Original Article

Severe Anaphylactic Reactions to Home Doses of Oral Immunotherapy for Food Allergy

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What is already known about this topic? Severe anaphylactic reactions to home doses are the main risk of OIT. Such reactions, involving vital sign impairment, may pose an immediate threat to life, and information regarding their rate and risk factors is missing.

What does this article add to our knowledge? High-grade anaphylactic reactions to home doses of OIT occur despite patient compliance with epinephrine treatment. Risk factors for such reactions include milk OIT, asthma, and house dust mite sensitization, but many occur without identified triggers.

How does this study impact current management guidelines? Appropriate treatment settings, alternative treatment approaches, or exclusion from treatment should be considered for patients who are at high risk for severe anaphylactic reactions during OIT. An approach to patients who have experienced such reactions should be established.

BACKGROUND: Severe anaphylactic reactions to home doses may occur during food allergy oral immunotherapy (OIT).
OBJECTIVE: To study the rate and risk factors for such reactions.
METHODS: We studied all patients aged greater than 3.5 years who completed OIT in a single center between April 2010 and January 2020. All home epinephrine-treated reactions (HETRs) were identified. High-grade HETRs (HG-HETRs) were defined as HETRs involving respiratory (SpO$_2$ of 94% or less), cardiovascular (low blood pressure), or central nervous system impairment (loss of consciousness). We investigated the rate and risk factors for HG-HETRs.
RESULTS: A total of 1,637 OIT treatments were studied: milk (880), peanut (346), tree nuts (221), sesame (115), and egg (75). Of 390 identified HETRs, 30 HG-HETRs occurred during 27 treatments (1.65% of all treatments). Nearly all (26 of 30) were during milk OIT in patients with house dust mite (HDM) sensitization and asthma (26 of 30 each). Of the 30 patients with HG-HETRs, 21 recovered with one or two epinephrine treatments, but nine (0.55% of all treatments) did not respond to a second dose of epinephrine and were deemed to have refractory anaphylaxis. Three patients required intensive care unit admission and three received epinephrine drip, but none required ventilatory support. Risk factors for HG-HETRs included milk OIT ($P = .031$), asthma ($P = .02$) and HDM sensitization ($P = .02$). No specific triggers for HG-HETR were identified. Of patients with HG-HETRs, 25.9% were fully desensitized, including the four non−milk treated patients; 22.2% were partially desensitized; and 51.9% failed.
CONCLUSIONS: High-grade HETRs are uncommon, particularly refractory anaphylactic reactions to home OIT doses. Although milk OIT, asthma, and HDM sensitization are the main risk factors for such reactions, identification of patients who are at risk is challenging.   © 2023 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2023;■:■-■)

Key words: Adverse reactions; Anaphylaxis; Epinephrine; Oral immunotherapy; Vital sign

INTRODUCTION

Oral immunotherapy (OIT) is an effective treatment for desensitizing food-allergic patients,[1-4] but adverse reactions are common. Allergic reactions to doses previously tolerated, which occur at home when patients are away from medical supervision, are most concerning.[1,5] Such reactions might be elicited in response to various augmenting environmental triggers,[6] which are sometimes difficult to avoid, such as viral infections.[7]

Abbreviations used
HDM- House dust mite
HETR- Home epinephrine-treated reaction
HG-HETR- High-grade anaphylactic home epinephrine treated reaction
OIT- Oral immunotherapy
SHTD- Single highest tolerated dose

The vast majority of home reactions are mild and are local and self-limited or are easily treated with antihistamines or bronchodilators.[8] However, reactions treated with epinephrine at home have been described.[9] In the absence of objective medical assessment, it is difficult to determine the actual severity of home reactions, because the treatment provided for these reactions is dictated by the severity of the reaction as well as by the level of anxiety of the patient and parent. Nevertheless, severe and even life-threatening reactions have been documented during OIT,[1,9] and recently a case of a fatal reaction after home dose consumption during baked milk OIT was published in the media.[10] It is therefore important to identify at-risk patients, as well as triggers for life-threatening reactions. In this study, we reviewed a large number of patients who underwent OIT treatments for over a decade in a single center in Israel, to investigate the frequency, risk factors, and triggers for high-grade (HG) anaphylactic reactions occurring for home doses. Such reactions were defined as reactions that were associated with vital sign impairment and met the criteria of grade V systemic allergic reaction according to the Delphi study grading system[11] or grade IV/severe grade III according to the Consortium for Food Allergy Research (CoFAR) grading, version 3.0.[12]

METHODS
Patients

All patients who started open-label OIT treatment at the Institute of Allergy, Immunology, and Pediatric Pulmonology at Shamir (formerly Assaf-Harofeh) Medical Center, Zerifin, Israel, between April 2010 and January 2020 and reached a final disposition of full desensitization, partial desensitization, or treatment failure by August 2022 were included in this study. All patients who started OIT by January 2020 reached a final disposition, except for 13 patients who had not yet completed OIT. Patients aged greater than 3.5 years, who had a diagnosis of IgE-mediated food allergy, based on IgE-sensitization together with a history of a recent (within the past year) objective reaction to the target food, were eligible for OIT. A history of severe anaphylactic reactions did not preclude enrollment into OIT. Asthma had to be stable for at least 3 weeks before OIT initiation. Patients with active eosinophilic gastrointestinal or autoimmune diseases were excluded. Patients with eosinophilic esophagitis in remission (normal gastroscopy and asymptomatic for several months) with no anticipated treatment modifications were included. A minimal tolerated dose of 5 mg protein for milk and 1 mg for all other foods was required to initiate OIT. Informed parental or patient (for those aged >18 years) written consent for treatment was obtained from all participants. We obtained approval for the documentation and publication of all patient data from the Helsinki Institutional Review Board Committee of Shamir Medical Center (Approval 136/12).

Oral immunotherapy protocol

Oral immunotherapy was performed for milk, peanut, egg, sesame, and tree nuts (walnut, cashew, hazelnut, or almond), as published elsewhere.[13-17] Briefly, the first 3 to 4 days took place in an ambulatory care setting and served to confirm the diagnosis of food allergy, because about 8.1% of patients referred to our center for OIT have been found to be nonallergic,[18] and to determine each patient's individualized single highest tolerated dose (SHTD) (the highest dose that does not elicit objective symptoms). Subsequently, patients consumed the SHTD daily until the next clinic up-dosing round. Cycles of dose escalation rounds followed by daily home consumption of the determined new doses were performed every 4 weeks until the treatment goal was achieved. The initial goal of treatment was to desensitize patients to a minimal maintenance dose that would provide protection in case of accidental exposure to small amounts of allergen: 180 mg protein milk (6 mL), 300 mg protein peanut (1 g peanut), 300 mg protein tree nut (2 g of walnut and hazelnut and 1.7 g of cashew), 1,500 mg protein egg (one-quarter omelet from one egg), and 240 mg protein sesame (1 g tahini). Subsequently, patients who wished to achieve free consumption of the treated food continued to up-dose to a full dose of milk at 7,200 mg protein, peanut at 3,000 mg protein, egg at 12,000 mg protein, sesame at 4,000 mg protein, and tree nuts at 3,900 mg protein. Patients who were unable to achieve the threshold of partial desensitization were deemed treatment failures.

Home treatment and reaction management guidelines

Patients were given detailed safety instructions, both oral and written, regarding home dose consumption (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) and the management of allergic reactions (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Children were required to remain under adult supervision for at least 1.5 hours after home dose consumption. Each patient was prescribed antihistamines, bronchodilators, and two epinephrine autoinjectors. Patients underwent training for proper operation of the epinephrine auto-injector as well as guidance to identify conditions demanding its use (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Specifically, patients were guided to administer epinephrine for reactions consisting of severe abdominal pain, significant shortness of breath, or lethargy, or whenever they had the impression of a severe reaction. After epinephrine administration, patients were instructed to go to a local emergency room (ER). For practical reasons, when complete resolution of the reaction occurred before patients entered the ER, they were allowed to stay in proximity to the ER for several hours without actual admission, to verify that symptoms did not reoccur. A staff physician was on call for 24 hours 7 d/wk for consultation.

Home treatment report

Patients were required to report daily on the administration of home doses and the occurrence of reactions. The report was first performed via e-mail (2010-2012), and subsequently by using an electronic Web reporting system.[19] In case of a reaction, patients were asked to provide detailed information, first by e-mail in free text and then through structured questions via the reporting system, including signs, symptoms, and organ systems involved. Patients were also asked to assess what the trigger of the reaction was, and to report the medications given and the ER attendance. Patients' reports were continuously monitored. Patients who attended an ER

were asked to send the full ER report. 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.

Data collection, interpretation, and statistical analysis

We collected information from documentation in patients' files and reports transmitted by e-mail and via the reporting Web site. All epinephrine-treated reactions to OIT doses, treated at home or by medical professionals, were identified and analyzed. These reactions served to screen for HG reactions, because it is unlikely that an HG reaction was not treated with epinephrine at home or in an ER. Home epinephrine-treated reactions (HETRs), which included vital sign impairment (SpO_2 of 94% or less; low blood pressure based on predicted values for age accompanied by symptoms of weakness, confusion, drowsiness; and HETRs with loss of consciousness) were defined as HG-HETRs. We analyzed and summarized the details of HG-HETRs and compared the characteristics of OIT patients with HG-HETRs with those of patients with non−HG-HETRs. Statistical analysis was performed using SAS software (version 9.4, SAS Institute, Inc, Cary, NC). Univariate analyses included χ^2 test (or Fisher exact test) for categorical variables and t test (or Wilcoxon two-sample test) for continuous variables. The study outcome was home reaction requiring epinephrine treatment and with vital sign impairment (yes/no) for all study food groups. Univariate logistic regression was implemented presenting the odds ratios (ORs) with 95% CIs. We performed stepwise multivariable logistic regression on factors found to be significant in the univariate analysis. Statistical significance was considered when P was less than .05.

RESULTS

A total of 1,637 OIT courses were completed between April 2010 and January 2020 and were included in this study: 880 to milk, 346 to peanut, 221 to tree nuts (146 walnut, 57 cashew, 16 hazelnut, and two almond), 115 to sesame, and 75 to egg. In addition, 1,327 patients underwent a single treatment, 123 patients underwent two consecutive OIT treatments, 16 patients three consecutive OIT treatments, and four patients four consecutive OIT treatments. The vast majority of patients with multiple OIT treatments were treated to different foods; however, 16 patients were treated twice for the same food, either following a previous failure or because of discontinuation owing to noncompliance. No patients who underwent consecutive OIT to multiple foods experienced HETRs to different foods. Table E3 (in this article's Online Repository at www.jaci-inpractice.org) lists patients' characteristics in all 1,637 treatments; their OIT results are presented in Figure E1 (in this article's Online Repository at www.jaci-inpractice.org). Home epinephrine-treated reactions (reactions treated with epinephrine either at home or administered by medical personnel) were experienced in 252 of the 1,637 treatments (15.4%). Most patients experienced a single HETR, but some experienced several HETRs during a single treatment. Overall, 390 HETRs (milk, n = 268; egg, n = 10; peanut, n = 57; sesame, n = 9; and tree nuts, n = 46) were analyzed in this study (Table I). A single HETR was experienced in 166 treatments, two were experienced in 53 treatments, three were experienced in 25 treatments, four were experienced in seven treatments, and five were experienced in three treatments . Reports of reactions were inadequate in 50 cases, included only information that epinephrine was

administered to treat a reaction with prompt resolution; therefore, these reports were considered non−HG-HETRs. Adequate information regarding symptoms experienced and organ systems involved during HETRs was available in 340 cases (87.2%) (Table I). In 64 of those, only subjective reports were reported (nine patients presented to an ER and were asymptomatic upon arrival). Of all 340 HETRs, the respiratory system was most frequently involved (90.9%), and multisystem reactions meeting anaphylaxis criteria[20] were reported in 266 reactions.

Management of HETRs

A single epinephrine dose was administered in 349 of these treatments (98.5%), whereas 41 cases (2.5% of all treatments) were treated with more than one epinephrine dose (Table I). Of the HETRs studied, 239 patients were admitted to a local ER, whereas the remaining patients had prompt resolution of symptoms, which reassured caregivers to remain in proximity to an ER without actual admission (most) or to stay at home (few) (Table I). Twenty-seven patients were hospitalized. In 11, the anaphylactic reaction was considered HG and is further detailed subsequently. Reasons for hospitalization in the additional 16 non-HG reactions included continued signs and symptoms (although not severe) that mandated observation, more than one epinephrine administration before or during ER treatment even when symptoms completely resolved, and the presence of additional factors unrelated to reaction severity, such as fever or social considerations.

Compliance with treatment instructions

Information regarding the location where the first epinephrine was administered was available for nearly all of the 390 HETRs analyzed (n = 381; 97.7%) (Table I). In 332 of those (87.1%), the first epinephrine dose was administered at home; in three patients, it was by an emergency medical services (EMS) team; in nine, it took place in a community clinic, and in 37 patients, epinephrine was first administered in the ER. Timely report of the reaction was provided in almost all cases (90.5%).

Characteristics of HG anaphylactic reactions

A total of 30 HG-HETRs occurred in 27 treatments (1.65% of all OIT treatments) during the study period (Tables II and III). Three patients experienced two HG-HETRs during the same treatment, all for milk. The first HG-HETRs in these patients were considered to be triggered by an avoidable factor, such as dosing before exercise or while fatigued; therefore, they were allowed to continue OIT. Nearly all HG-HETRs (26 of 30) were during milk OIT (2.95% of milk OIT treatments), and nearly all (26 of 30) were in patients with house dust mite (HDM) sensitization and asthma. Two HG-HETRs occurred to peanut (0.58%), one was to sesame (0.87%), and one was to tree nuts (0.45%). Monthly clinical assessment of asthma control, including spirometry in those who are old enough, is routinely performed in all patients. Of those with HG-HETRs, 23 had asthma and 20 performed spirometry. At OIT initiation, 11 patients were already treated with daily inhaled corticosteroids as controller therapy. An additional eight patients were started on daily inhaled corticosteroids either a month before or during the week of OIT initiation, after in-clinic assessment. During OIT up-dosing clinic visits, seven patients were deemed to have uncontrolled asthma and inhaled corticosteroid treatment was initiated (n = 2) or the dose of inhaled corticosteroid was increased (n = 5). There was only one case of an HG-HETR that

TABLE I. Characteristics and treatment of all HETRs

Characteristics	Parameter		HETR (n = 390)
Food-treated (HETRs [n (%)] [% treatments])	Milk OIT (n = 880)		268 (68.7%) (30.5%)
	Egg OIT (n = 75)		10 (2.6%) (13.3%)
	Peanut OIT (n = 346)		57 (14.6%) (16.5%)
	Sesame OIT (n = 115)		9 (2.3%) (7.8%)
	Tree nut OIT (n = 221)		46 (11.8%) (20.8%)
Organ systems involved (available information) (n = 340)	Objective symptoms		276 (81.2%)
	Skin		237 (69.7%)
	Gastrointestinal		118 (34.7%)
	Respiratory		309 (90.9%)
	Cardiovascular		6 (1.7%)
	Multisystem		266 (78.2%)
Epinephrine treatment (n = 390)	>1 epinephrine dose		41 (10.5%) (2.5%)*
Further treatment required (available information) (n = 330)	Pre-epinephrine medications		216 (65.5%)
	Emergency room treatment		239 (72.4%) (14.6%)*
	Hospitalization		27 (8.2%) (1.6%)*
	Intensive care unit admission		3 (0.9%) (0.18%)*
	Intravenous epinephrine		3 (0.9%) (0.18%)*
Compliance with epinephrine use instructions (available information) (n = 381)	First epinephrine dose given at:	Home	332 (87.1%)
		Emergency medical services	3 (0.8%)
		Community clinic	9 (2.4%)
		Emergency room	37 (9.7%)
	Non-delayed report		344 (90.5%)

HETR, home epinephrine-treated reaction; *OIT*, oral immunotherapy.
*Percentage of 1,637 OIT treatments.

was considered to be triggered by asthma exacerbation. Importantly, in 21 patients the HG-HETR was not preceded by previous HETR during treatment and therefore could not have been anticipated. Median duration between the beginning of OIT and the occurrence of HG-HETR was 150 days (interquartile range, 60-343 days; range, 4-1,164 days), and the interval from recent up-dosing was 16 days (interquartile range, 9-28 days; range, 1-136 days). High-grade-HETRs occurred to the entire range of doses, from 2.5 to 7,200 mg protein, but mostly to doses lower than 500 mg (Figure 1) for all treated foods (see Figures E2 and E3 in this article's Online Repository at www.jaci-inpractice.org). The augmenting triggers reported for these reactions were exercise (n = 4), fatigue (n = 5), concurrent illness (n = 3), a hot shower shortly after a dose (n = 2), asthma exacerbation, and menstruation (n = 1 for each), whereas in 14 cases no potential trigger was identified.

Of the 30 HG-HETRs, 21 responded to one or two epinephrine treatments (Table II). Whereas most were discharged after observation (15 of 21 patients), six were hospitalized. In 13 (milk, n = 10; peanut, tree nuts, and sesame, n = 1 each) of these 21 patients, vital sign impairment was evident before epinephrine was administered. In some, oxygen saturation was measured by the parents at home, a practice we discourage,

and assessment by medical personnel after epinephrine administration was unremarkable. In others, epinephrine was not given at home, and vital sign impairment was evident by EMS team or in an ER, followed by epinephrine administration and the quick resolution of symptoms. One patient reportedly vomited, lost consciousness, and improved after epinephrine injection, but developed severe abdominal pain and extensive urticarial rash subsequently in the ER, and responded well to a second dose of epinephrine. Three of these 13 patients were hospitalized for observation. In an additional eight patients (milk, n = 7; peanut, n = 1), hypoxemia was evident after epinephrine had already been administered (Table II). Four of them did not receive a second epinephrine dose, likely reflecting quick resolution of hypoxemia upon arrival to the ER. Three patients, all of whom were undergoing milk OIT, were hospitalized for observation.

For the comparison between patients who experienced HG- versus non–HG-HETRs, each patient was represented once, and the most severe reaction was used (Table IV). The two groups were comparable according to patients' age, skin prick test result to the treated food, and severity of reactions before OIT or during in-clinic up-dosing, or in the SHTD. Milk was the treated food in 85.2% of HG-HETRs, compared with 64.4% in non–HG-HETRs (Table IV). Overall, 2.5% of milk OIT

TABLE II. Characteristics of high-grade home epinephrine-treated reactions responsive to epinephrine treatment

No.	Age, y	Sex (male = 1)	Treated food	Asthma	Suspected trigger	First epinephrine location	Vital signs impairment	Treatment after first epinephrine	Hospitalization	Final disposition
Vital sign impairment before epinephrine administration										
1	10.9	1	Milk	+	Hot shower	EMS	SpO_2 = 93% in EMS		−	A_2
2	5.4	0	Milk	+	Disease	ER	SpO_2 = 91% in ER	Oxygen, corticosteroids	−	A_1
3	7.8	1	Sesame	−	Unknown	ER	SpO_2 = 92% in ER	—	−	A_1
4	10.3	1	Milk	+	Unknown	Home	Decreased consciousness plus BP = 88/56 at home (BP = 119/89 after epinephrine)	BD at home	−	F
5	5.9	0	Walnut	−	Unknown	Home	SpO_2 = 88% at home	BD, steroids	−	A_1
6	13.7	0	Milk	−	Menstruation	Home	Severe abdominal pain plus BP decrease from 120/80 to 105/61 at home	—	−	A_2
7	7.8	0	Milk	−	Unknown	Home	SpO_2 = 88% at home	Oxygen, BD, steroids	+	A_2
8	15.4	0	Milk	+	Exercise	Home	Reduced SpO_2 (location unknown)		−	F
9	6.1	1	Peanut	+	Disease	ER	SpO_2 = 89% in ER	BD, steroids	−	A_1
10	10.6	1	Milk	+	Unknown	Home	Reduced SpO_2 (location unknown)		+	F
11	8	1	Milk	+	Unknown	Home	Cyanosis in EMS, SpO_2 not documented	Oxygen, BD, steroids	−	F
12	9.0	0	Milk	+	Asthma flare-up	ER	SpO_2 = 84% in ER	Steroids	+	F
13	11.7	0	Milk	+	Hot shower	Home	Loss of consciousness	Epinephrine owing to abdominal pain and rash	−	A_1
Vital sign impairment in ER/EMS after epinephrine administration										
14	4.5	0	Milk	+	Unknown	Home	SpO_2 = 88%	Intravenous epinephrine, BD, steroids, antihistamines	+	F
15	8.6	1	Milk	+	Fatigue	Home	SpO_2 = 93%	BD	−	F
16	10.3	1	Milk	+	Fatigue	Home	SpO_2 = 87%	Oxygen, BD, steroids	+	F
17	11.0	0	Milk	+	Fatigue	Home	SpO_2 = 91%	Oxygen, BD, steroids	−	F
18	8.4	1	Peanut	+	Unknown	Home	SpO_2 = 84%	Second epinephrine and BD	−	A_1
19	14.7	1	Milk	+	Exercise	Home	Information of impaired vital signs	BD, steroids	−	F
20	5.6	0	Milk	+	Unknown	Home	Reduced SpO_2 in EMS	Epinephrine, oxygen	−	A_2
21	4.2	0	Milk	+	Unknown	Home	SpO_2 = 75% pre-epinephrine, 94% after epinephrine two times	Oxygen, BD	−	F

A_1, full desensitization, unlimited consumption of treated food; A_2, desensitization to limited amount of treated food; *BP*, blood pressure; *ER*, emergency room; *EMS*, emergency medical services; *F*, failure.

TABLE III. Characteristics of high-grade home epinephrine-treated reactions refractory to epinephrine treatment

No.	Age, y	Sex (male = 1)	Treated food	Asthma	Suspected trigger	First epinephrine location	Vital signs impairment	Treatment after first epinephrine dose	Hospitalization	Final disposition
1	11.3	0	Milk	+	Fatigue	Home	Reduced BP and SpO$_2$	Second intramuscular epinephrine dose, oxygen	+	F
2	7.6	0	Milk	+	Fatigue	Home	BP = 74/40 after epinephrine and intravenous epinephrine	Intravenous epinephrine	ICU	A$_2$
3	14.9	0	Milk	+	Unknown	Home	SpO$_2$ = 90% after epinephrine two times	Third epinephrine dose, corticosteroids	−	A$_1$
4	5.3	1	Milk	+	Unknown	Home	BP 70/40, O$_2$ saturation = 90% after epinephrine	Second and third epinephrine doses, oxygen, BD	+	A$_2$
5	11.3	0	Milk	+	Exercise	Home	SpO$_2$ = 85% after epinephrine two times	Oxygen, BD, steroids	−	F
6	8.0	1	Milk	+	Disease	Home	SpO$_2$ = 85% after epinephrine two times	Oxygen, BD, steroids	-	F
7	10.3	1	Milk	+	Unknown	Home	SpO$_2$ = 80%, pH 7.29 after epinephrine	Intramuscular plus intravenous epinephrine doses, oxygen, BD	ICU	F
8	7.8	1	Milk	+	Exercise	Home	SpO$_2$ = 54% after epinephrine two times, pH 7.32	Third and fourth epinephrine doses, ketamine, oxygen	ICU	F
9	7.8	1	Milk	+	Unknown	Home	Reduced consciousness, BP 93/40 after epinephrine two times	Third epinephrine dose, oxygen	−	A$_2$

A_1, full desensitization, unlimited consumption of treated food; A_2, desensitization to limited amount of treated food; BD, bronchodilators; BP, blood pressure; F, failure; ICU, intensive care unit.
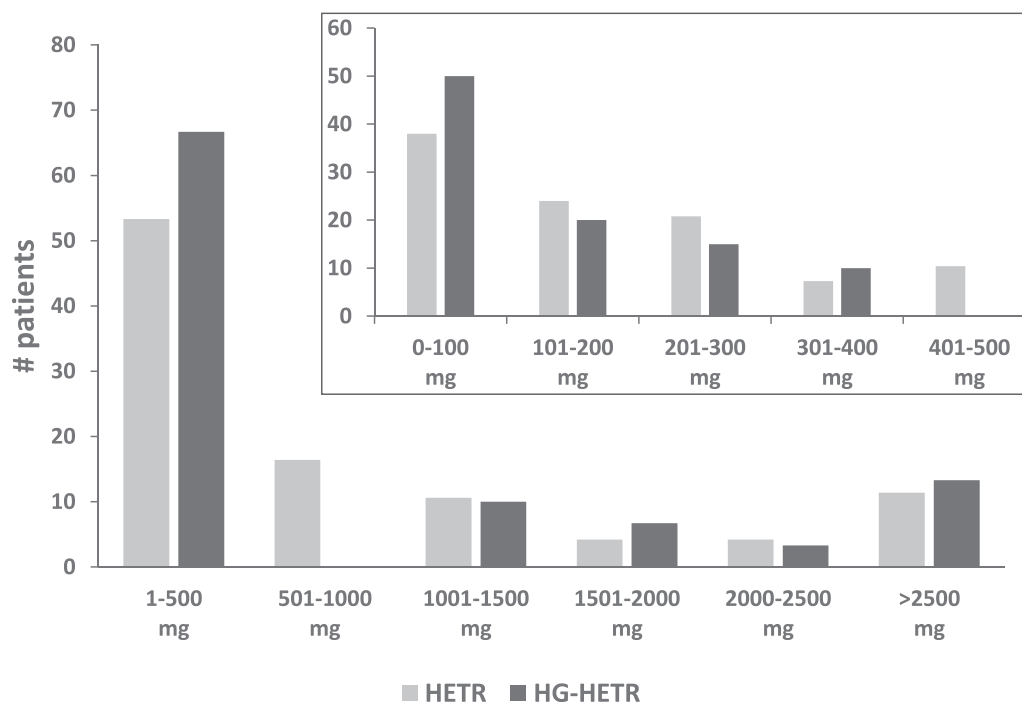

FIGURE 1. Rate of home epinephrine-treated reactions (HETRs) for various doses. Rate of HETRs and high-grade (HG) HETRs experienced for a range of doses, presented as intervals of 100 mg until 500 mg protein, and of 500 mg through the entire range.

TABLE IV. Characteristics of patients who experienced home epinephrine-treated reaction (HETRs): comparison of those who experienced high-grade (HG) anaphylactic reaction and those who did not

Characteristics	Parameter	Non—HG-HETR (n = 225)	HG-HETR (n = 27)	P
Demographics	Age, y (median [interquartile range])	8.1 (5.8-12.1)	8.4 (6.1-11)	NS
	Male sex	140 (62.2%)	13 (48.1%)	NS
	House dust mite sensitization	154 (68.4%)	24 (88.9%)	.033
	Asthma	141 (62.7%)	23 (85.2%)	.02
	Skin prick test, mm	8 (6-10)	9 (7-10)	NS
Pre-OIT	Anaphylaxis	172 (76.8%)	20 (74.1%)	NS
	Epinephrine	132 (58.7%)	17 (63%)	NS
	Emergency room	162 (73%)	20 (76.9%)	NS
	Hospitalization	58 (26%)	9 (34.6%)	NS
Food treated	Milk OIT	145 (64.4%)	23 (85.2%)	.031
	Non-milk OIT	80 (35.6%)	4 (14.8%)	
	Egg OIT	6 (2.7%)	0	
	Peanut OIT	32 (14.2%)	2 (7.4%)	
	Sesame OIT	7 (3.1%)	1 (3.7%)	
	Tree nut OIT	35 (15.5%)	1 (3.7%)	
OIT	Single highest tolerated dose, mg	22.5 (12-50)	22.5 (12.5-45)	NS
	Epinephrine induction	109 (48.4%)	14 (51.8%)	NS

NS, not significant; *OIT,* oral immunotherapy.
Data are shown as n (%) unless otherwise specified.

treatments were associated with an HG-HETR, compared with only 0.5% of OIT treatments for all other foods. Also, patients who experienced HG-HETR were more likely to have asthma (*P* = .02) and HDM sensitization (*P* = .02). Upon multivariable stepwise logistic regression, using variables that were selected *a priori*, based on significance on univariate analysis (ie, milk allergy, HDM sensitization, and asthma as covariates), both milk OIT (adjusted OR = 3.3; 95% CI, 1.09-10.03; *P* = .035) and HDM sensitization (adjusted OR = 5.5; 95% CI, 1.26-24.3; *P* = .023) remained significant predictors for HG-HETRs. On the other hand, asthma was excluded from the multivariable model because it was insignificant, controlling to the other two factors (*P* = .1736). In an additional comparison, there were no significant differences in the prevalence of augmenting factors (such as exercise, disease, and fatigue) for HG- versus non—HG-HETRs (Figure 2). Of note, 40% of reactions in both groups occurred to unidentified augmenting triggers. Patients who experienced HG-HETRs had a significantly higher rate of treatment failure, compared with those with non—HG-HETRs (52% vs 26%; *P* = .022) (Figure 3). However, despite the severe reactions experienced, many patients with HG-HETRs were eventually fully (26%) or partially (22%) desensitized (Figure 3 and Tables II and III). All four patients with HG-HETRs to non-milk foods were fully desensitized.

There were nine cases of refractory anaphylaxis[21] (ie, an anaphylactic reaction not responding to the second dose of epinephrine; 0.55% of all OIT treatments), all undergoing milk OIT and all in patients with asthma and HDM sensitization (Table III). Before the start of OIT, two of these patients had experienced no anaphylactic reactions, another two had experienced a reaction involving two or more organ systems and were treated with epinephrine but did not seek additional medical care, and the remaining four had been hospitalized for treatment of an anaphylactic reaction after epinephrine administration. Despite the reaction severity, five of them were discharged after

ER treatment. Four patients, representing the most severe reactions in this entire cohort, were hospitalized. Three patients were admitted to an ICU, and two required an intravenous epinephrine drip. No patients were intubated or required ventilatory support.

DISCUSSION

This study, which was based on a large set of OIT treatments, reports on the incidence of severe home reactions associated with vital sign impairment, and aimed to identify risk factors for such reactions. We identified 30 cases of HG-HETRs in 1,637 OIT treatments. Of those, there were nine cases of refractory anaphylaxis and three patients who required ICU admission. Identified risk factors for HG-HETRs were milk OIT, HDM sensitization, and asthma. This information should be considered when planning future OIT treatments.[22]

One of the main goals of an OIT treatment program is to identify patients who are at risk for severe reactions, so a joint decision can be made regarding their inclusion or exclusion from treatment. The most prominent risk factor identified in this study for experiencing HG-HETRs was undergoing OIT for milk. Milk was previously shown to be a risk factor for HETR and for a worse treatment outcome.[23] In this study, not only was milk associated with the highest risk for HG-HETRs, apparently it was also associated with the most severe reactions, because all nine cases of refractory anaphylaxis, three cases requiring intravenous epinephrine, and three cases of ICU admissions occurred in milk-treated patients. Interestingly, tree nuts, which are associated with higher rates of HETRs compared with peanut and sesame,[23] did not pose an extra risk for very severe reactions. These data support our previous reports that milk is a food allergen that poses a particular risk for allergic patients. The underlying reasons behind this particular risk deserve additional studies.
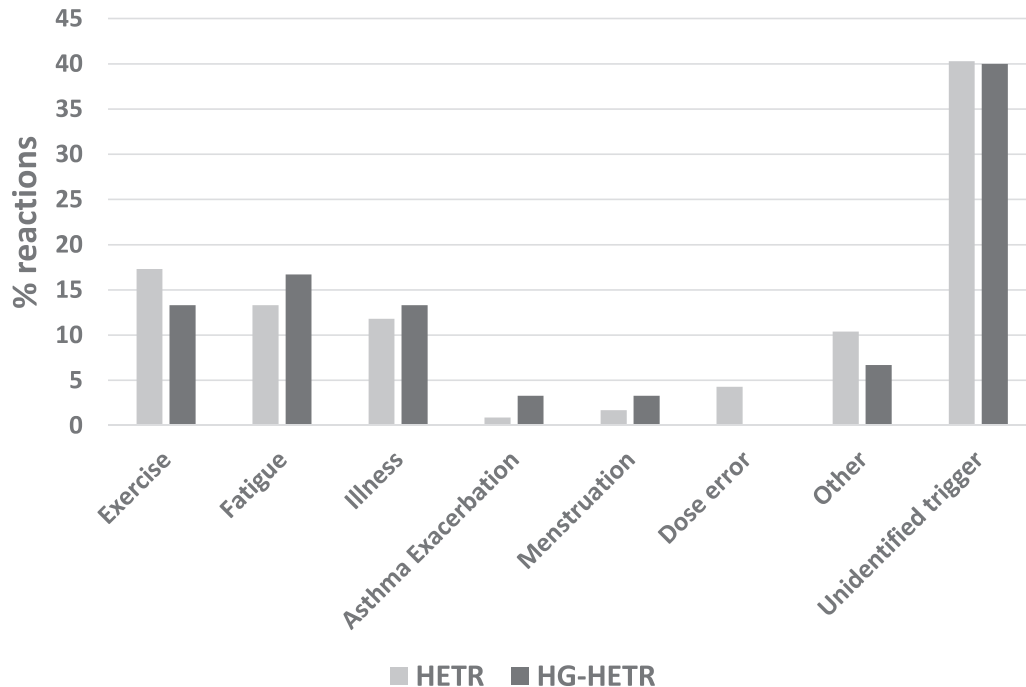
FIGURE 2. Relative contribution of various triggers for home epinephrine-treated reactions (HETRs). Various triggers for HETRs and high-grade (HG) HETRs are demonstrated with their relative contributions. *Other*, dosing on an empty stomach, accidental dose aspiration, excitement, high environmental temperature, and overdose.

The role of asthma as a risk factor for severe reactions in food-allergic patients is controversial. Asthma was described by some as a risk factor for refractory and even fatal anaphylaxis in food-allergic patients.[9,24] Indeed, the tragic fatality to baked milk OIT occurred in a patient with asthma.[10] In contrast, in the UK

Fatal Anaphylaxis Registry, most cases did not have evidence of poorly controlled asthma.[25] We previously reported that regardless of severity, asthma poses increased risk for HETRs during milk OIT.[26] In the current study, 20 of the 21 HG-HETRs that did not improve after a single dose of
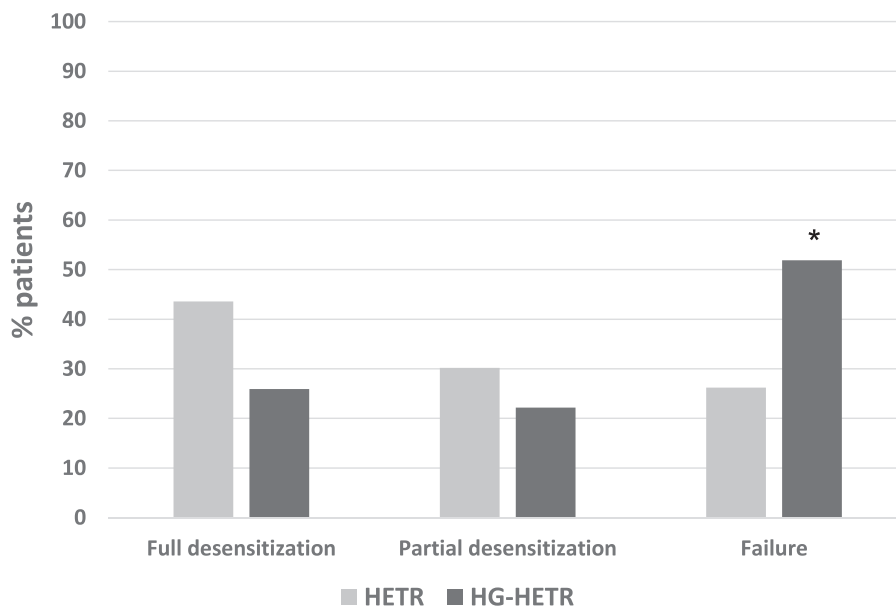

FIGURE 3. Treatment outcome based on occurrence of home epinephrine-treated reactions (HETRs). Treatment outcome: full desensitization, partial desensitization, and failure, combined for all treated foods, in patients with HETRs and with high-grade (HG) HETRs. *Significant difference was found between among patients who experienced only HETRs and those who experienced HG-HETRs ($P = .022$).

epinephrine, as well as all nine cases of refractory anaphylaxis were experienced by patients with asthma. However, asthma did not remain a risk factor for HG-HETRs upon multivariate analysis. Also, asthma exacerbations were not identified as a major trigger for HETRs, likely reflecting its control given the monthly assessment including spirometry performed on every clinic up-dosing. House dust mite sensitization remained a significant predictor for HG-HETRs, with the highest OR upon multivariate analysis. This suggests that sensitization to aeroallergens is also an important risk factor for severe reactions, as previously described.[8] Still, HDM sensitization accounts for the vast majority (over 80%) of allergic rhinitis in Israel[27,28] and is often associated with asthma. Therefore, it is difficult to separate these two factors.

Near-fatal and fatal reactions upon incidental exposure to allergenic foods occur most often in adolescents and young adults.[29] During OIT, adult patients experience more HETRs compared with children and adolescents, but that likely reflects only a food allergy with more severe features (such as lower reaction threshold or higher specific IgE levels) rather than the effect of age itself.[30] Interestingly, HG-HETRs were not associated with older age, and five of nine cases of refractory anaphylaxis (55.6%) occurred in patients aged less than 10 years.

Triggers for adverse reactions during OIT were previously reported,[31] and patients are accordingly instructed regarding how to avoid or handle the daily dose. No significant differences were found between patients' reported triggers for HG-HETRs and those previously reported for HETRs.[6] It is concerning that in 14 of 30 cases of HG-HETRs (46.7%) and in four of nine cases of refractory anaphylaxis (44.4%), no potential trigger additional to regular dosing was identified. Moreover, two patients who experienced an HG-HETR after exposure to an avoidable trigger subsequently experienced a similar reaction for which they could not identify a trigger. In addition, most HG-HETRs (67%) were evoked in the beginning of the build-up phase to doses lower than 400 mg protein, and 50% of those reactions were to doses lower than 100 mg, which does not support the influence of an increase in dose on the occurrence of HG-HETRs. Altogether, these findings emphasize that it is patients' characteristics rather than the treatment protocol or environmental triggers that comprise the main risk factor for severe reactions.

Delayed epinephrine administration increases the risk for mortality from anaphylaxis.[21,32] Unlike the reported low compliance with epinephrine self-carriage and self-administration,[33] all of the patients in the current study had epinephrine autoinjectors readily available, and most (87.1%) used the epinephrine autoinjector at home. In the remaining cases, patients were promptly brought to a medical facility (EMS, clinic, or ER) and were treated there. The time duration between the development of a severe reaction requiring epinephrine treatment and the administration of this drug cannot be estimated, but it is possible that under patients' lower awareness and availability of epinephrine, more HG-HETRs would have developed. All cases of refractory anaphylaxis developed despite home epinephrine administration, which emphasizes that severe and fatal reactions can occur even with timely epinephrine administration.[21,32] We cannot rule out that epinephrine administration in the current patients was not delayed, even when it was given at home.

The findings of this study raise two important issues. The first relates to exclusion criteria for high-risk patients (milk OIT, asthma, and HDM sensitization) from OIT. Because asthma and

HDM sensitization were present in many (about 40%) of milk-allergic patients in this study, this policy seems controversial. Also, the history relating to the amount of allergenic protein that caused a reaction before OIT is inaccurate. Naturally, the risk for severe home reactions, occurring even months after a stable desensitization state, should be acknowledged and discussed with patients. These patients should be treated in well-experienced centers. The second issue pertains to managing patients after such a reaction. These patients are at high risk for severe and even fatal reactions from accidental exposure to milk.[34] Also, some of them experience a severe reaction to high doses that could be reduced, and many eventually achieve partial or full desensitization. However, in view of the accumulating experience, including the risk for recurrent HG-HETRs and the high failure rate among these patients, we now recommend a significant dose reduction to a protective dose (ie, 300 mg protein) or, if that is not feasible, stopping milk OIT. Other treatment strategies, including biological drugs (eg, omalizumab)[35] with or without OIT, should then be thoroughly discussed with patients, considering all potential short- and long-term risks and benefits. High-grade HETRS to foods other than milk are much rarer and milder, and resulted in full desensitization.

This study had several limitations. First, it evaluated only reactions occurring during the dose escalation phase, as we receive regular patients' reports only during this stage of OIT. The rate of HETRs during maintenance is significantly lower and might reflect different risk factors. Second, this study reflects the experience of a single center, and the findings should be compared with other centers, treating different populations and using different protocols. In addition, there might have been some severe reactions that were not treated or were erroneously attributed to another health condition, and there might have been mild reactions that were overtreated with epinephrine. However, in the absence of objective medical assessment at home, epinephrine administration was used in this study as a marker for patients' confidence in their experiencing an allergic reaction and in its severity. Finally, some patients may have had an impaired vital sign that resolved after epinephrine administration and normalized by the time patients were examined in the ER. However, if such reactions occurred, that suggests that they responded promptly to epinephrine.

Severe reactions to home treatment doses might occur during OIT. While compliance with the prompt use of epinephrine is mandatory to begin OIT, it does not provide full protection from such reactions. Although these reactions are rare, they should be considered when discussing OIT with patients, especially those with asthma and HDM sensitization who undergo milk OIT, and a joint decision should be made regarding the inclusion of such patients in treatment.

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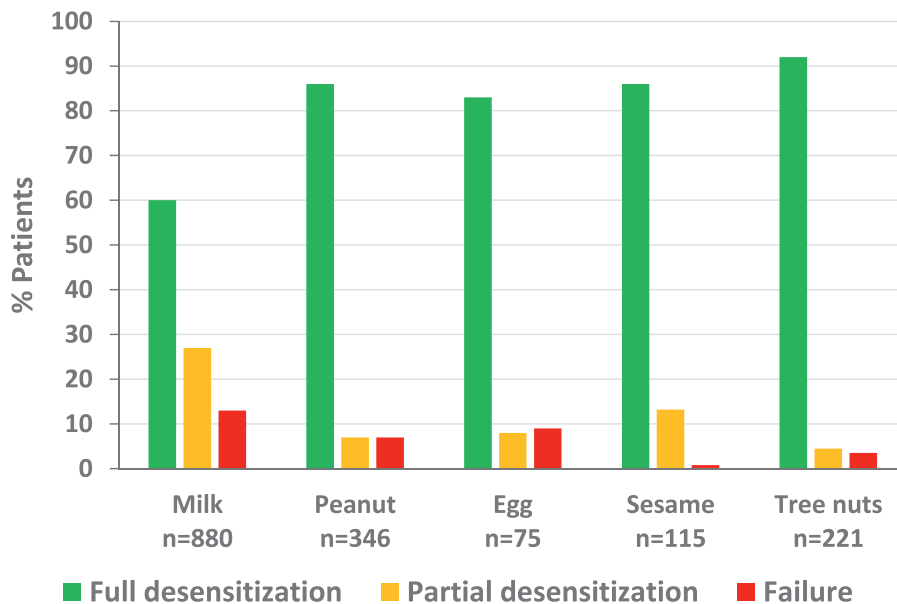
ONLINE REPOSITORY

FIGURE E1. Oral immunotherapy outcome for each treated food. Treatment outcome (full desensitization, partial desensitization, or failure) for the various treated foods is displayed.
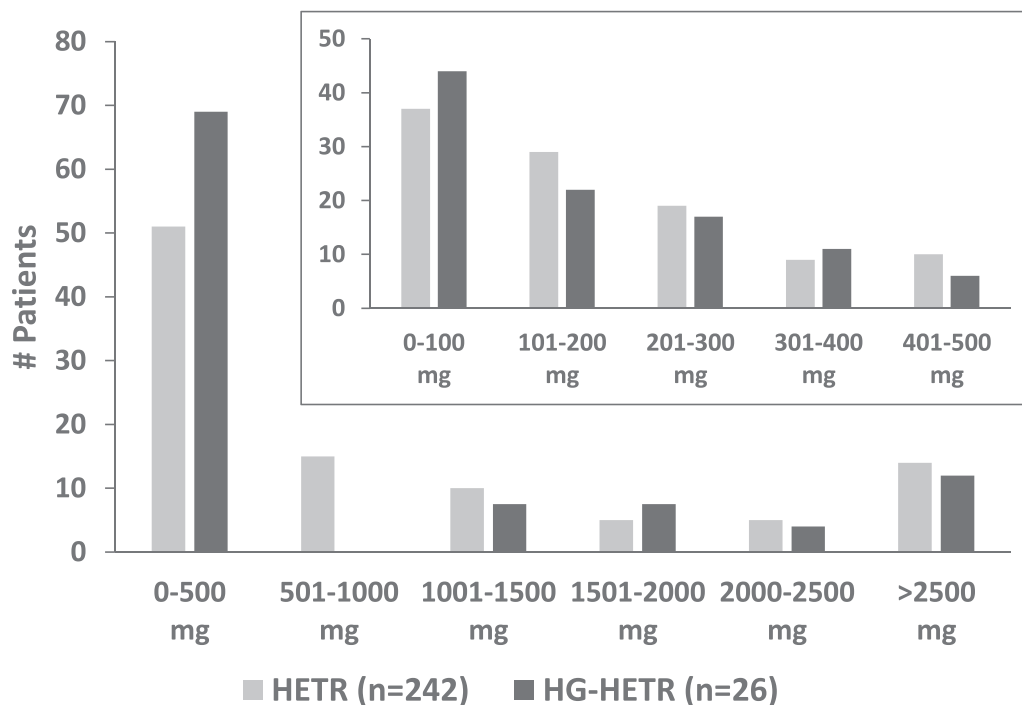

FIGURE E2. Rate of home epinephrine-treated reactions (HETRs) for various doses during milk oral immunotherapy. Rate of HETRs and high-grade (HG) HETRs experienced during milk oral immunotherapy, for a range of doses presented in intervals of 100 mg until 500 mg protein and in intervals of 500 mg to the maximal dose.
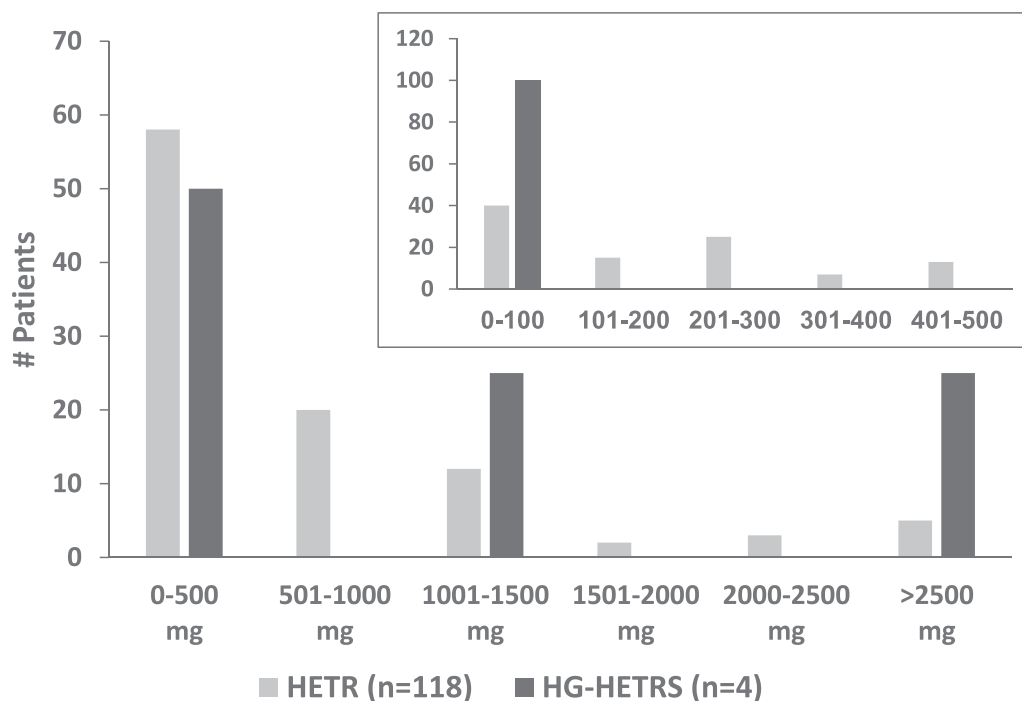
FIGURE E3. Rate of home epinephrine-treated reactions (HETRs) for various doses during oral immunotherapy to foods other than milk. Rate of HETRs and high-grade (HG) HETRs experienced during oral immunotherapy for egg, peanut, sesame, and tree nut, for a range of doses presented in intervals of 100 mg until 500 mg protein and in intervals of 500 mg through to the maximal dose.

TABLE E1. Instructions for safe home dosing

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

TABLE E2. Action plan for home reactions to oral immunotherapy doses

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

TABLE E3. Characteristics of study population

Characteristics	Parameter	OIT Treatments (n=1637)
Demographics	Age, y (median [IQR])	7.2 (5.4-10.4)
	Male sex	993 (60.6%)
	Asthma	792 (48.4%)
	House dust mite sensitization	1066 (65%)
	Skin prick test wheal size, mm (median [IQR])	8 (6-12)
Pre-OIT	Anaphylaxis	927 (56.6%)
	Emergency room treatment	819 (50%)
	Epinephrine administered	555 (33.9%)
	Hospitalization	218 (13.3%)
OIT	Epinephrine induction	355 (21.7%)
	Single highest tolerated dose (mg protein) (median [IQR])	45 (12.5-120)

IQR, interquartile range; *OIT*, oral immunotherapy.