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Matrix effect on baked egg tolerance in children with IgE-mediated hen's egg allergy.

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ABSTRACT

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Matrix effect on baked egg tolerance in children with IgE-mediated hen's egg allergy.

Pediatr Allergy Immunol

Background. Children with IgE-mediated hen's egg allergy (IgE-HEA) often tolerate baked egg within a wheat matrix.

Objective. To evaluate the influence of wheat matrix and the effects of little standardized cooking procedures on baked egg tolerance.

Methods. 54 children with IgE-HEA were enrolled. They underwent prick by prick (PbP) tests and open oral food challenges (OFC) performed with baked HE within a wheat matrix (a home-made cake, locally called ciambellone), baked HE without a wheat matrix (in a form of an omelette, locally named frittata) and boiled HE. Three months after passing ciambellone OFC, parents were asked to answer a survey.

Results. 88% of children tolerated ciambellone, 74% frittata, 56% boiled HE. Negative predictive value of PbP performed with ciambellone, frittata and boiled HE was 100%. No IgE-mediated adverse reactions were detected at follow-up carried out by the survey.

Conclusions. Wheat matrix seemed to be relevant only in few cases. If our results will be confirmed by larger studies, a negative PbP with ciambellone, frittata or boiled HE will allow patients with IgE-HEA to eat these foods without undergoing OFC. Moreover, our study showed that very strict standardized cooking procedures do not seem to be essential, in order to guarantee tolerance towards baked HE.

Key Words: baked egg, cooking standardization, hen's egg allergy, matrix effect, negative predictive value, prick by prick test

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INTRODUCTION

In 2008, Lemon-Mulé et al (1), reported that 70% of children with IgE-mediated hen's egg allergy (IgE-HEA) tolerated baked hen's egg (HE) in form of a muffin. These authors obtained similar results in children presenting with IgE-mediated cow's milk allergy (IgE-CMA) (2). Patients' quality of life (QoL) improved a lot, -children did not have to avoid culprit food in an extensive and strict way anymore. Moreover, the existence of several allergic phenotypes was proved, as some patients did not tolerate muffin.

However, these studies were not the first on this matter. In 1997, Urisu et al (3) reported that 50% of egg-allergic patients tolerated hen's egg when cooked at 90°C for 60 minutes. Nine years later, Des Roches et al (4) noticed that 73% of egg-allergic children tolerated egg baked in a cake. More recently, Bloom et al (5), investigated on tolerance towards extensive heated egg and milk. In conclusion, tolerance towards baked milk and egg was confirmed by several studies, and in 2014, an important position paper on food allergy (FA) management cited extensive heated products as a dietary option (6).

Heating plays a key role in achieving tolerance towards baked HE or milk. In fact, high and prolonged temperature reduces proteins' allergenicity by destroying conformational epitopes, altering allergens tridimensional structure, so that specific IgE binding capacity decreases (7). Another theory proposed to explain baked food tolerance, is the "matrix effect" (7). This one would work on proteins, fats and sugars interactions, which are thought to reduce IgE binding to allergen epitopes by covering them. On the contrary, no significant influence of the fat content of the matrix was found on the eliciting dose or severity of the reaction in oral food challenge (OFCs) with heated, but not extensively heated, hen's egg (8).

The primary objective of our study was to evaluate the importance of wheat matrix effect on reducing baked HE allergenicity. Secondary objectives were: a) to evaluate negative predictive value (NPV) of prick by prick (PbP) performed with baked or boiled HE; b) to follow up tolerance maintenance, after patients passed OFCs performed with HE baked in a wheat matrix.

METHODS

Eligible patients were children presenting with suggestive history of IgE-HEA of various severity, who rigorously avoided HE. They were enrolled prospectively and consecutively at pediatric allergy unit of Agostino Gemelli hospital (Rome), Fatebenefratelli hospital (Benevento), Belcolle hospital (Viterbo), Mazzoni hospital (Ascoli Piceno) and Senigallia Civil

hospital (Senigallia). Exclusion criteria were: a) chronic disease or chronic therapies which influenced immune response; b) need to continue therapy with oral anti-histamines or steroids; c) denied informed consent. In all eligible children skin prick tests (SPT) were performed, according to international guidelines (9), with raw (ie unheated) HE, commercial extracts of HE albumen and yolk, negative control and histamine (Lofarma, Italy). In our experience SPT performed with raw HE has a higher sensitivity than SPT performed with albumen commercial extract, therefore we chose the former as the reference standard. Patients presenting with positive raw HE SPT underwent open raw HE (unheated egg mixed with fruit juice) oral food challenge (OFC) performed according to international guidelines (10). OFC was not performed in patients who experienced anaphylaxis, as defined by Sampson et al (11), within 12 months of our evaluation. We did not establish any positive raw HE SPT cut-off as an exclusion criterion for performing an OFC.

Among eligible patients, we enrolled children who met the following criteria: a) children with history of anaphylaxis due to HE occurred within 12 months from clinical evaluation and positive raw HE SPT; b) children with history of immediate adverse reaction due to HE (not anaphylactic or anaphylactic but occurred more than 12 months before clinical evaluation), positive raw HE SPT and failed raw HE OFC.

Among enrolled patients, we performed prick by prick (PbP) tests with HE baked with a wheat matrix as a cake (locally named “ciambellone”), baked “frittata” (which was made by beating the egg until the yolk and white were completely mixed, firstly the mixture was fried in olive oil for 3 minutes and later it was baked in a oven at 180° for at least 30 minutes), HE's albumen and yolk boiled for 10 minutes. Parents cooked the foods at home. Irrespective of obtained PbP mean wheal diameter, patients underwent open OFCs with the above mentioned types of processed HE. Processed HE PbPs were performed also before each specific OFC was conducted. We established a gap of two weeks between different OFC, so that all tests were performed within 3 months from the initial assessment. The first OFC was performed with ciambellone, the second with baked frittata and the third with

boiled HE. If a subject failed an OFC, the sequence was stopped. A flow-chart of the study is described in figure 1.

Ciambellone OFC was considered to be passed if patients took a total dose containing at least 3 grams of HE proteins, without any adverse reaction. Baked frittata and boiled HE OFCs were considered to be passed if patients consumed a total dose corresponding to 1 egg (albumen and yolk), containing about 6 grams of HE proteins, without any adverse reaction. The above mentioned doses were chosen, basing on Italian children usual intake. It's quite rare that a child under the age of 2 is able to eat more than 100 grams of ciambellone (or muffin). After passing an OFC, patients were allowed to eat tested food (cooked in the same way), but only when OFCs' sequence ended. In particular, after passing ciambellone OFC, children were allowed to eat every baked food containing HE proteins within a wheat matrix, on condition that the food was baked at 180°C for at least 30 minutes. Moreover, they could eat it in any physical and emotive state (physical exercise, fever, stressful situations). Three months after ciambellone OFC was passed, parents were asked to answer a questionnaire, which was sent via e-mail, in order to report if any adverse reaction occurred at home. Survey questions are listed in the appendix (see electronic repository).

Statistical analysis

We reported demographic and clinical patients characteristics as mean and standard deviation for continue variables and percentage for categorical ones. Chi-square test was used to calculate percentage differences among populations. Data were obtained with IBM SPSS Statistics 20.

Standardization of procedures

In order to limit any adverse reaction, literature highly recommends to follow strict and precise cooking procedures to make baked HE products with a wheat matrix, such as in the form of a cake (1, 12). In our study, we gave parents minimal cooking rules to follow. For example, we did not mention baking tray's shape, or its dimension, notice that they could both influence food thickness and change the heating grade. However, we gave patients food recipes. Ciambellone has to be prepared with 1 HE, 100 grams wheat flour, 50 grams sugar, 1 teaspoon of baking powder. The cake was baked at 180°C for at least 30 minutes in pre-heated ventilated oven. Ciambellone's final weight was 200 grams and it contained almost 6 grams of HE proteins. Baked frittata recipe was: 1 HE beated until the yolk and white were completely mixed, then it was fried in olive oil for 3 minutes and later it was baked at 180°C for 30 minutes in pre-heated ventilated oven. Boiled HE was simply made placing 1 HE into boiling water for 10 minutes.

Food was always prepared by parents at home. Just once, we prepared ciambellone, frittata and boiled HE by ourselves, in order to measure food internal temperature. It was made by placing a cooking-thermother (Tescoma) into the inner part of the food, just few seconds after it was cooked.

PbP with ciambellone, frittata and boiled HE were performed with a special technique in order to improve test's sensitivity and negative predictive value (NPV). Ciambellone PbP was accomplished adding few drops of water to a little piece of cake, mixing and manipulating the compound until a soft ball-cake was obtained. The last one was pricked with ALK lancet (at least 20 times in different areas), then it was pressed and rubbed on the same lancet. Patients forearm skin was pricked with the lancet, passing through the soft ball-cake. The above mentioned was finally pressed and rubbed on patients forearm skin spot. PbP tests were performed twice on both forearms and two wheals diameters mean was

reported. PbP with frittata and boiled HE was performed in the same way, except for the absence of water drops. PbP results were considered to be positive if the mean wheal size was > 3 mm greater than the negative control.

The study was approved by the Ethic Committee of Agostino Gemelli hospital - Catholic University of Sacred Heart (Coordinator Center) and other hospitals Ethic Committees. Informed consent was obtained from the patients and/or the guardians.

RESULTS

Patients

Fifty-four patients were enrolled between 1st February 2014 and 31st January 2015. Sixty-five percent were males; mean age + SD (range) at diagnosis was 1.78 ± 3.15 years (6-193 months), particularly, mean age $\pm$ SD (range) of patients who experienced anaphylaxis within 12 months from clinical evaluation was 1.5 ± 1.9 years (range: 6-67 months). Seventy-eight percent of patients received an IgE-HEA diagnosis due to suggestive non anaphylactic clinical history (presence of immediate symptoms isolated or in various combinations, without any serious respiratory or cardiovascular involvement: urticaria was present in about 80% of cases, in 20% of cases along with rhinitis and in 25% of cases along with vomiting, in 20% of cases there were lip angioedema, rhinitis and cough), positive raw HE SPT and failed raw HE OFC. Twenty-two percent of patients received an IgE-HEA diagnosis due to history of anaphylaxis (22% experienced lethargy, hypotonia, cold and sweaty skin, vomiting, angioedema and flushing; 22% presented with urticaria, abdominal pain, vomiting and stridor; 12% experienced stridor and flushing; 44% had urticaria and asthma) occurred within 12 months from our evaluation and positive raw HE SPT. In 4 cases SPT performed with albumen commercial extract were negative, while SPT with raw HE were positive; all these children failed raw HE OFC. Sixty-three percent of patients presented with exclusive IgE-HEA, while 37% also suffered from IgE-CMA. Seventy-two percent presented with other

atopic diseases: 67% of them was affected by atopic eczema, 20% presented with FA other than HEA and CMA, 6% suffered from rhino-conjunctivitis and 15% were asthmatic.

PbP and OFC results

In table 1 PbP and OFC results performed with raw and processed HE are listed.

Tested food internal temperatures were: ciambellone = 105 °C, baked frittata = 99.9 °C, boiled HE = 91.8 °C.

OFC performed with processed HE

Eighty-eight percent (44/50) patients passed ciambellone OFC, 74% (31/42) frittata OFC, and 56% (28/50) boiled HE OFC. Only the difference between children who failed ciambellone OFC (12%) and those who failed boiled HE OFC (44%) was statistically significant ($p < 0.01$). In table 2 we compared some features of patients who reacted and those who passed processed HE OFCs: difference between PbPs mean wheal diameter was statistically significant ($p < 0.05$). Children who had a history of anaphylaxis failed boiled HE OFC more frequently than children without a history of anaphylaxis (41% vs 28%, $p < 0.05$). Moreover, according to Mehr et al's predictive parameters (presence of asthma, multiple FA and/or inhalant allergies) (13), we compared patients who failed ciambellone OFC and those who passed it and we didn't find any significant difference between the two groups.

Among patients who failed one or more processed HE OFC, 7/23 (30%) had anaphylaxis (3 had asthma and urticaria; 2 asthma, abdominal pain and nausea; 1 asthma, lethargy, hypotonia, pallor and perioral cyanosis; 1 urticaria, abdominal pain, vomiting and stridor), 6/23 (26%) had a generalized non-anaphylactic adverse reaction (2 had urticaria and

vomiting, 3 urticaria and rhinitis, 1 urticaria, vomiting and rhinitis) and 10/23 (44%) experienced a single-organ adverse reaction (5 urticaria, 4 vomiting, 1 rhinitis). Not every child performed all tests, this was mainly due to: a) parents logistical problems (90%); b) parents fear of adverse reactions (10%). Seventy-eight percent (42/54) patients underwent all processed HE challenges. 26/42 (62%) passed them all. Thirty-eight percent (16/42) failed one challenge: 6/16 failed ciambellone OFC (38%) and stopped the sequence, 5/16 (31%) failed baked frittata OFC and stopped the sequence, 5/16 (31%) failed boiled HE OFC.

PbP performed with processed HE

We noticed a great difference between children presenting with positive processed HE PbPs and those who had a corresponding failed OFC. For instance, ciambellone PbP was positive in 52% of cases, while OFC performed with the same food was failed only in 12%. Therefore, similarly to fresh food, positive PbP performed with processed HE doesn't always predict a failed OFC.

OFCs were always failed when PbP mean wheal diameters were: ciambellone >7 mm (sensitivity = 43%, specificity = 100%, positive predictive value [PPV] = 100%, negative predictive value [NPV] = 91%), baked frittata >7 mm (sensitivity = 50%, specificity = 100%, PPV = 100%, NPV = 84%), boiled HE >12.5 mm (sensitivity = 17%, specificity = 100%, PPV = 100%, NPV = 59%). OFCs were always passed when PbP mean wheal diameters were: ciambellone <3 mm (sensitivity = 100%, specificity = 57%, PPV = 25%, NPV = 100%), baked frittata <3 mm (sensitivity = 100%, specificity = 57%, PPV = 43%, NPV = 100%), boiled HE <4 mm (sensitivity = 100%, specificity = 61%, PPV = 67%, NPV = 100%).

Follow-up after passing ciambellone OFC

All patients answered the survey. 15% continued avoiding cakes prepared with HE and other baked products made with HE, except biscuits (containing very small HE amount). 6% exclusively ate ciambellone prepared following our recipe. 79% of patients consumed HE baked with a wheat matrix in the form of various foods. These ones were prepared with various cooking procedures (but always respecting the heating degree of 180 ° C and cooking time of at least 30 minutes). Moreover, as we did not give parents any specific advice, children ate baked HE products (i.e. cakes, biscuits and other baked products) each time they liked. For instance, they took these products while they were ill or during physical exercise.

Four children (14%) experienced mild adverse reactions. One child presented with itchy mouth and tingling throat within 2 hours from baked frittata ingestion. In this case, parents decided to eliminate HE from child's diet. The others reported respectively worsening of atopic eczema, diarrhea and cough, two hours after eating ciambellone; they all went on eating baked HE and they did not experience an adverse reaction anymore.

DISCUSSION

Our results confirm that, in children with IgE-HEA, prolonged and extensive heating increases tolerance towards HE proteins. A novelty described in our research is tolerance towards extensively heated HE without a wheat matrix (baked frittata). In fact, matrix effect seems to be relevant in only a few cases: in our series, ciambellone was tolerated by 88% of children, and frittata OFC was passed in 74% of cases. Summing-up 14% patients needed the matrix effect.

We believe that the key role on tolerance is played by heating time. In fact, processed HE foods internal temperatures were quite similar. We measured 105° for ciambellone, 99.9 °C for frittata and 91.8 °C for boiled HE. The low percentage of boiled HE-tolerant children could be due to food heating duration, which was shorter than ciambellone and baked frittata ones (10 minutes vs 30 minutes). As reported by Bencharitiwong et al (14), to eliminate decisively detectable IgE binding, a temperature of >90 °C prolonged for at least 30 minutes is necessary. In any case, our results would bring some practical benefits to IgE-HE allergic children. For example, they would be allowed to eat HE in the form of a baked frittata, which is tasty and easy to make. This would be convenient in terms of palatability and patients' QoL.

To date, baked HE tolerance should always be assessed by an OFC. In fact, current guidelines (6) recommend that: "For known allergic patients who are not consuming baked egg or milk proteins, an observed food challenge with a serving portion of a muffin or other appropriate food is warranted to ensure safe consumption". As OFC is an expensive and risky procedure, many authors tried to find different tests, both in vivo and in vitro, to predict tolerance towards offending food. In table 3 we listed principal HE prospective studies results (1, 4, 15-17). These tests evaluated predictivity of IgE serum levels and SPTs when performed with commercial extracts. Focusing on these results, we noticed that processed HE tolerance's predictive value was high (NPV >95%) only when the test was negative, and this fact is very rare in IgE-HE allergic children. Some authors evaluated SPT effectiveness when performed with processed food. Faraj et al (18) were the first to study muffin PbP's NPV, their estimated value was 94.8%. Secondly, Tan et al (16) reported muffin PbP's NPV of 88%. In our study, every negative PbP corresponded to a passed OFC, so that NPV was 100%. We believe the keystone is PbP technique. In fact, Faraj et al (18) mixed 1 gram of muffin with 10 ml of water using a tongue depressor; afterwards they put a drop of this solution on patients forearm skin and pricked it with a lancet passing through the drop. Now, our concern is about the possibility that the lancet passed through the slurry without

capturing any muffin particle (as it was mixed in 10 ml of water): this would cause false negative results. In the methods section, we described point by point techniques we used to perform solid food PbP. Described procedures seem to be more effective, as in our study a negative PbP always predicted a passed OFC. Further larger studies would allow patients to avoid an OFC in case of a negative PbP.

At follow up, no child presented with objective symptoms associated to IgE-mediated adverse reactions. Notice also that our children were allowed to eat every food containing HE proteins baked with a wheat matrix in any physical and emotive state. Ciambellone's recipe used in our study was simple and the only thing we stressed parents about was heating temperature and timing. We did not specify anything about baking trays shape and size, or cake's thickness, as some authors did (12). Moreover, we did not ask parents to pay attention to culprit food's position in commercial ingredients lists. Some authors proposed it (19), as this could influence offending food's quantity contained in industrial goods. In the end, we believe that very strict standardization of cooking procedures is not necessary to guarantee tolerance towards processed food. Moreover, reducing cooking procedures standardization, patients QoL increases.

Weakness of the study

Twelve patients didn't undergo raw HE OFC, as they experienced anaphylaxis in the last 12 months before our evaluation. Thus, the lack of diagnostic OFC may lead to include patients who have outgrown their egg allergy. However, 9/12 children failed at least one processed egg OFC. Moreover, after the study was concluded, patients who tolerated all processed foods (3/12), underwent raw HE OFC and failed it.

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Table 1- Raw and processed HE PbP and OFC outcomes.

	PbP N° positive patients/total tested patients (%)	OFC N° positive patients/total tested patients (%)
Ciambellone	25/52 (48%) ^	6/50 (12%) °
Frittata	22/40 (55%)	11/42 (26%)
Boiled albumen	39/54 (72%) ^	22/50 (44%) °
Boiled yolk	26/54 (48%)	----- *

*Legend: HE = hen's egg, PbP = prick by prick, OFC = oral food challenge, * = OFC was performed with mixed boiled albumen and yolk, ° ^ = $p < 0.05$*

Table 2 –Features comparison between patients who reacted to HE processed food vs those who tolerated it.

	Failed ciambellone OFC (n=6)	Passed ciambellone OFC (n=44)	Failed baked frittata OFC (n=11)	Passed baked frittata OFC (n=31)	Failed boiled egg OFC (n=22)	Passed boiled egg OFC (n=28)
Age (mean + SD) yrs	5.5 ± 3.1 yrs	4 ± 4.2 yrs	5.7 ± 4.1 yrs	4.5 ± 4.2 yrs	4.2 ± 4.1 yrs	3.6 ± 3.9 yrs
PbP wheal diameter (mean + SD) mm	5.6 ± 1.9 * mm	1.9 ± 2.2 * mm	6.4 ± 2.3 ^ mm	2 ± 2.4 ^ mm	8.9 ± 2.9 ° mm	3.1 ± 3.5 ° mm
History of Anaphylaxis (%)	2 (33%)	8 (18%)	3 (28%)	5 (16%)	9 # (41%)	3 # (28%)

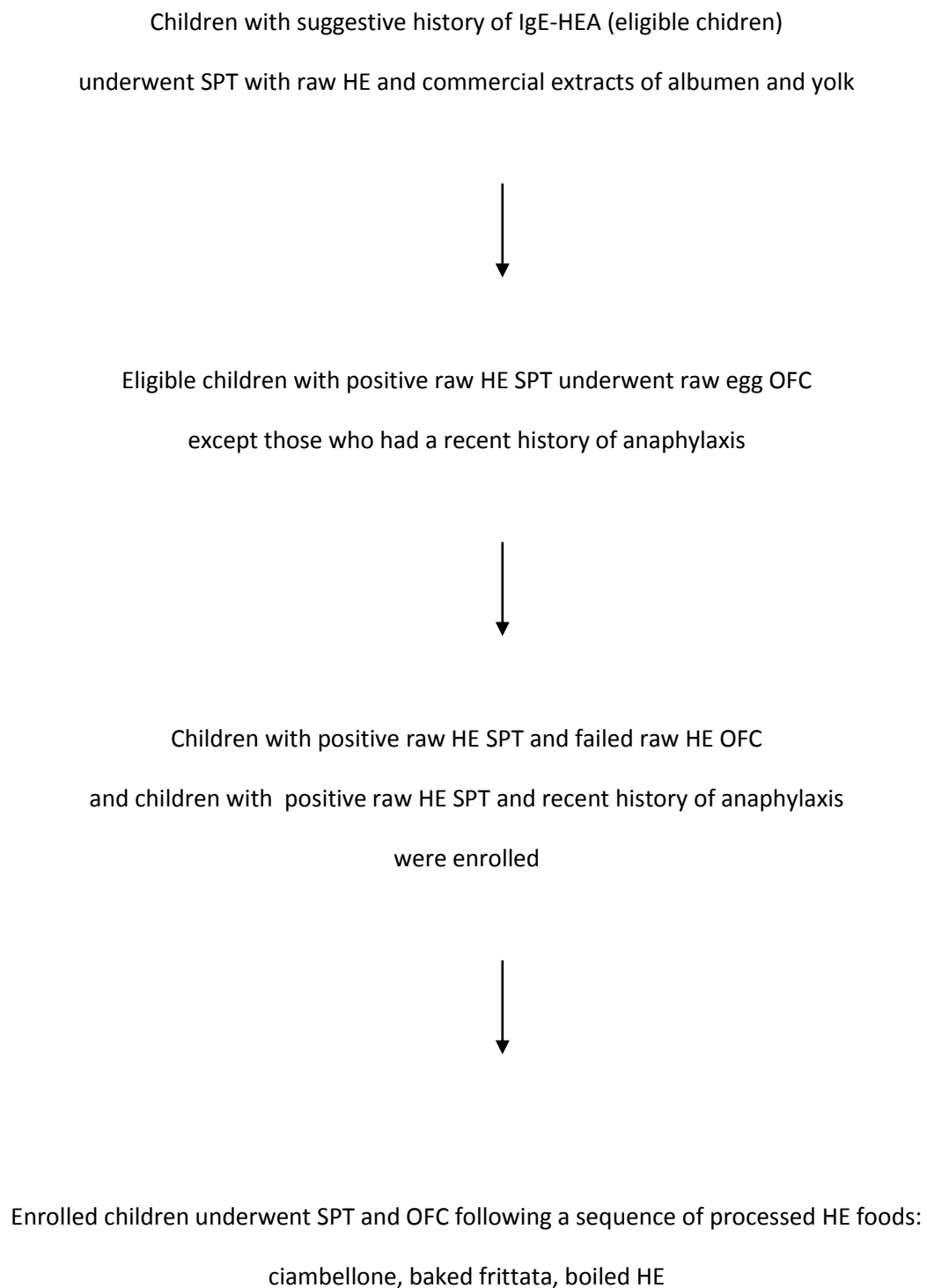
*Legend: OFC = oral food challenge; PbP = prick by prick; *, °, ^, # = p<0.05*

Table 3. Prospective studies on baked HE tolerance acquisition related to their PPV and NPV

First author, year (ref)	Performed test and results	Predictivity
Lemon Mulè, 2008 (1)	Ovomucoid serum specific IgE (UniCAP) > 50 ku	PPV = 90%
Lemon Mulè, 2008 (1)	White egg extract SPT < 5 mm	NPV = 95%
Peters, 2013 (14)	Yolk egg extract SPT > 11mm	PPV = 82% NPV not reported
Tan, 2013 (15)	Ovomucoid SPT (extract) > 11 mm	PPV = 100%
Vazquez-Ortiz et al, 2013 (16)	Ovalbumin-sIgE/sIgG4 <2.49	NPV = 89.5%

Legend: NPV = negative predictive value, PPV = positive predictive value, SPT = skin prick test

Figure 1 - Flow chart



Legend: HEA = hen's egg allergy; SPT = skin prick test; HE = hen's egg; OFC = oral food challenge.

APPENDIX 1. Follow-up questionnaire

1. Name and Surname
2. Date of birth
3. How long has it been since your child underwent his/her ciambellone OFC? ☐ 3 months ☐ 3-6 months ☐ >6 months
4. Can your child now eat hen's egg in all forms and grades of heating? ☐ Yes; eating hen's egg both processed (ciambellone, cakes, biscuits, custard) and raw (ice-cream, mayonnaise and other products made with raw hen's egg) ☐ No; still avoiding hen's egg except baked egg products, such as ciambellone, cakes, muffins, biscuits and extensively heated hen's egg without a wheat matrix (baked frittata). ☐ No; avoiding hen's egg except baked in biscuits ☐ No; avoiding all forms of egg, including baked products.

4bis. To date, does your child eat ciambellone prepared exclusively following our recipe or even other baked products ?

- Yes; only eating ciambellone prepared following medical recipe.
- No; also eating other baked products.

5. How often does your child eat baked hen's egg (such as in a form of ciambellone or other baked products)?

- Daily
- Once in a week
- Once in two weeks
- Less than one time per month
- Never

6. **How long after the ciambellone OFC did your child continue to have it in his or her diet?**

- ☐ Stopped directly after the OFC
- ☐ Less than a month
- ☐ Between one and six months

7. **On average, does your child still eat approximately the same amount of baked egg as he or she consumed during his or her OFC?**

- ☐ Yes
- ☐ No; he or she eats less
- ☐ No; he or she eats more
- ☐ No; he or she does not eat muffin at all

8. **Did your child have any symptoms that you thought might have been caused by the ciambellone after you got home from the OFC ?**

- ☐ Yes

- No

8bis. If yes to Question 8: what were these symptoms?

- Itchy mouth or tingling mouth or throat between 2-8 hours
- Itchy mouth or tingling mouth or throat >8 hours
- Hives between 2-8 hours
- Hives >8 hours
- Occurrence or worsening of eczema between 2-8 hours
- Occurrence or worsening of eczema >8 hours
- Abdominal pain between 2-8 hours
- Abdominal pain >8 hours

- Vomiting between 2-8 hours
- Vomiting >8 hours
- Diarrhea between 2-8 hours
- Diarrhea >8 hours
- Cough or wheeze between 2-8 hours
- Cough or wheeze >8 hours

9. **If yes to Question 8bis: did these symptoms influence your child's diet?**

- Yes; I completely stopped giving baked egg in all its forms.

- No; I continued with approximately the same amount of ciambellone as the challenge
- No; but I reduced the amount of hen's egg in the mixture or the amount of ciambellone
- No; but I changed to hen's egg in biscuits

10. **Did your child show any symptoms in the months after you continued baked egg in his or her diet that you thought were related to the baked egg?**

- Yes
- No

Please report culprit food (ciambellone/cakes/frittata/other commercial baked products)

11. **If yes to question 10bis: did these symptoms influence your child's diet?**

- Yes; I completely stopped giving baked egg in all its forms.
- No; I continued with approximately the same amount of ciambellone as the challenge

- No; but I reduced the amount of hen's egg in the mixture or the amount of ciambellone
- No; but I changed to hen's egg in biscuits

12. Has your child ever eaten baked egg (ciambellone or other baked products), while she/he was in a fever?

- Yes
- No

13. If yes to Question 12, did any adverse reaction occur? Please, state below culprit food and type of problem (for example: ciambellone → worsening of eczema).

14. Has your child ever eaten baked egg (ciambellone or other baked product), within 2 hours before or after performing physical activity?

- Yes
- No

14bis. If yes to question 14, did any adverse reaction occur? Please, state below culprit food and type of problem (for example: ciambellone → worsening of eczema).

15. How useful was the ciambellone OFC in relieving your concerns relating to your child's hen's egg allergy?

- ☐ A lot
- ☐ A little bit
- ☐ Not at all

16. If your child passed OFC, how useful was being able to add baked egg into your child's diet ?

- ☐ A lot
- ☐ A little bit
- ☐ Not at all
- ☐ I Was not able to introduce because of ongoing symptoms