers was available for 239 (88.5%) of the reported HETRs (Figure 1). Of these HETRs, 69 (28.9%) could not be attributed to any specific trigger. The breakdown into the different triggers is detailed in Figure 1 and their relative rate is presented in Figure E2 (available in this article's Online Repository at www.jaci-inpractice.org). The leading identified trigger for HETRs was physical exercise performed temporally close to the administration of the home dose,

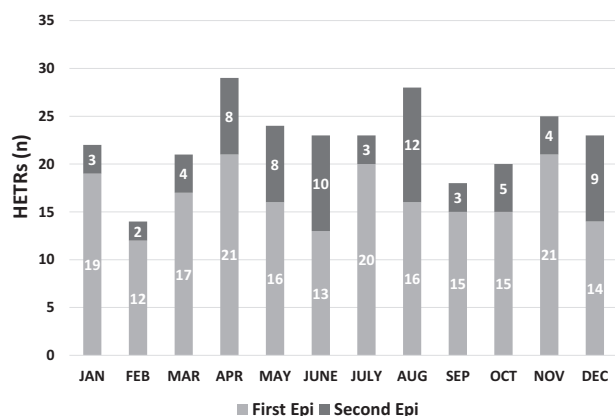


FIGURE 2. The monthly incidence of first HETRs (light gray) and second HETRs (dark gray). *Epi*, Epinephrine.

triggering 20% of such reactions. These were followed by dose consumption during concurrent illnesses (16.7%) and under conditions of fatigue, in which patients need rest owing to either sleep deprivation or increased activity (13.8%). Dosing errors and dosing on an empty stomach were also relatively frequent triggers (4.6% and 4.2%, respectively). Less-frequent reported triggers included dosing during menstrual periods, asthma exacerbations, excitement, periods with increased symptoms of allergic rhinitis, or high environmental temperatures, and taking the dose during nonroutine conditions (ie, vacations). Few HETRs were triggered by accidental aspiration of the dose, which is provided in a liquid form. The relative contribution of the various triggers reported was constant throughout the 4-week interval between dose escalations. In 62 of the 70 patients who had 2 HETRs, a report of a trigger was available for both the first and the second reaction. In most cases ($n = 35$), different triggers for each reaction were identified. In 13 cases of recurrent HETR, the trigger was not identified in both reactions. In 14 additional cases, the reported triggers for the second HETRs were identical to those of the first (concurrent illness, $n = 6$; physical exertion, $n = 5$; and dose error, asthma exacerbation, and fatigue, $n = 1$ each).

Patients experiencing more than 2 HETRs

Twenty-seven patients (17 males), aged 3.9 to 23.8 years, experienced 38 additional HETRs (beyond the first 2 that were analyzed previously) during the buildup phase of a single OIT treatment. These additional HETRs occurred mostly to milk ($n = 33$), and much less to peanuts ($n = 3$), egg ($n = 1$), and walnut ($n = 1$). Nineteen patients experienced a total of 3, 5 patients experienced 4, and 3 experienced 5 HETRs. In 7 of these reactions, sufficient information was not available, and in an additional 7, the epinephrine was given for inappropriate reasons, such as providing epinephrine for a nonmedical reason or without any reaction to the dose (Table E4). The respiratory system was involved in 26 cases, the skin in 22, the gastrointestinal in 11, and the cardiovascular (hypotension) in 1 case. In 8 reactions, only 1 organ system (respiratory system, $n = 4$; skin and gastrointestinal, $n = 2$ each) was involved. Three of these reactions involved subjective symptoms only such as pruritus and abdominal pain. A trigger was identified in 13 of these reactions,

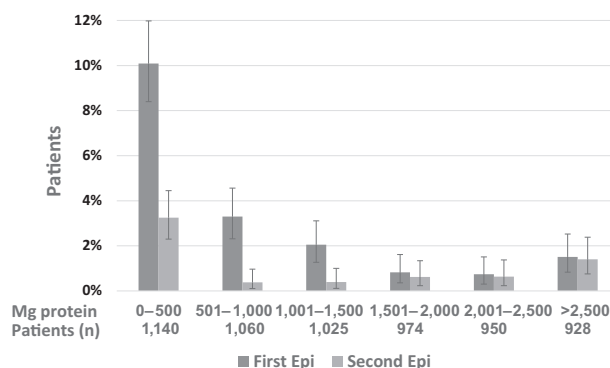


FIGURE 3. The rate of HETRs (first and second) experienced for a range of doses are presented in intervals of 500 mg protein, with 95% CI. All patients who received the relevant doses were included within each specific range. *Epi*, Epinephrine.

consisting primarily of physical exercise, fatigue, or a concurrent infection (Table E4).

DISCUSSION

The current study utilizes data, collected from a large group of patients who underwent OIT using a single standardized protocol for various foods, to characterize triggers for HETRs. We found that physical exercise, concurrent illnesses, and fatigue during dose consumption are the main risk factors for such reactions. The highest rate of HETRs was observed for doses of 300 mg protein or less and their incidence gradually decreased as time elapsed since the last dose increase. This information could be used to develop strategies to minimize severe home reactions and to improve OIT safety.

Several potential triggers for adverse reactions during OIT were previously described.^{3,10,16,19–21,29–34} However, these descriptions were based on case reports or studies with small sample sizes, precluding the ability to draw conclusions about the relative risk of each of these triggers. Our study demonstrates the relative frequency of different factors associated with HETRs in a large patient population. We found that physical exercise, concurrent infection, and dosing while fatigued were the most common triggers followed by dosing on an empty stomach and dosing errors. Together, these factors comprise nearly 60% of the triggers for HETRs and affect most OIT-treated patients. Other factors, such as dosing during a menstrual period, while excited, in the setting of high environmental temperatures, or during changes in patients' regular schedule, are likely triggers for HETRs in only a minority of patients.^{21,35}

One potential factor that requires a separate discussion is asthma. Asthma is a significant risk factor for anaphylactic and even fatal reactions in food-allergic patients.³⁶ Patients with asthma also have more adverse reactions during OIT regardless of asthma severity.^{17,37} Interestingly, although asthma was diagnosed in nearly 70% of our patients, asthma exacerbations were not reported as a common trigger for HETRs in our patient population. Of note, patients' asthma control is routinely monitored both clinically and using spirometry at every clinic visit, likely improving their compliance and control. Nevertheless, we cannot rule out that patients with asthma have an inherent risk for severe adverse reactions during OIT, even when their asthma is well controlled.

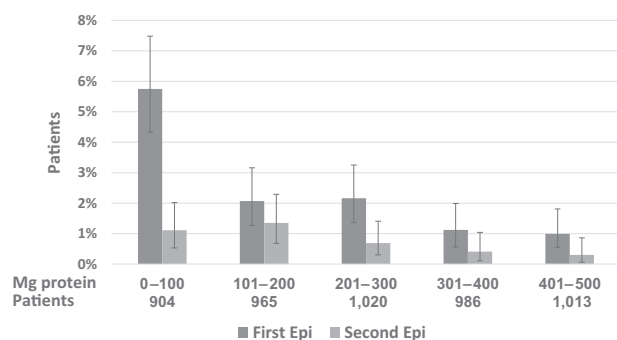


FIGURE 4. The rate of HETRs (first and second) experienced for a range of high-risk doses up to 500 mg protein presented in intervals of 100 mg protein, with 95% CI. All patients who received the relevant doses were included within each specific range. *Epi*, Epinephrine.

Seasonality of anaphylactic reactions to foods, both on random exposures and during OIT, has been described in several studies, and was attributed mainly to pollen seasons.^{15,20,38,39} The highest incidence of HETRs in our population was observed in April and a high incidence was observed in May as well—both comprise the mid-spring season in Israel. Although the most common inhaled allergen in Israel is house dust mite,²⁶ this seasonal effect can be attributed to the peak pollen season. Unfortunately, data on seasonal allergens in our patients were not available. Alternatively, it could be related to the spring vacations and national holidays that take place during these months. This is supported by the high rate of HETRs during the summer, June-July, and especially in August, the peak vacation season in Israel. Another peak in HETRs was observed in November-December, likely related to the increase in viral infections. In contrast, February, a month with no national holidays and minimal pollens, was associated with the lowest rate of HETRs.⁴⁰

Two protocol-associated factors were identified to be related with HETRs in this study. The first is the time interval between dose escalations. Most OIT studies use intervals of 1 to 2 weeks or even less between dose escalations, with longer intervals in cases of home reactions.^{2,3,41} Our protocol consists of 4-week intervals. Most HETRs occurred during the first week and their rate significantly decreased from the first 3 weeks to the fourth week following dose escalations, suggesting that desensitization improves with time and reduces the risk for adverse reactions. Importantly, this difference was identified only for the first HETRs and not for the second HETRs. It is possible that patients who experience more than 1 HETR represent a subgroup of patients who are less well desensitized or require even longer intervals. This protocol-dependent factor suggests that protocol adaptations (increased precautions and longer intervals) might be needed in high-risk patients. The second finding is that the highest rate of HETRs was observed to allergen doses of 300 mg protein or less. This was true for both first and second HETRs. It is likely that the most severe patients react to lower doses and discontinue treatment before reaching high doses. Patients reaching a dose greater than 300 mg protein are still at risk for HETRs and need to be aware of it. It should be noted, however, that the risk for HETRs at these doses is significantly lower. Furthermore, maintaining patients on a 300-mg dose is not likely to lead to full

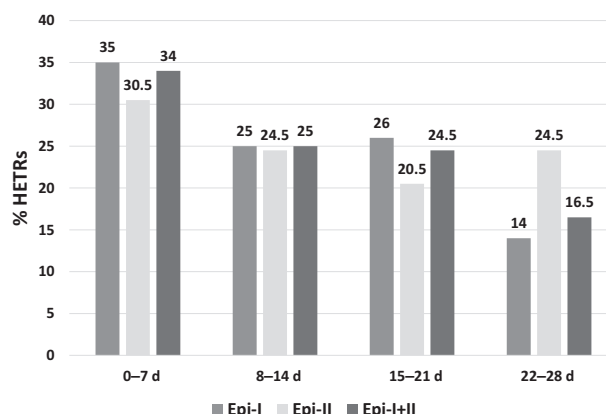


FIGURE 5. The rate of HETRs experienced during the 4-week interval of the home treatment periods. *Epi*, Epinephrine.

desensitization even long term.⁴² Therefore, these aspects should be discussed with patients who are interested in reaching ad lib consumption.

Of note, despite thorough and usually immediate investigation and information collection from multiple sources, in 28% of HETRs, no trigger was identified. Conversely, under the complete lock-down posed by the COVID-19 pandemic, there was an almost complete disappearance of HETRs, suggesting that most HETRs, including those with no identified trigger, are likely triggered by environmental factors.¹⁸ It is plausible that the triggers in these cases have been milder (ie, mild upper respiratory infection) and, therefore, overlooked.

This study has several limitations. First, HETRs might not necessarily reflect all or only the most severe reactions patients experience during OIT. However, they represent an objective indication of patients' perception of a severe anaphylactic reaction and are associated with worst-treatment outcome.¹⁷ Second, this study evaluated the up-dosing phase only, mainly because adverse reactions during maintenance are typically milder and less frequent,⁴³ and have less of an impact on treatment outcome.^{30,43} Third, although patients could report their own perceived triggers, the list of the potential triggers provided in the reporting system could bias patient's assessment. Lastly, this study reflects the experience of a single medical center, treating a limited population with certain characteristics, and with specific frequencies of different food allergies. Therefore, our findings need to be compared with those of other centers, in different countries, that utilize different protocols.

In summary, the current study demonstrates the relative contribution of various triggers of HETRs in a large group of OIT-treated patients. It also shows that certain protocol-related factors are associated with such reactions. This information should be examined in other patient populations using different protocols so it can be used to improve the safety of OIT, both at a protocol level and in specific precautions provided to patients.

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ONLINE REPOSITORY

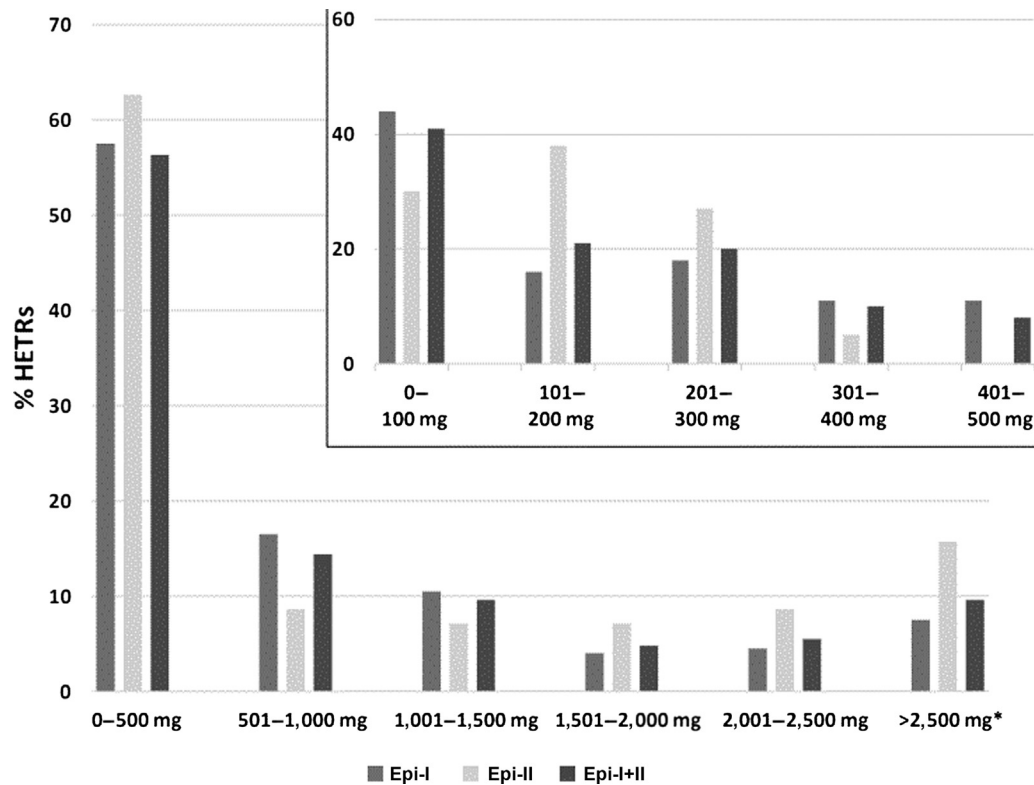


FIGURE E1. Doses eliciting HETRs. The percentage of HETRs (first, second, and total) experienced for a range of doses presented in intervals of 500 mg protein (main graph) and 100 mg protein (inset graph). *Epi*, Epinephrine. *Maximal 6000 mg milk protein.

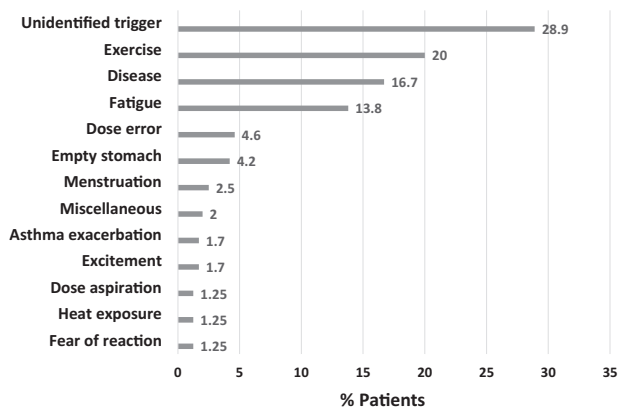


FIGURE E2. The relative contribution of various triggers for HETRs.

TABLE E1. Instructions for safe home dosing

Instruction	Condition
Avoid	Physical exertion 30 min before and 2 h after taking the dose
	Taking the dose while fatigue
	Taking the dose on an empty stomach
Avoid dosing and seek medical consult	Asthma exacerbation or wheezing
	Missing treatment on >2 adjacent d
Premedication with antihistamine	Mild symptoms of disease/runny nose
Premedication with antihistamine and dose reduction (one-half to one-third the regular dose)	Significant disease symptoms: fever, cough

TABLE E3. Characteristics of the study population

Characteristics	Parameter	OIT treatments (n = 1,270)
Demographics	Age (y), median (IQR)	6.8 (5.2–10.3)
	Male sex, n (%)	765 (60.2)
	Asthma, (%)	637 (50.2)
	HDM sensitivity, n (%)	788 (62)
	SPT wheal size (mm), median (IQR)	8 (6–10)
Pre-OIT	Anaphylaxis, n (%)	766 (60.3)
	Emergency room treatment, n (%)	656 (51.6)
	Epinephrine administered, n (%)	425 (33.5)
	Hospitalization, n (%)	190 (15)
OIT	Epinephrine induction, n (%)	279 (21.9)
	SHTD (mg protein), median (IQR)	45 (15–200)

HDM, House dust mite; IQR, interquartile range; SPT, skin prick test.

TABLE E2. Action plan for home reactions to OIT doses

Grade of reaction	Symptoms	Treatment
Mild	Rash, perioral swelling, runny nose, sneezing, mild abdominal pain/vomiting	Antihistamines
Moderate	Cough	Antihistamines and inhaled bronchodilator
Severe	Dyspnea/shortness of breath, severe abdominal pain, drowsiness, an impression of a severe reaction	Epinephrine and treatment at a medical emergency center

TABLE E4. Triggers for 3 or more HETRs during a single OIT

Trigger/explanation	n
Missing information	7
Unjustified*	7
Exercise	3
Fatigue	5
Concurrent infection	4
Dose error	1
Nonidentified trigger	11

*Unjustified reasons for epinephrine administration included providing epinephrine for a nonmedical reason or without any reaction to the treatment dose; deliberate epinephrine administration in attempt to shorten the observation time after dose consumption (3 occasions), attempt to prevent a reaction after detection of overdose consumption, playing with the epinephrine autoinjector, misinterpretation of signs of respiratory infection as an allergic reaction, fear of potential reactions.