Original Article

Patient Characteristics and Risk Factors for Home Epinephrine-Treated Reactions During Oral Immunotherapy for Food Allergy

Liat Nachshon, MD[a,b], Naama Schwartz, PhD[c], Lior Tsviban, MD[d], Michael B. Levy, MD[a], Michael R. Goldberg, MD, PhD[a,d], Naama Epstein-Rigby, MD[a], Yitzhak Katz, MD[a,d], and Arnon Elizur, MD[a,d] *Zerifin, Tel Aviv, and Haifa, Israel*

What is already known about this topic? Studies of risk factors for severe reactions during oral immunotherapy (OIT) described thus far, including age, asthma, degree of sensitization, pre-OIT reaction severity, and initial reaction threshold, are limited and require validation in a large cohort.

What does this article add to our knowledge? Milk OIT is a risk factor for home epinephrine-treated reactions and for poor outcome following such reactions. Epinephrine-treated reactions before OIT or during clinic updosing, asthma, and a lower tolerated dose provide additional risk factors.

How does this study impact current management guidelines? The identified risk factors for home epinephrine-treated reactions during OIT and for high failure rate following such reactions enable stratification of patients' risk and might assist in patient selection for OIT.

BACKGROUND: Oral immunotherapy (OIT) is effective in desensitizing food-allergic patients but adverse events limit its applicability.
OBJECTIVE: To identify risk factors for home epinephrine-treated reactions during the build-up phase of OIT.
METHODS: A retrospective cohort study of patients older than 3.7 years undergoing OIT for food allergy at Shamir Medical Center between April 2010 and March 2019. All patients with a final disposition of full desensitization, partial desensitization, or failure were analyzed. Risk factors and outcome of home epinephrine-treated reactions were examined.
RESULTS: A total of 1037 patients (mean age, 8.4 years) who underwent 1100 OIT treatments (milk, n = 710; peanut, n = 213; egg, n = 50; sesame, n = 57; and tree nuts, n = 70) reached a final disposition and were analyzed. Full desensitization was achieved in 763 (69.4%) treatments, partial desensitization in 219 (19.9%), and 118 (10.7%) failed. Epinephrine was administered to 121 patients (11.7%) during 10.8% of treatments. Milk OIT was a significant risk factor both for epinephrine-treated reactions (odds ratio, 2.15; 95% CI, 1.25-3.68) and for low rate of full desensitization following such reactions compared with nonmilk OIT (18.2% vs 73.9%, respectively; $P < .0001$). Risk factors during milk OIT included asthma, pre-OIT reaction severity, lower tolerated dose, and epinephrine-treated reactions during clinic updosing, whereas risk factors during nonmilk OIT were male sex and lower tolerated dose.
CONCLUSIONS: Milk OIT poses a significant risk for home epinephrine-treated reactions during OIT and for poor outcome following such reactions. Together with the additional risk factors described for both milk and nonmilk OIT, this information may assist in patient selection for treatment. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: *Oral immunotherapy; Food allergy; Adverse reactions; Epinephrine; Desensitization; Milk allergy; Asthma; Emergency room; Tolerated dose*

INTRODUCTION

The prevalence of food allergy has increased in recent decades.[1,2] Food allergy is associated with a risk of life-threatening reactions and with impairment in quality of life of patients and families.[3,4] Oral immunotherapy (OIT) has become a promising treatment for patients with IgE-mediated food allergy, with desensitization rates ranging from 60% to 90%,[5-8] positively affecting patient and families' quality of life.[9]

[a]Institute of Allergy, Immunology and Pediatric Pulmonology, Shamir Medical Center, Zerifin, Israel
[b]Department of Medicine, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[c]School of Public Health, University of Haifa, Haifa, Israel
[d]Department of Pediatrics, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
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Corresponding author: Liat Nachshon, MD, Institute of Allergy, Immunology and Pediatric Pulmonology, Yitzhak Shamir (formerly Assaf Harofeh) Medical Center, Zerifin 70300, Israel. E-mail: liatna2@gmail.com.
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Abreviations used
ER- Emergency room
HDM- House-dust mite
OFC- Oral food challenge
OIT- Oral immunotherapy
SHTD- Single highest tolerated dose
SPT- Skin prick test

The main concern limiting the widespread use of OIT is the risk of anaphylactic reactions.[10] Although OIT protocols differ in their starting dose, rate and interval of updosing, and target maintenance dose, most are composed of rounds of in-clinic updosing separated by periods of 2 to 4 weeks of home dosing.[5,7] Adverse reactions were reported both for in-clinic updosing of OIT and for home doses.[6,7,11,12] Although any adverse event is not desirable, reactions occurring in the clinic setting, similar to reactions occurring during subcutaneous immunotherapy, are supervised, and can be promptly treated. In contrast, reactions occurring at home might receive inadequate treatment and induce greater stress.[13] In addition, these reactions, which are dependent on patients' subjective interpretation, might be inaccurately or only partially reported.[14] Most home reactions described in OIT studies were classified as mild; however, reports of moderate and even severe systemic reactions exist.[10-12] Such reactions occur mainly during the updosing phase of OIT and are a major cause for treatment failure.[12,15-18]

Recently, the Food and Drug Administration approved the first drug for treating peanut allergy in children,[19] an approval that will likely make OIT more readily available for the practicing allergist. It is therefore not surprising that along with its approval, the Food and Drug Administration has required a Risk Evaluation and Mitigation Strategy to mitigate the risk of anaphylaxis associated with this drug. This requirement further emphasizes the importance of identifying patient characteristics that are associated with a greater risk for severe reactions for improving patient selection and care during OIT.

Several studies reported potential risk factors for severe reactions during OIT, including an older age, concomitant asthma, degree of sensitization on skin or blood tests, pre-OIT reaction severity, and initial reaction threshold.[20] However, these studies were limited either by small sample sizes, or, in the case of meta-analyses, by the different OIT protocols, patient selections, and adverse events reporting.[20] In this study, we examined risk factors for home reactions requiring epinephrine during the updosing phase of OIT in a large single-center treatment program of 1037 patients undergoing 1100 OIT treatments using a common protocol adjusted for the treated food. We chose epinephrine-treated reactions as the outcome, because in the absence of a medical judgment of the severity of reactions experienced at home, this measure provides an objective indication of patients' perception of such reactions.

METHODS

Patients

In a retrospective cohort study, all patients older than 3.7 years who began an open-label OIT treatment program at the Institute of Allergy, Immunology and Pediatric Pulmonology at Shamir Medical Center, Zerifin, Israel, between April 2010 and March 2018 were enrolled. Those who reached a final disposition of full desensitization, partial desensitization, or failure, as detailed below, by March 2019 were studied. Patients with evidence of IgE-mediated allergy to the target food, defined by a positive skin prick test result and/or specific serum IgE, together with a positive oral food challenge, or a clinical history of a recent reaction to the specific food, were evaluated to assess their eligibility for OIT treatment. Diagnostic inclusion criteria for patients in OIT to milk, peanut, egg, sesame, or tree nuts (walnut, cashew, hazelnut, or almond) are included in this article's Online Repository at www.jaci-inpractice.org, as previously described.[15-18] A minimal tolerated dose of 5 mg for milk protein 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 not excluded. 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 (SPTs) were performed to the treated food and to house-dust mite (HDM), as detailed in this article's Online Repository at www.jaci-inpractice.org and as previously described.[21,22] HDM sensitivity was used as a surrogate marker for allergic rhinitis because the vast majority of patients with allergic rhinitis in Israel are sensitized to HDM.[23,24] All patients underwent spirometry, with or without a bronchodilator before OIT. Patients with current asthma, defined as asthma symptoms experienced, or medications used, in the year before treatment, were asked about their asthma symptoms on each updosing clinic visit and spirometry was performed (Minispir, Mir, Rafamedical, Yavne, Israel). Patients with uncontrolled asthma were first stabilized for 2 to 3 weeks before OIT initiation.

OIT protocol

The OIT treatment protocols for milk, peanut, sesame, and tree nuts are detailed in this article's Online Repository at www.jaci-inpractice.org, and were previously published.[15-18] Egg-OIT followed a similar protocol. Briefly, on treatment start, patients underwent an initial 4-day dose-escalation phase. The first 2 days consisted of an oral food challenge (OFC) and the following 2 days served to verify the safety of the identified single highest tolerated dose (SHTD), defined as the highest dose given during the food challenge days that elicits no objective symptoms. Subsequently, the treatment continued, with monthly dose escalations performed in an ambulatory care setting. The target maintenance dose for full desensitization to milk was 7200 mg protein; peanut, 3000 mg; egg, 12,000 mg; tree nuts, 3900 mg; and sesame, 4000 mg. Patients who were able to tolerate less than the target dose but an amount of at least 180 mg protein of milk (6 mL), 300 mg peanut (~1 peanut) or tree nuts (>1/4 walnut), 1500 mg egg (1/4 egg), and 240 mg protein of sesame (1 g of Tahini) without adverse reactions were considered partially desensitized. Patients unable to tolerate the above-mentioned minimal protein amounts at the end of build-up 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 precautions as detailed in this article's Online Repository at www.jaci-inpractice.org. Each patient was prescribed antihistamines, bronchodilators, and 2 up-to-date epinephrine autoinjectors. A staff physician was on call 24/7 for consultation. Patients were asked to

TABLE I. Characteristics of study population

Characteristic	Parameter*	Home epinephrine (n = 121)	No home epinephrine (n = 979)	*P* value
Demographic	Age (y), median (IQR)	7.8 (5.6-11.8)	6.8 (5-10.2)	.012
	Sex: male	75 (62)	590 (60.3)	.86
	Asthma	85 (70.2)	472 (48.2)	<.0001
	HDM sensitivity	89 (73.5)	572 (58.4)	.014
	SPT wheal size (mm)	8 (6-10)	7 (5-10)	.002
Pre-OIT	Anaphylaxis	97 (80.1)	571 (58.3)	<.0001
	ER treatment	87 (71.9)	465 (47.5)	<.0001
	Epinephrine administered	75 (62)	271 (27.7)	<.0001
	Hospitalization	40 (33)	130 (13.3)	<.0001
OIT	Epinephrine induction	55 (45.5)	179 (18.2)	<.0001
	SHTD (mg protein)	22.5 (12.5-45)	60 (20-200)	<.0001

IQR, Interquartile range.
*Continuous variables are presented as medians (IQR). Categorical variables are presented as n (%).

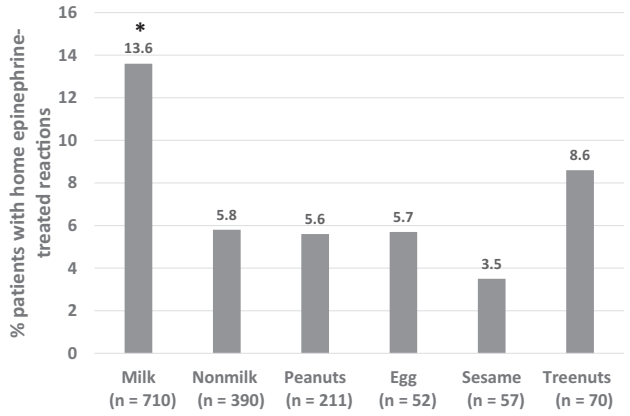

FIGURE 1. The percentage of patients experiencing home epinephrine-treated reactions during OIT for milk, peanut, egg, sesame, and tree nuts. *A significant difference was found between milk and nonmilk OIT ($P < .0001$) but not between nonmilk foods.

send a daily report of their home dose consumption via a web-based reporting system, as detailed in this article's Online Repository at www.jaci-inpractice.org and as previously described.[25] For any reaction consisting of severe abdominal pain, shortness of breath, or lethargy, or whenever in doubt, patients were advised to administer epinephrine autoinjector and go to a local emergency room (ER). Following such reactions, patients were contacted by phone and were asked to send the report from the local ER. On the basis of circumstances leading to the reaction, staff physicians would then make a joint decision about permanent or temporary protocol modification or discontinuation of treatment.

Statistics

The associations between potential risk factors and home epinephrine-treated reactions were explored using χ^2 test (or Fisher exact test) for categorical variables. For continuous variables, the student *t* test (or Wilcoxon 2-sample test) was implemented. Stepwise multivariable logistic regression was used, presenting adjusted odds ratios with correspondence 95% CI. The model goodness of fit was explored via C-statistics as well as the Hosmer and Lemeshow goodness-of-fit test. Time to home epinephrine-treated reactions was presented with Kaplan-Meier curve, and the log-rank test was used to explore the difference between the milk and nonmilk OIT curves. Statistical analysis was done using SAS 9.4 software (SAS Institute, Cary, NC). Significance was determined when the *P* value was less than .05.

RESULTS

Study population

A total of 1285 patients began OIT during the study period. Nine milk-allergic patients with an SHTD of less than 5 mg protein and 8 children who were unable to cooperate with in-clinic dose consumption were excluded. Of the 1268 remaining patients, 1037 patients, who underwent 1100 OIT treatments (45 underwent 2 consecutive treatments and an additional 9 patients underwent 3 consecutive OIT treatments for different foods) during this time, reached a final disposition and were analyzed. Milk OIT was administered to 710 patients, peanut to 213, egg to 50, sesame to 57, and tree nut OIT to 70 patients. Patients studied were at a mean age of 8.4 years, range 3.7 to 36.5 years, and 664 (60.4%) were males. Asthma was diagnosed in 544 (49.5%) treatments. The median (interquartile range) SHTD of all OIT treatments was 50 (15-180) mg protein. Mean treatment duration was 8.7 ± 7 months. Final disposition was full desensitization in 763 treatments (69.4%), partial desensitization in 219 (19.9%), and 118 (10.7%) treatments failed.

Characteristics of home epinephrine-treated reactions

Epinephrine was administered to 121 patients (11.7%) (milk, 98; peanut, 12; egg, 3; sesame, 2; tree nuts, 6) for home reactions during 11% of OIT treatments. None of the patients who underwent more than 1 OIT treatments experienced home epinephrine-treated reactions. Epinephrine-treated reactions occurred as early as the first day of home treatment and continued at a constant rate throughout the first 8 months of OIT (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Their rate subsequently decreased as treatment progressed, but such reactions still occurred up to almost 2 years into treatment in occasional patients.

Risk factors for home epinephrine-treated reactions

Patients who experienced epinephrine-treated reactions at home were older (median, 7.8 vs 6.8 years; $P = .012$), their SPT

TABLE II. Multivariable analysis for home epinephrine-treated reactions

Parameter	Univariable analysis	Multivariable analysis			
	Crude OR	Adjusted OR	95% CI		*P* value
			Low	High	
Age	1.05	1.02	0.98	1.06	.44
Asthma	2.44	1.38	0.88	2.16	.16
HDM	1.79	1.68	1.05	2.69	**.03**
SPT food (mm)	1.07	1.05	0.98	1.11	.16
Anaphylaxis	2.94	1.19	0.69	2.07	.53
ER before treatment	3.12	1.73	1.04	2.88	**.04**
Hospitalization before treatment	3.33	1.70	1.03	2.80	**.04**
Epinephrine induction	3.73	1.98	1.26	3.09	**.003**
Milk OIT	2.56	2.15	1.25	3.68	**.006**
SHTD (mg) (for every 50 units)	0.83	0.89	0.82	0.96	**.004**

OR, Odds ratio.
C-statistics = 77.6%.
Hosmer and Lemeshow goodness-of-fit test ($P = .587$).
Bold indicates statistical significance ($P < .05$).

TABLE III. Characteristics of patients undergoing milk vs nonmilk OIT

Characteristic	Parameter*	Milk OIT (n = 710)	Nonmilk OIT (n = 390)	*P* value
Demographic	Age (y)	7.5 (5.2-11.1)	6.4 (5.0-9.2)	<.0001
	Sex: male	420 (59.1)	244 (62.6)	.25
	Asthma	376 (53.4)	180 (46.1)	.03
	HDM sensitivity	375 (52.8)	285 (73)	<.0001
	SPT wheal size (mm)	7 (5-10)	8 (6-10)	<.0001
Pre-OIT	Anaphylaxis	495 (69.7)	173 (44.3)	<.0001
	ER treatment	402 (56.6)	150 (38.5)	<.0001
	Epinephrine administered	255 (35.9)	91 (23.3)	<.0001
	Hospitalization	141 (19.9)	29 (7.4)	<.0001
OIT	Epinephrine induction	190 (26.8)	44 (11.3)	<.0001
	SHTD (mg protein)	60 (22-180)	40 (10-150)	<.0001
	Treatment duration (mo)	7 (3.8-11.7)	7.1 (3.8-11.4)	.96

IQR, Interquartile range.
*Continuous variables are presented as medians (IQR). Categorical variables are presented as number (%).

wheal size to the treated food was higher (8 mm vs 7 mm; $P = .002$), and they had a higher rate of HDM sensitivity (73.5% vs 58.4%; $P = .014$), a characteristic of allergic rhinitis in almost all Israeli patients,[23,24] and asthma (70.2% vs 48.2%; $P < .0001$), compared with those who did not (Table I). In addition, these patients had a more severe food allergy as evidenced by the higher level of treatment required for their pre-OIT reactions ($P < .0001$) (Table I). This was also reflected in a higher rate of epinephrine-treated reactions during clinic visits for updosing (which mostly represented the 2-day OFC at OIT entry) (45.5% vs 18.2%; $P < .0001$) and in a lower SHTD (median, 22.5 mg vs 60 mg; $P < .0001$) at the beginning of OIT (Table I). The risk for home epinephrine-treated reactions significantly decreased with SHTD of more than 60 mg protein ($P < .0001$) (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Of the various foods treated, milk was the one associated with the highest risk for home reactions requiring epinephrine, 13.8% of patients compared with 3.5% to 8.6% for other foods ($P < .0001$) (Figure 1). A diagnosis of HDM sensitivity ($P = .03$), pre-OIT ER visits ($P = .04$) or hospitalizations ($P = .04$) due to a reaction to the treated food, milk OIT ($P = .006$), a lower SHTD ($P = .004$), and epinephrine-treated reactions during clinic visits for updosing ($P = .003$) remained independent significant risk factors for home epinephrine-treated reactions in a stepwise logistic multivariable regression analysis (Table II).

Milk versus nonmilk OIT

Milk-allergic patients (n = 710) were slightly older (median, 7.5 vs 6.4 years; $P < .0001$) and more had asthma (53.4% vs 46.1%; $P = .03$) compared with those undergoing OIT to other foods (n = 390) (Table III). Patients undergoing milk OIT had significantly more severe reactions (anaphylaxis, epinephrine, ER visits, and hospitalizations) before treatment ($P < .0001$). However, SPT wheal size to milk was lower (7 mm vs 8 mm; $P < .0001$), and the SHTD of milk-allergic patients was significantly higher (less severe) at the start of OIT (60 mg vs 40 mg; $P < .0001$) compared with non−milk-allergic patients. Still, milk-allergic patients experienced significantly more reactions requiring epinephrine during clinic visits for updosing (26.8% vs 11.3%; $P < .0001$). The increased rate of home epinephrine-treated reactions during milk OIT was evident after the first 2

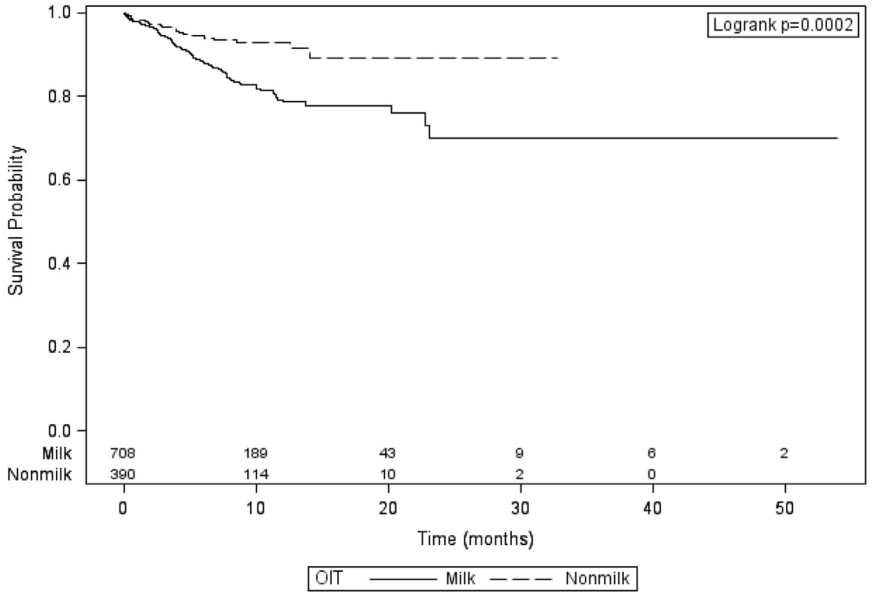

FIGURE 2. Time to home epinephrine-treated reactions in milk- and non−milk-treated patients. Kaplan-Meier curves demonstrating the time to the first home reaction requiring epinephrine in patients undergoing OIT for milk allergy and those undergoing OIT for other foods. Vertical lines represent censored patients.

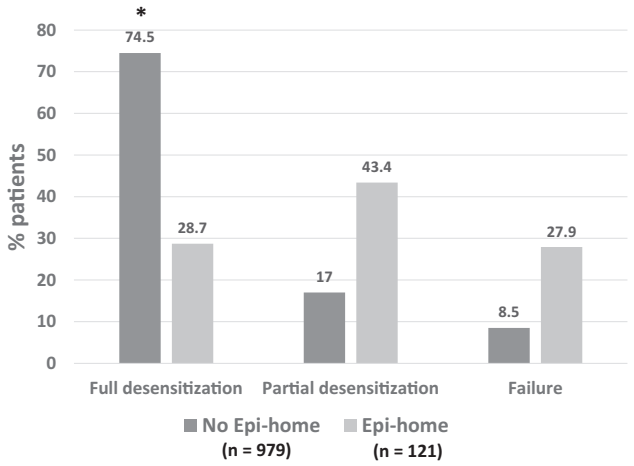

FIGURE 3. Outcome of OIT in patients with and without home epinephrine-treated reactions. The percentage of patients achieving full desensitization, partial desensitization, or treatment failures among those who experienced home epinephrine-treated reactions and those who have not. *Significant differences were found in the rate of full desensitization between the 2 groups ($P <$ .0001).

months and up to a year of treatment (Figure 2). The difference in the rate of epinephrine-treated reactions between milk and nonmilk OIT was highest at lower SHTD and was not significant at doses greater than or equal to 60 mg protein (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org). We next examined whether the different target doses used for the various foods affected our results. Only 4 patients received epinephrine for reactions to doses greater than 3000 mg protein and all were treated to milk. Excluding these patients from the analysis did not affect the results.

Treatment outcome of patients treated with home epinephrine

The rate of achieving full desensitization decreased sharply from 74.5% of patients without to 28.7% of those with home reactions requiring epinephrine ($P <$ .0001) (Figure 3). Many of these patients achieved partial desensitization, enabling protection from life-threatening reactions in case of accidental exposures to foods that may contain their allergenic proteins, but the failure rate was significantly higher compared with patients without such reactions (27.9% vs 8.5%) (Figure 3). Although increased failure was observed in both milk- ($P <$ .0001) and non−milk-treated ($P =$ .042) patients with home reactions requiring epinephrine, full desensitization was achieved by most non−milk-treated patients (73.9%) compared with only a minority in milk-treated patients (18.2%) ($P <$ .0001) (Figure 4).

Identifying patients at risk for home epinephrine-treated reactions

We repeated the multivariable analyses for milk- and non−milk-treated patients. During nonmilk OIT, male sex ($P =$ .017) and an SHTD of less than 60 mg ($P =$ .024) were the only significant risk factors for home epinephrine-treated reactions (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). In addition, in the nonmilk OIT group, use of epinephrine during clinic visits was also associated with home epinephrine-treated reactions but statistical significance was not met, likely due to the small number of patients requiring epinephrine for home reactions in this group. In contrast, in the milk OIT group, asthma, ER treatment due to a reaction to the treated food before OIT, a lower SHTD at OIT initiation, and epinephrine-treated reactions during clinic visits (mostly reflecting OFC at OIT entry) remained significant risk factors for

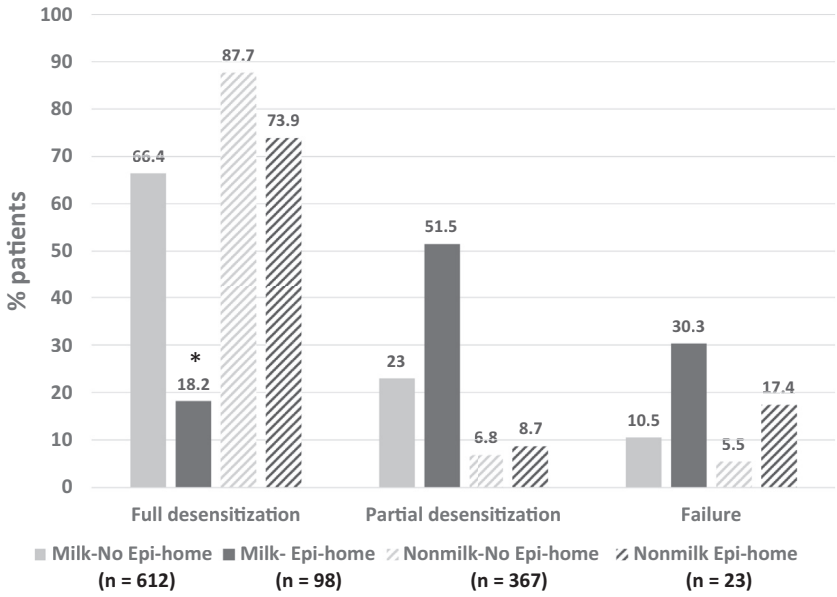

FIGURE 4. Outcome of milk and nonmilk OIT in patients with and without home epinephrine-treated reactions. The percentage of patients achieving full desensitization, partial desensitization, or treatment failures among those who experienced home epinephrine-treated reactions and those who have not. *A significant difference was noted in the rate of full desensitization between home epinephrine-treated milk and nonmilk OIT patients ($P < .0001$).

home epinephrine (Table E1). The predicted probabilities for home epinephrine-treated reactions during milk OIT, using various combinations of the risk factors identified, are presented in Table IV. Pre-OIT characteristics (asthma, ER visit, and epinephrine on OFC) determined most of the variability in the risk for home epinephrine-treated reactions (5%-39% for a given SHTD) (Table IV). The SHTD determined at study entry could affect this risk by up to 2.5-fold for a given set of pre-OIT characteristics, an effect that was evident primarily at high SHTD.

DISCUSSION

In this single-center study of a large cohort of 1100 OIT treatments for various food allergies using a single protocol, we identified risk factors for home epinephrine-treated reactions during build-up. Milk OIT was unique, both in its risk for such reactions and in its significantly worse outcome following these reactions compared with nonmilk OIT. Additional risk factors identified, determined before or early in the course of OIT, might enable a personalized risk assessment for each patient before and during treatment.

Several risk factors for adverse events during OIT were previously described.[7,11,20,26-28] However, these descriptions were limited by the small sample sizes included, ranging from 41 to 81 patients,[26,27] or, in the case of meta-analyses, by the variable patient selections, different protocols, and various adverse event reporting methods.[7,11] In addition, most previous studies grouped clinic and home doses together and did not separate mild from severe reactions.[7,26,27] Also, information regarding home reactions was based on a retrospective patient report with no medical judgment and was subjected to a recall bias.[7,11,13,14,27,28] Although all OIT-induced adverse events should be minimized, severe reactions occurring at home involve a significantly increased risk, generate more anxiety, and often lead to treatment cessation.[13] Therefore, minimizing the frequency of these reactions is of major importance. Our study, using a large group of patients undergoing OIT for various foods over a 9-year period at a single center and using a single protocol, enabled us to overcome these limitations. In addition, the use of an electronic system with required daily reports on home dose consumption and induced reactions reduced the likelihood of a recall bias.[25]

Milk OIT comprised the most significant risk factor for home epinephrine-treated reactions in our patient population. Milk-allergic patients had more severe food-allergic reactions compared with patients with allergies to other foods even before entering OIT. It is doubtful that the age differences (median of 1.2 years older in milk-allergic patients) or their slightly higher rate of asthma (53.1% vs 46.2%) could account for their increased severity. Furthermore, milk-allergic patients were able to tolerate a significantly higher dose at the beginning of OIT (median, 60 mg protein) compared with non−milk-allergic patients (median, 40 mg protein). Taken together, these data raise, for the first time, the concept that inherently milk allergy is associated with a greater risk compared with other food allergies. Moreover, home epinephrine-treated reactions during milk OIT were associated with significantly worse treatment outcomes, with only 18.2% achieving full desensitization, compared with 73.9% in nonmilk OIT. Indeed, milk is the leading cause of food allergy−associated mortality in Israel[29,30]; however, it should be noted that the leading causes for food-associated fatal reactions depend on geography, because peanuts, tree nuts, and seafood are the leading causes for fatal reactions in different countries.[31-33] This may be attributed to different dietary habits or to different patient populations. Studies on

TABLE IV. Predicted probabilities for home epinephrine-treated reactions during milk OIT

SHTD	Asthma	Epinephrine during clinic visit	ER before treatment	Predictive probability for home epinephrine
5	No	No	No	5%
5	Yes	No	No	10%
5	No	Yes	No	10%
5	No	No	Yes	13%
5	Yes	Yes	No	19%
5	Yes	No	Yes	23%
5	No	Yes	Yes	24%
5	Yes	Yes	Yes	39%
60	No	No	No	4%
60	Yes	No	No	8%
60	No	Yes	No	9%
60	No	No	Yes	11%
60	Yes	Yes	No	16%
60	Yes	No	Yes	20%
60	No	Yes	Yes	21%
60	Yes	Yes	Yes	35%
300	No	No	No	2%
300	Yes	No	No	4%
300	No	Yes	No	4%
300	No	No	Yes	5%
300	Yes	Yes	No	8%
300	Yes	No	Yes	10%
300	No	Yes	Yes	11%
300	Yes	Yes	Yes	20%

epinephrine-treated reactions during milk versus nonmilk OIT in different populations are required.

Given the marked differences between milk and nonmilk OIT, it is primarily the milk-allergic patients who are in need for further risk stratification to identify those patients who would benefit from OIT. Although the recent Food and Drug Administration approval was granted solely for a peanut product, it might drive practicing allergists to provide OIT for additional foods. Milk, which lacks the technical and financial limitations of peanut OIT for it can be easily diluted to achieve small doses, and is also associated with nutritional deficiencies,[34] might serve as an attractive food to treat, making patient selection extremely important. We found several factors (epinephrine-treated reactions before OIT, asthma, a lower SHTD, and reactions requiring epinephrine during clinic updosing) to provide that information. Although some of these factors were previously described, the large sample size enabled us to develop a statistical model to accurately determine, on an individual level, a patient's risk, ranging from minimal (2%) to very high (39%) for home epinephrine-treated reactions. Given that these reactions translate into treatment outcome, this information might prevent unnecessary exclusion of low-risk milk-allergic patients from OIT, and enable early identification and exclusion of patients deemed to be at too high risk, patients who might be good candidates for alternative protocols using biologicals or modified proteins.[35] Unlike milk OIT, only male sex and a low SHTD were identified as risk factors for home epinephrine-treated reactions in nonmilk OIT. Although the rate of these reactions is small and their outcome is sufficiently reassuring to not exclude patients from nonmilk OIT, additional studies are needed to identify treatment modifications that would further reduce the risk for such reactions.

For both milk and nonmilk OIT, a longer duration of being on treatment had a beneficial effect, and severe reactions occurred less as treatment progressed. This matches previous descriptions of reduced rate of adverse reactions with longer duration of OIT.[36,37] These findings indicate that patients can be encouraged that the risk for epinephrine-treated reactions will decrease as they continue to consume the allergenic food.

This study has several limitations. First, epinephrine-treated reactions did not necessarily reflect, all or only, the most severe reactions patients experienced. Some severe reactions might have not been treated with epinephrine and some of the epinephrine-treated reactions might have not been quiet severe,[38] especially given that patients were guided to liberally use self-injectable epinephrine. However, given the inherent limitations of home treatment assessment, the use of epinephrine is an objective indication of patients' perception of a severe anaphylactic reaction, and the effect of these reactions on treatment outcome supports their use as an outcome measure. In addition, we performed a multivariable analysis in all the patients, examining risk factors for in-clinic reactions requiring epinephrine treatment. We found that similar risk factors (milk OIT, reaction severity before treatment, SHTD, and HDM sensitivity) were associated with such reactions, providing further support to our findings (data not shown). Another limitation is that this study examined reactions during the build-up phase only. Although reactions experienced during maintenance are less frequent and likely have a small effect on treatment outcome,[39,40] further study is required for understanding patients' risk for such reactions during long-term maintenance treatment. A few patients in this study underwent OIT more than once. We chose to include all their treatments given that they were done sequentially and to different foods, and because most risk factors identified (severity of food allergy, SHTD, and epinephrine during updosing) were food-specific. Finally, data on allergic rhinitis and atopic dermatitis were not consistently available and were not included in the analysis. HDM sensitivity was used as a surrogate marker for allergic rhinitis. The fact that HDM sensitivity was associated with home epinephrine-treated reactions supports its close association with allergic rhinitis in our study population, because allergic rhinitis was previously shown to associate with severe reactions during OIT.[11]

CONCLUSIONS

Milk and nonmilk OIT differ significantly, both in the risk they pose for severe anaphylactic reactions and in their outcome once such reactions occur. The additional risk factors described in this study might help identify patients at high risk for severe reactions and assist in patient selection for OIT. Further research is needed to identify treatment modifications that would reduce the risk for severe allergic reactions during OIT. Validation of our findings in prospective OIT studies on different populations and among different treatment protocols is required.

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ONLINE REPOSITORY

METHODS

Patients

Inclusion criteria for entering OIT included a positive OFC or a clinical history of an immediate (within 2 hours of exposure) reaction (cutaneous, gastrointestinal, respiratory, and/or systemic symptoms) to the offending food following accidental ingestion in the past year together with evidence of sensitization to the specific food, based on a positive SPT result and/or specific serum IgE ($\geq$0.35 kUA/L). Patients with uncontrolled asthma, eosinophilic esophagitis, autoimmune diseases, inflammatory bowel diseases, malignancy, or a medical contraindication to receive adrenaline, or inability to adhere to protocol were excluded.

Pre-OIT assessment

A comprehensive medical history was obtained from each patient/parent including the occurrence of previous reactions, treatments provided including the use of injectable adrenaline, emergency department visits, and hospital admissions. Patients/parents were asked about other atopic diseases including additional food allergies. SPTs were performed using commercial extracts for milk, egg, and peanut (1:10 wt/vol; Alk-Abelló, Port Washington, NY). In cases of suspected tree nut or sesame allergy, SPT was also done with locally produced standardized high protein extracts.[E1,E2] SPTs were performed on the volar surface of the forearm of all patients with single peak lancets (Heinz Herenz, Hamburg, Germany) and mean wheal diameter was measured after 20 minutes. Histamine (1 mg/mL; ALK-Abelló) and saline were used as positive and negative controls. A positive SPT result was defined as a wheal diameter greater than or equal to 3 mm over the negative control.

OIT protocol

Patients underwent an individualized dose-escalation phase that consisted of a 4-day induction in an ambulatory care setting to determine the SHTD. The first 2 days consisted of an OFC and the following 2 days served to verify the safety of the SHTD identified. This SHTD was then consumed at least once a day at home for 24 days under specific precautions, as detailed below. Subsequently, patients returned for monthly dose escalations performed in an ambulatory care setting, followed by monthly periods of home treatment with fixed doses of the treated food until they reached full or partial desensitization, or failed treatment.

Home treatment protocol

Patients were instructed to avoid physical activity 30 minutes before and 2 hours after the dose, and not to take the dose on an empty stomach. Anticipatory home treatment guidance to patients and parents was given. Each patient received antihistamines, bronchodilators, and 2 up-to-date Epi-Pens with instructions to administer at any severe reaction (severe abdominal pain, dyspnea, or apathy). A staff physician was on call 24/7 for consultation, and patients were instructed to send a daily report of their home dose consumption, including any experienced reactions and any treatments provided, via e-mail or a web-based reporting system.[E3] A 30% reduction in the daily dose and antihistamine for 5 days was recommended if mild reactions occurred and/or during viral infections. Dose reduction by 30% for the duration until the next updosing in clinic was performed in cases of repeated or severe reactions requiring adrenaline.

Patients were instructed to send a daily report of their home dose consumption via a web-based reporting system, or, on special occasions, via an e-mail. This report included questions about the doses consumed, reactions experienced, and treatments provided.[E3] The patients' electronic reports were monitored continuously by staff members, and patients were contacted and instructed (via e-mail $\pm$ phone call) regarding any required changes in their treatment. The electronic sources (e-mail and the web reporting system) and clinic charts of all study participants were explored.

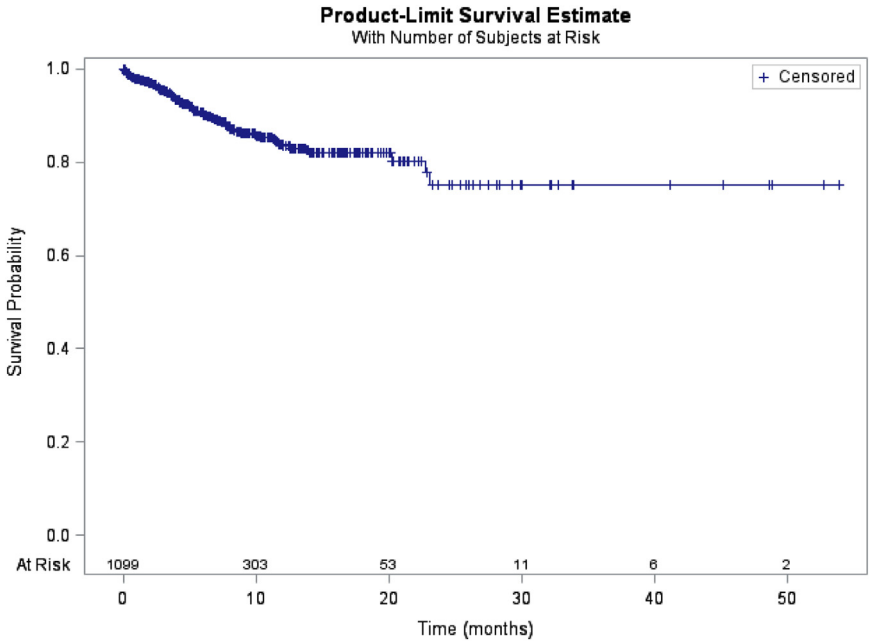

FIGURE E1. Time to home epinephrine-treated reactions in the entire population. A Kaplan-Meier curve demonstrating the time to the first home reaction requiring epinephrine in the entire study population. Vertical lines represent censored patients.

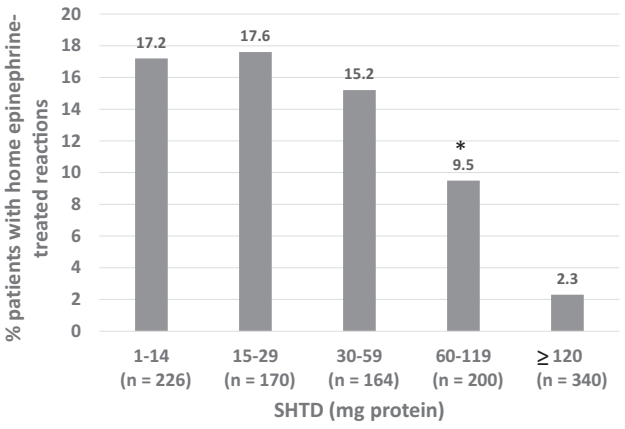

FIGURE E2. The percentage of patients experiencing home epinephrine-treated reactions for a given range of SHTD. *A significant difference was found between patients with a SHTD of less than 60 mg (16.7%) and patients with a SHTD of more than 60 mg protein (4.9%) ($P < .0001$).

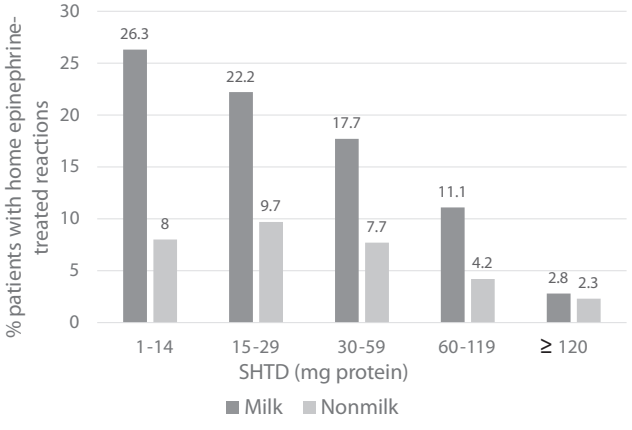

FIGURE E3. The percentage of patients experiencing home epinephrine-treated reactions for a given range of SHTD during milk vs nonmilk OIT. A significant difference was found between milk and nonmilk patients for SHTD 1 to 14 mg ($P < .0001$) and 15 to 59 mg ($P = 0.011$) but not for SHTD more than 60 mg protein.

TABLE E1. Multivariable analysis for home epinephrine-treated reactions during milk and nonmilk OIT

Parameter	Food treated							
	Milk				Nonmilk			
	Adjusted OR	95% CI		*P* value	Adjusted OR	95% CI		*P* value
		Low	High			Low	High	
Asthma	2.0	1.12	3.35	.008	0.86	0.36	2.1	.74
ER before treatment	2.77	1.56	4.89	.0005	1.28	0.54	3.0	.58
Epinephrine during clinic visit	2.2	1.37	3.53	.001	2.2	0.77	6.34	.14
SHTD mg (for every 50-unit increase)	0.85	0.76	0.96	.006	0.95	0.84	1.08	.42*

The model Hosmer and Lemeshow goodness-of-fit test P value = .7574 with C-statistic = 70.6%.

*A significant association was found for SHTD when used as a categorical variable with SHTD < 60 mg as well as for sex on stepwise logistic regression analysis in non−milk-allergic patients. After adjusting to SD < 60, for males the odds for home Epi use were 4.5 (95% CI, 1.31-15.55) times higher compared with females (P = .017). In addition, after adjusting to sex, for patients with SD < 60, the odds for Epi home use were 3.24 (95% CI, 1.17-9.0) times higher compared with patients with SD ≥ 60 (P = .0236).

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