

ORIGINAL ARTICLE

A structured graduated protocol with heat denatured eggs in the treatment of egg allergy

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Abstract

Background: Most children with egg allergy (EA) can tolerate extensively heated and baked egg (EHBE). Consumption of EHBE may promote faster resolution of EA; however, no consensus exists as to the required amounts and treatment protocols.

Objective: To evaluate the efficacy and safety of a structured graduated exposure protocol (SGEP) with EHBE in promoting tolerance to eggs in EA children under 2 years of age.

Methods: In a case-control study, EA children aged < 2 years who were treated with SGEP including EHBE were compared to children treated with strict avoidance. Data were collected from records and telephone questionnaires. Analysis was performed using non-parametric Kaplan-Meier and Cox proportional hazard regression models.

Results: Thirty-nine egg-allergic children with a median age at intervention of 16 months (interquartile range: 13-19) were treated with SGEP and followed to a median age of 39 months (26.8-50.0). The median age at resolution of EA was compared to a matched group of 80 children treated with strict avoidance at least until 2 years of age or earlier natural resolution and followed to a median age of 69 months (46-104). The median estimated age at EA resolution in the SGEP group was 24 months (95% CI, 19.5-28.5 months), compared to 78 months (95% CI, 53-102) in the control group, $P < .001$. At last follow-up, 82% of treated children were tolerant to lightly cooked eggs vs 54% of controls, $P = .001$.

Conclusion: A structured protocol with EHBE appears to promote faster resolution of EA.

KEYWORDS

atopic dermatitis, egg allergy, food allergy, heat denatured proteins, structured graduated protocol, wheezing

1 | INTRODUCTION

Immediate-type (IgE-mediated) reactions to foods may be life-threatening and impair QoL in children and their families.¹⁻³

Egg allergy is one of the most common IgE-mediated childhood food allergies,⁴ with an estimated prevalence of 0.5%-8.9%,^{5,6} also reported as the trigger in 7%-12% of all pediatric anaphylaxis presentations.⁷ Although recommended, absolute avoidance is challenging, accidental exposures and reactions occur frequently,⁸ engendering significant anxiety, social limitation, and impairment of QoL.⁹

In most cases, the onset of egg allergy is in the first or second year of the infant's life and may resolve spontaneously with time. However, studies show that although a common tendency for tolerance development exists, the rate of resolution differs between children, and some patients may remain allergic to eggs throughout their childhood.¹⁰

The timing of tolerance development appears to be dependent on factors such as comorbidity with other allergic diseases (AD, asthma) and their severity, egg-specific IgE levels and/or the extent of the wheal size of the skin prick test (SPT), severity of clinical response to food exposure, and other geographic and environmental factors.¹⁰ In the EuroPrevall birth cohort, more than 50% of egg-allergic children developed tolerance within 12 months after diagnosis.¹¹ In contrast, in the United States, in a tertiary hospital cohort, only 50% of the children with egg allergy at 1 year of age developed tolerance at the age of 6 years (72 months).⁵ In a recent study from Australia, egg IgE diversity predicted the rate of resolution in their cohort, with 90% of the children reacting to one egg allergen, developing tolerance by 4 years of age, while only 60% of multiple-sensitized children resolving by that age.¹²

Oral immune therapy (OIT) protocols are currently under investigation for the treatment of egg allergy, usually involving graduated exposures to the natural egg proteins. Indeed, most studies of egg allergy do not focus on very young children perhaps because, as previously detailed, there is a relatively high rate of spontaneous resolution. However, it is also true that most published OIT protocols, although successful in desensitizing patients, have a significant incidence of adverse events, and although most of these may be mild to moderate in severity, they would not be appropriate for treatment of very young children.¹³

Heat treatment of eggs especially within a wheat-based food matrix causes denaturation and changes the tertiary structure of the allergenic proteins and, with it, changes the conformational epitopes recognized by most egg-allergic individuals.¹⁴ In a non-randomized clinical trial, 70% of EA children exhibited tolerance to heat-processed eggs. Inclusion of these foods in their regular diet was shown to be associated with earlier resolution of allergy.¹⁴

The aim of this study was to assess the safety and efficacy of treating egg-allergic children below the age of two with a structured graduated exposure protocol (SGEP) to heat denatured egg proteins.

Key Message

In children with egg allergy (EA) who are able to tolerate extensively heated and baked egg (EHBE), a structured graduated exposure protocol (SGEP) enables safe early introduction of eggs and eggs containing foods and hastens the resolution of EA. An early intervention with a SGEP including EHBE in egg allergic toddlers seems feasible and safe in the hands of trained and experienced allergy teams, promotes earlier resolution of egg allergy and may improve quality of life and nutritional status.

1. What is known on this subject?

Egg allergy (EA) is one of the most common food allergies in childhood. Though the natural history is favorable, some children remain allergic throughout their childhood. Quality of life (QoL) is severely impaired, and allergic reactions secondary to accidental exposures frequently occur in these children. Most children with EA can tolerate extensively heated and baked eggs.

2. What does this article add to our knowledge?

In children with EA who are able to tolerate extensively heated and baked egg, a structured graduated exposure protocol enables safe early introduction of eggs and egg-containing foods and hastens the resolution of EA.

3. How does this study impact current management guidelines?

An early intervention with a SGEP including EHBE in egg-allergic toddlers seems feasible and safe in the hands of trained and experienced allergy teams, promotes earlier resolution of egg allergy, and may improve QoL and nutritional status.

2 | PATIENTS AND METHODS

2.1 | Study design

This was a case-control study comparing egg-allergic children aged <2 years who were treated with a SGEP with EHBE with egg-allergic children who were treated with strict avoidance at least until 2 years of age. In the intervention group, children were followed up for at least 4 years or until they achieved tolerance (if they achieved tolerance at an earlier age). The control group consisted of children who were diagnosed and followed with immediate-type egg allergy in community-based allergy clinics and referred to our hospital-based clinic for the performance of an open oral food challenge. All the reported clinical reactions in this study are as a result of exposure to cooked or fried eggs. Data were collected from medical records

of children from Sheba Medical Center, Meuhedet Health Services, and Clalit Health Services specialist allergy clinics, in addition to validated telephone questionnaires. The study was approved by the hospital ethics committee, and informed consent was obtained from all patients.

Egg tolerance, for the purpose of this study, is defined as the ability to eat 1 egg formed as hardboiled, scrambled, or lightly cooked egg, with no allergic symptoms, also known as a negative oral food challenge (OFC). In our questionnaire, we also enquired as to the consumption of raw eggs in the form of mayonnaise or uncooked egg whites.

2.2 | Population

In the intervention group (IG), we included children with IgE-mediated egg allergy diagnosed by OFC or by positive SPT and/or positive IgE along with a clinical history of an immediate allergic reaction after exposure to cooked or fried eggs in the past year, starting a SGEP treatment with EHBE, before 2 years of age.

In the control group, we enrolled children with IgE-mediated egg allergy diagnosed by OFC or by positive SPT and/or positive IgE along with a clinical history of an immediate allergic reaction after exposure to eggs, followed in community allergy clinics. They were referred to the hospital-based allergy clinic for one of the two following reasons:

(a) For performing a lightly cooked egg challenge, if a young patient with a previous allergic response to lightly cooked egg had either diminished skin tests or more than 2 years without an accidental adverse reaction to eggs. The lightly cooked egg challenge was performed, and if successful, the natural resolution of egg allergy was recorded; if unsuccessful, children were then challenged with baked egg.

Or (b) for a baked egg challenge, if the child had an accidental allergic response to lightly cooked eggs during the past year.

Egg-allergic children with a positive reaction to EHBE were excluded from our control group. We also excluded from the control group all patients with any history of allergic reactions to baked egg, due to the hypothesis that these children may suffer a more persistent form of allergy and, therefore, their inclusion would bias the analysis.

2.3 | Structured graduated exposure protocol

Structured graduated exposure protocol is a 3-phased protocol, each phase beginning with an OFC under allergist supervision with an egg product that was prepared by the patient's parents who were given a precise recipe detailing quantities and heating temperatures—of baking and frying.¹⁵ The 1st OFC is a “cookie” containing ~1 gr egg protein after frying and baking. If no allergic reaction is elicited, the patient then begins a 3-month phase of home-based treatment during which he/she consumes daily the same product (“cookie”) that was proven safe during the challenge. A child who failed the 1st OFC was asked to perform the OFC again after 6 months with a reduced amount of EHBE proteins. The 2nd OFC is a pancake containing ~1 gr egg protein fried in matrix. If no allergic reaction is elicited, the patient then begins a 3-month phase of home-based treatment during which he/she consumes daily the same product (pancake) that was proven safe during the challenge. The 3rd OFC is “lightly cooked eggs,” containing 1 egg (~5–6 gr egg protein), as an omelet/fried egg. If no allergic reaction is elicited, then the patient can introduce all eggs except raw egg to his regular diet—raw egg challenge may be performed after a significant decrease in his allergy tests (IgE or SPT; Figure 1). Before the 3rd OFC, patients are instructed to continue avoidance of any egg products other than the one that was tested and proven safe. During the whole treatment, they continue to carry automatic epinephrine injectors.

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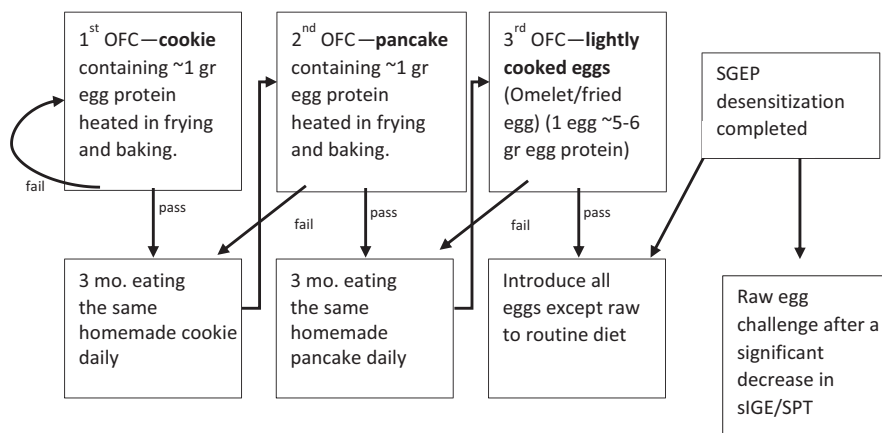


FIGURE 1 Structured graduated exposure protocol

TABLE 1 Demographics

	Intervention group children treated with SGEP before 2 y of age (39)	Control group (80)	P-value
Gender (male)	21 (56%)	51 (64%)	.445
Birthweight (avg.)	3338.05g, SD 412.73	3289.96g, SD 580.93	.653
Mode of birth (C-section)	5 (13%)	16 (22%)	.205
Wk of gestation (avg.)	38.3, SD 6.78	38.9, SD 2.35	.486
Initial breast-feeding	28 (71%)	48 (64%)	.407
Atopic dermatitis	21 (53%)	41 (52%)	.897
Asthma/wheezing	3 (7%)	28 (35%)	.001
MMRV	36 (92%)	62 (88%)	.539
Immediate reactions to MMRV	1 (2.5%)	3 (4%)	.990
Other comorbid food allergies	20 (51%)	45 (56%)	.154
Family history of asthma	19 (48%)	45 (59%)	.597

same product (pancake) that was proven safe during the challenge. The 3rd OFC is "lightly cooked eggs," containing 1 egg (~5-6 gr egg protein), as an omelet/fried egg. If no allergic reaction is elicited, then the patient can introduce all eggs except raw egg to his regular diet—raw egg challenge may be performed after a significant decrease in his allergy tests (IgE or SPT).

2.4 | Statistical methods

Descriptive statistics are derived from the analysis of variance (IBM SPSS Statistics Ver 25 and JMP v13.1). The statistical analysis applied to this comparative cohort study is based on non-parametric Kaplan-Meier and Cox proportional hazard regression models. The adequacy of the comparison between the cohorts was established

by comparing age at presentation, severity of the allergic reaction, feeding patterns, and the presence or absence of other atopic phenotypes. The impact of the intervention on time to achieve tolerance was tested for significance, overall and in separate phenotype groups.

3 | RESULTS

Thirty-nine egg-allergic children (21 [56%] male) with a median age at intervention of 16 months (IQR 14-19) were started on treatment with SGEP before 2 years of age and followed to a median age of 39 months (IQR 26.7-50). The control group consisted of 80 egg-allergic children (51 [64%] male) who were managed with strict

TABLE 2 Characteristics of the initial allergic reaction to eggs

	Intervention group—children treated with SGEP before 2 y of age (39)	Control group—after 2 y of age (80)	P-value
Age at initial allergic reaction (mean)	8.3 mo	10.7 mo	.113
Initial anaphylaxis	17 (50%)	24 (32%)	.068
Initial reaction in skin	28 (77%)	55 (71%)	.481
Initial GI symptoms	0 (0%)	4 (5%)	.167
Initial respiratory symptoms	6 (16%)	10 (13%)	.605
Initial epinephrine treatment	3 (1%)	2 (3%)	.193
Initial antihistamine treatment	18 (50%)	23 (32%)	.062
SPT wheal (mm)	8.2 (95% CI, 7.3-9.2)	6.09 (95% CI, 5.2-6.9)	.003
Initial egg white IgE (IU/L)	15.6 (95% CI, 7.3-23.9)	27.87 (95% CI, 16.8-38.9)	.115
Age at last follow-up (mo, avg.)	41.31 (95% CI, 35.2-47.4)	80.92 (95% CI, 66.7-95.1)	.001

avoidance at least until 2 years of age or until allergy resolution and followed to a median age of 69 months (IQR 46-104).

Comparison of baseline characteristics showed no significant differences between the intervention group and the control group. Atopic dermatitis was diagnosed in more than 50% of the children in both groups. About 90% of the children in both groups were vaccinated with MMRV. Approximately 2.5% of all vaccinated children reported a skin rash after this vaccine (see Table 1).

The initial allergic reaction occurred at a median age of 9 months (IQR 6-10) in the intervention group and 10 months (IQR 7-12) in the control group (not significant). Anaphylactic reactions (involving more than one system) were reported in 50% of the children in the intervention group and 32% of the children in the control group ($P = .068$). However, only a minority were treated with epinephrine (see Table 2).

More than 70% of the children in both groups had cutaneous manifestation as part of their initial reaction ($P = .481$). No significant difference was found between the control and intervention groups in the initial egg-specific IgE (IU/L) ($P = .115$; see Table 2).

At last follow-up, all children in the intervention group were able to tolerate some form of egg-containing diet. 10% ate only baked eggs, while 82% (95% CI, 70%-95%) ate lightly cooked eggs on a regular basis (see Table 3). Twenty-two of 39 (76%) children could eat raw eggs without any allergic reaction. In the control group, 27.5% of the children did not eat any eggs at all. 17.5% of the children ate baked eggs only, and 54% (95% CI, 43%-65%) could tolerate lightly cooked eggs (see Table 3).

Calculated via the Cox proportional hazard regression model, the median age at resolution of egg allergy in the SGEP group was 24 months (95% CI, 19.5-28.5 months), compared to 78 months (95% CI, 53-102) in the control group ($P < .001$; see Figure 2).

In children with an initial anaphylactic reaction, the difference in median resolution time between the intervention and control groups was pronounced, with the median age at resolution of egg allergy of 29 months (95% CI, 25.6-32.3) in the intervention group, Vs 169 months (95% CI, 56.9-281.1) in the control group ($P < .001$; see Figure 3).

3.1 | Evaluation of safety

Only 9/39 (23%) of children in the intervention group had any allergic reaction recorded during the SGEP.

Reactions consisted of facial edema, itching, rash, or vomiting. They received medical treatment in the clinic and were observed until resolution of all symptoms. All children continued on a modified SGEP and are currently consuming eggs in their regular diet.

TABLE 3 Current egg-containing diet

	SGEP group	Control group	P-value
No eggs	0	29%	.005
Baked eggs only	10%	11%	.358
Lightly cooked eggs	82%	54%	.002

Only three reactions occurred at home. Of these, one was reported as peri-orbital edema and the second was reported as a localized rash around the mouth; both of these reactions did not require treatment and resolved spontaneously. Both the patients with these reactions eventually completed the protocol and now eat eggs freely. The third reaction was anaphylactic (ie, rash and vomiting) and required epinephrine and steroids. The patient with this reaction stopped the protocol and continues to avoid eggs.

4 | DISCUSSION

The study was performed to evaluate a SGEP with EHBE in children with IgE-mediated egg allergy before 2 years of age. In the hands of an experienced allergy team, a SGEP with EHBE seems to be safe in this age-group. Only three children reacted at home: Two had mild peri-orbital edema or local rash that did not necessitate treatment and did not prevent them from completing the protocol, and only one child needed injectable epinephrine at home and treatment was stopped.

The natural history of egg allergy shows significant variation over time and geography.^{13,16} Our control group represents the current "real-life" natural history of disease in our community, with 20% of the children resolving their allergy before 2 years of age and more than 50% with persistent allergy into the school years.

An early intervention with SGEP seems to shorten significantly the median time to allergy resolution in children capable of ingesting EHBE (from 78 months VS 24 months in the intervention group, $P < .001$). In the subgroup of patients with an initial anaphylactic reaction, that difference is even more pronounced (from 169 to 29 months in the intervention group, $P < .001$).

The mechanism of action of our protocol was not specifically studied, but most likely involves both gradual decreases in egg-specific IgE and increases in protective IgG and cellular regulatory mechanisms, similar to the previously published changes in egg-allergic children ingesting EHBE.¹⁷ Also, exposure to allergenic proteins with the abrogation of the IgE-mediated response most likely results in an isolated cellular recognition and uptake of the short linear epitopes that are exposed after heat denaturation. This exposure most likely promotes the development of egg-specific anergy, deletion of antigen-specific T cells, and transformation into allergen-specific adaptive regulatory T (Treg) cells.¹⁸

The reasons for the abysmally rare use of epinephrine in the treatment of young toddlers with a first-time multisystemic (anaphylactic) reaction to a food are unknown but are consistent with the results of other investigator's findings. This finding emphasizes continuing gaps in recognition and understanding of the role of epinephrine in multisystemic, anaphylactic reactions and allergic food reactions in children. It is still incumbent on all specialists in the field to increase awareness of parents and medical teams through continuing education.¹⁹

Published protocols of oral IT for egg-allergic children vary in the population enrolled, the intensity and length of exposure,

FIGURE 2 Cox regression of egg allergy resolution over time in children on SGEP vs controls. Analysis of age at tolerance of eggs between controls, that is, the natural history of egg allergy resolution, and the intervention group. Intervention consisted of a structured graduated introduction protocol consisting of initial extensively heated and baked cookies, followed by pancakes and then cooked eggs. Median age at resolution of EA was 24 mo in the intervention group, vs 78 mo in controls ($P < .001$)

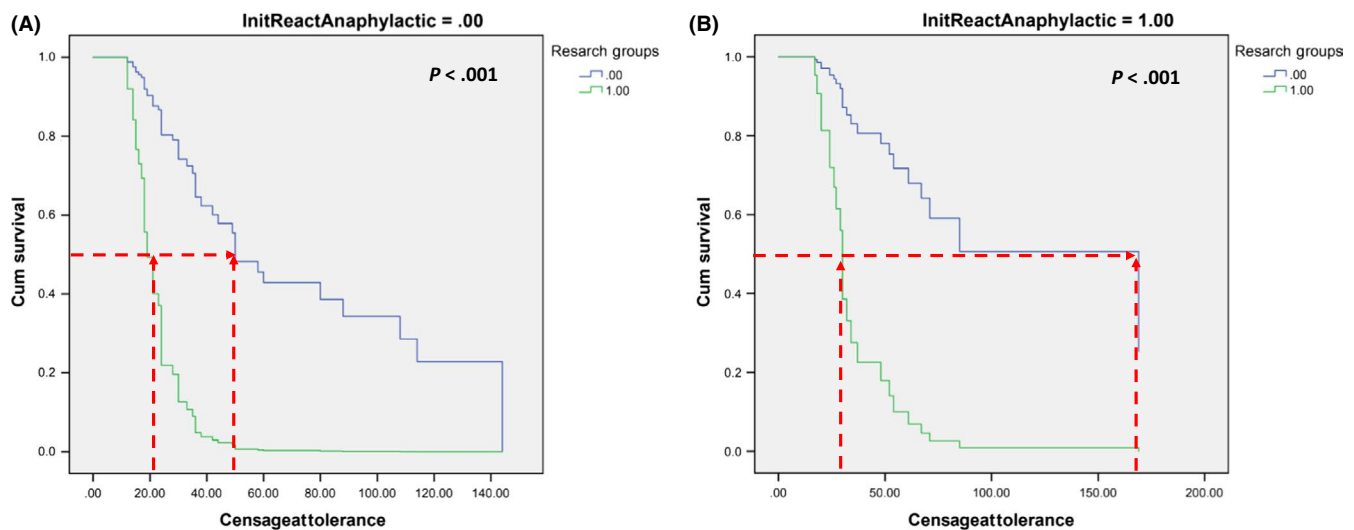
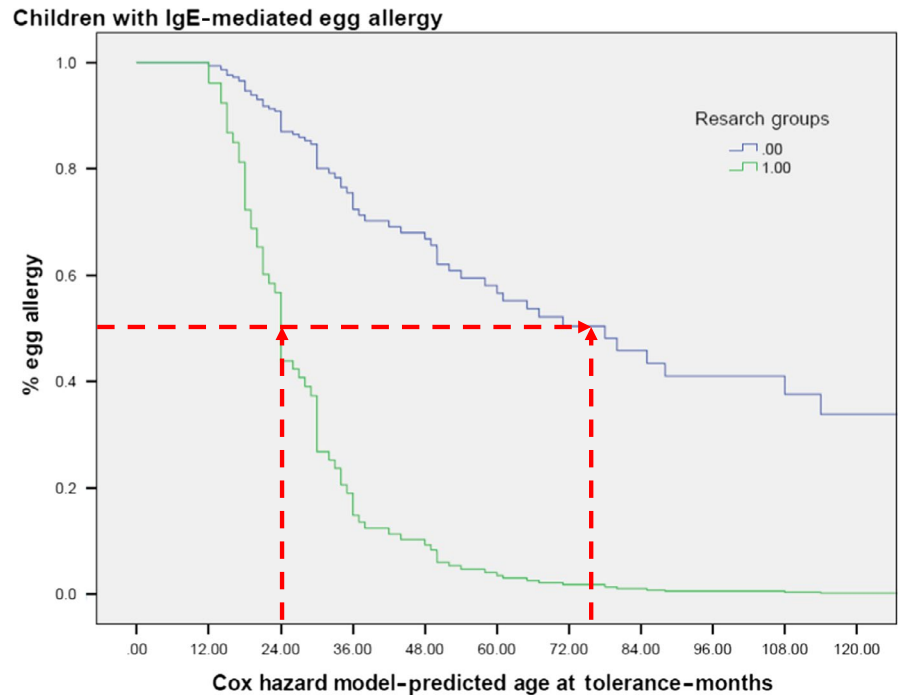


FIGURE 3 Cox regression of egg allergy resolution over time in children with and without initial anaphylactic reaction in both groups. Analysis of age at egg tolerance in EA children with (panel b) and without (panel a) initial anaphylaxis. Panel a: In children without initial anaphylaxis, the median age at resolution of egg allergy was 21 mo (95% CI, 18-23.9) in the intervention group, Vs 50 mo (95% CI, 37.4-62.5) in the control group ($P < .001$). Panel b: In children with initial anaphylaxis, the median age at resolution of egg allergy was 29 mo (95% CI, 25.6-32.3) in the intervention group, Vs 169 mo (95% CI, 56.9-281.1) in the control group ($P < .001$)

and outcomes and rates of adverse reactions. A Cochrane review of oral immunotherapy for egg allergy concluded that the quality of evidence is limited and the incidence of adverse effects significant (69%),²⁰ precluding the adaptation of these protocols for use in young children. In contrast in our EHBE protocol, very few reactions were documented, most of them within the context of an observed challenge under medical supervision, which makes this protocol a viable treatment option for young children.

4.1 | Limitations

Currently, we do not know enough about long-term outcomes and complications for any of the published treatment protocols of food allergy, including our own. However, in our study, over the years of follow-up many of the children showed significant decreases in their skin tests and their egg-specific IgE and continued tolerance of eggs and egg-containing diets. Therefore, long-term complications are not expected. However, long-term follow up is a

Target statement	Meaning Equivalence (MEF) Included in BOM	Surface Similarity (SSF) Not Included in BOM
Finding 1: The quality of life of patients and families affected with a food allergy to staple foods (milk, egg, sesame, peanut) is severely impaired	Food allergy in children impacts negatively on day to day activities of the whole family	Educating patients on strict avoidance and carrying an epinephrine autoinjector, is completely effective in avoiding accidental exposures in preschool children The availability of an epinephrine autoinjector and knowledge of its use in the event of accidental exposure, normalizes the QOL of food allergic families
	The incidence of accidental exposures to allergenic foods in preschool children is high	
	The currently recommended management of FA in children is: Patient education, strict avoidance and carrying an epinephrine autoinjector	
Finding 2: All children suspected of an allergic reaction to foods should be referred to a center that includes appropriate facilities, medical and support staff, experienced in the diagnosis and treatment of children with food allergies as early as possible!	The diagnosis of food allergy in children should be performed soon after the suspected event	Recommending strict avoidance of suspected allergenic foods is the best treatment for all young children with a suspected food allergy
	There are no age limitations on the performance of diagnostic allergy tests, such as skin prick tests or observed food challenges, provided these are performed by well trained and experienced medical teams	Laboratory test such skin tests or specific IgE to food can accurately diagnose food allergy in children
Finding 3: The natural history of Egg allergy (EA) in children is still favorable as in most - it seems to resolve with time	The median age at resolution of EA (by which time 50% of children have resolved their allergies) is between 4 - 5 years	Food allergy in children always resolves in the first years of life
	Children with EA and an initial anaphylactic reaction to eggs, are less likely to resolve their EA	Early avoidance and late introduction of allergenic foods is beneficial in preventing food allergy in children
Finding 4: A majority of children with IgE mediated EA are capable of consuming certain amounts of extensively heated and baked egg (EHBE) proteins	Some children with EA can develop immediate, life threatening reactions to the ingestion of EHBE.	families of children with IgE mediated EA, should be encouraged to try baked egg products at home
	A minority of children with EA are allergic also to heat denatured egg products. These are the most severely affected and least likely to resolve their allergies	All forms of heated and baked egg are similarly safe
Finding 5: In EA toddlers, capable of ingesting EHBE safely, a slow, graduated exposure protocol (SGEP) with EHBE can promote earlier resolution	The median age at EA resolution in toddlers capable of ingesting EHBE safely and treated with SGEP including EHBE, is significantly lower than in children treated with avoidance	EA allergic preschool children capable of ingesting EHBE safely and treated with SGEP including EHBE are developing true long term tolerance to egg
	Most preschool children capable of ingesting EHBE safely and treated with SGEP including EHBE will be able to tolerate all forms of egg in their regular diet before entering school	EHBE is not a form of oral immunotherapy in food allergic children and therefore the follow- up recommended for these children is similar to patients with natural resolution of EA (none)
Finding 6: A protocol of SGEP including EHBE, seems safe in children less than 2 years of age.	A protocol of SGEP including EHBE, performed by medical teams trained and experienced in the treatment of food allergy in children, is safe	All children with IgE mediated EA should be treated with an SGEP with EHBE

FIGURE 4 Generalizability of the study findings. We present a formal application of the Meaning Equivalence Reusable Learning Objects (MERLO) statements to define a boundary of meaning (BOM) representing the generalizability of findings in this paper. The BOM represents what can and what cannot be inferred from the study and enables researchers to design studies that are capable of challenging or reproducing the published results

requirement for any proposed treatment of food allergy in infants and children.

At last follow-up, all children in the intervention group were able to tolerate some form of egg-containing diet. However, the permanent state of this tolerance induction is yet unknown, and whether or not they will require lifelong continuous exposure to eggs or may revert back to allergy if this exposure is interrupted. Therefore, there is a need for developing tests able to distinguish between true tolerance and desensitization.

When and how to treat egg allergy is a complicated question. On the one hand, in most children, egg allergy would most likely resolve spontaneously without intervention. However, in some, this spontaneous resolution may occur late in childhood, and those whose allergy will not be resolved without intervention are hard to predict. From our data, it seems that children experiencing an anaphylactic reaction on their initial egg hypersensitivity reaction may have a more persistent form of egg allergy and therefore may be a target population for early intervention, to exploit the window of opportunity for desensitization in the early years.²¹

4.2 | Generalizability

Recently, problems with reproducibility and generalizability of published research have increasingly concerned the scientific community. In order to provide a formalized generalizability of findings, we present a methodology developed in the context of pedagogy focused on conceptual understanding (Figure 4). Specifically, we apply the Meaning Equivalence Reusable Learning Objects (MERLO) statements to define a boundary of meaning (BOM) representing a generalizability of findings in this paper. The BOM represents what can and what cannot be inferred from the study and enables researchers to design studies that are capable of challenging or reproducing the published results. MERLO statements are derived from alternative representations of a conceptual target statement. These alternatives are classified as meaning equivalence findings (MEF) representing legitimate conclusion of the study or a generalized inference in the opinion of the authors. The surface similarity findings (SSF) are similarly sounding affirmations, but their meaning is not supported by the conclusions of the study and they are not claimed as generalizable and/or reproducible.²²⁻²⁵

5 | CONCLUSION

A SGEP with EHBE seems to be safe and effective in shortening the time to egg allergy resolution in young egg-allergic children.

CONFLICTS OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

AUTHOR CONTRIBUTION

Leora Gotesdyner designed and implemented the data collection instrument, collected data, performed interviews, carried out initial analyses, drafted and revised the manuscript. Yuri Zeldin, Diti Machnes Maayan, Tali Stauber, Ramit Maoz Segal, Inga Binson, Mira Dinkin, Larisa Dinkowitz, Danit Shahar, Michal Deutch, Mazal Yaron, Ayelet Nevet, Avner Reshef, and Nancy Agmon-Levin recruited patients, performed clinical follow-up, collected the data, and reviewed the manuscript. Adi Efron helped in designing the data collection instrument, collected the data, and performed interviews. Ron S Kenett conceptualized and designed the study, performed critical statistical analysis for study design, performed data analysis, and reviewed and revised the manuscript. Mona I Kidon conceptualized and designed the study, recruited patients, performed clinical follow-up, coordinated and supervised data collection, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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