Clinical Reviews in Allergy & Immunology (2018) 55:118–138
https://doi.org/10.1007/s12016-018-8669-0

The Impact of Baked Egg and Baked Milk Diets on IgE- and Non-IgE-Mediated Allergy

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Published online: 8 March 2018

Abstract

Baked milk (BM) and baked egg (BE) diets are increasingly used in the management of milk and egg allergy, rather than avoidance. Children with tolerance versus reactivity to BM and BE may have smaller skin prick test and lower specific IgE, and BM-tolerant children have less basophil reactivity and more peripheral T regulatory cells. However, most milk- and egg-allergic children tolerate BM and BE and an individual's reactivity is unpredictable. Non-reactivity is due to conformational changes in the allergens. Significant differences in the published advice about methods of introduction exist from graded introduction at home to a medically supervised full dose. These approaches carry different risks and may have different immunological effects. Reactivity to BM is a predictor of a severe milk allergy. Therefore, medical supervision for BM and BE introduction is prudent. The baked diet allows dietary liberation. Most, but not all, BM- and BE-tolerant children continue eating the baked foods. The prognosis of children who can eat BM and BE is favorable with likely resolution of their allergy over the next few years. Murine models of BE diets demonstrate that heated egg can impart clinical protection against anaphylaxis and cause immune changes. Most observational human studies of BM and BE diets demonstrate clinical resolution of allergy and favorable immune changes versus regular care controls. However, the one randomized controlled trial for the BE diet in BE-tolerant children did not support an immune-modifying effect of the BE diet. Another study of BE immunotherapy is expected to be completed in 2018. There is currently no evidence for prevention of allergy with the baked diets. There may be a future role for BM and BE in liberating the diets of individuals with non-IgE-mediated allergy given recent studies that a subset of these patients can consume BM without a clinical reaction.

Keywords Immunotherapy · Baked · Heated · Milk · Egg · Food allergy

Background

Milk and egg allergy are a significant problem in childhood. While the exact prevalence of food allergies is difficult to state [1], food allergies affect up to approximately 8% of children and milk and egg are the among the most common causative foods in the USA [2] and in Europe [3]. Food allergies impact the daily lives of children and their families [4]. Milk and egg are contained in many foods children typically socially enjoy such as pizza and cake and thus impact children in many aspects of their lives. Additionally, parental perception of children's quality of life is affected by the duration of cow's milk exclusion diets [5]. For most food allergies, the standard of care is avoidance and preparation for accidental exposure by carrying epinephrine auto-injectors to be administered as first-line treatment for anaphylaxis [6]. There are significant potential nutritional deficiencies to restrictive diets, especially to milk [7].

Milk and egg allergy typically has the best prognosis of food allergies, and in many children the allergy is outgrown by school age [8]. However, it is now known that some children have persistent milk [9, 10] and egg allergy [11].

There is an enormous need to treat food allergies, and multiple approaches are being investigated. One with great potential is oral immunotherapy (OIT). However, wide adoption of OIT with intact foods had been hindered by the risk of allergic reactions, limited ability to induce a long-term tolerance, high

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numbers of dropouts, and poor long-term results [12]. Specifically to milk, there was disappointment in the long-term results of all 32 children who completed OIT to milk at Johns Hopkins with only 31% of milk OIT clinical trial patients tolerating full-dose servings of milk after completing immunotherapy [13].

For many years, it has been known that some egg-allergic children can eat heated egg without allergic reaction [14, 15]. The same phenomenon was formally described for milk [16]. There is now no doubt that most egg- and milk-allergic children can eat the baked form without an allergic reaction [17–19]. Baked milk (BM) and baked egg (BE) diets are accepted clinical practice in the management of milk and egg allergy [20, 21]. There are also now data that some children with non-IgE-mediated allergy can tolerate baked diets as reported for eosinophilic esophagitis (EoE) [22] and for food protein-induced enterocolitis (FPIES) [23]. The uncertainty remains about whether the prognosis of these children is altered by consuming the baked diet.

This review will focus on hen's egg (egg) or cow's milk (milk). We will discuss the molecular features of egg and milk, which alter with heat and with baking into a matrix. We will discuss the testing which predicts BM and BE tolerance. We will review the immune effects of the baked diets in murine models and humans. We will present the studies in which baked diets were introduced, distinguishing between baked diets in people known to tolerate the baked product and baked diets in those reactive to the baked product. We will discuss whether the modified food is driving immune changes or is just a marker for a milder phenotype. We will also briefly consider data on prevention of allergy with baked diets.

Allergenicity of Milk and Egg Is Altered by Heat

Milk

Heat treatment has long been recognized to have the potential to alter allergenicity of proteins. Guinea pig experiments dating back to the 1970s recognized that heating milk could alter its allergenicity [24], and it was postulated that heating whey may reduce the allergenicity of infant formulas [25]. Now it is well recognized that the processing of food proteins alters their structure and potential to induce allergy [26–28]. The allergenic characteristics of a protein are determined by both the epitopes formed by the sequential amino acids and epitopes arising from the three-dimensional shape of the protein, called conformational epitopes. Heating causes a loss of the conformational epitopes and largely preserves the sequential epitopes.

The predominant allergens in cow's milk are caseins and whey [29, 30]. Casein (Bos d 8) is the major protein in cow's milk, and it accounts for 80% of the total protein content. Caseins are further subdivided into αS1-casein (Bos d 9), αS2-casein (Bos d 10), β-casein (Bos d 11), and κ-casein (Bos d 12). Whey proteins account for 20% of the total amount of proteins present in cow's milk. The major whey proteins consist of β-lactoglobulin (Bos d 5), α-lactalbumin (Bos d 4), immunoglobulins (Bos d 7), bovine serum albumin (Bos d 6), and lactoferrin. Casein is the major heat-stable allergen, and it is detectable regardless of the time of heating [26–28], whereas the whey proteins are altered by heat. Typical commercially available milk is heated by pasteurization (70–80 °C for 15–20 s), sterilization (110–120 °C for 10–20 min), or ultra-high-temperature sterilization (135–145 °C for 0.5–4 s) [31], or milk powders can be made by vacuum evaporation and then spray-drying the milk with hot air for 20 seconds up to minutes. The powder is then reconstituted with water to create a liquid milk product. These methods may alter the allergenicity of milks, although human clinical studies are lacking and these commercially processed milks should not be considered as equivalent to extensively heated/baked milk in terms of allergenicity [28]. In this review, we will refer to all of these liquid, non-cooked milks as liquid milk (LM).

Egg

Egg white (EW) and egg yolk differ in their protein constituents and allergenicity. EW is more likely to be the cause of food allergies than the yolk. The major allergens in egg are ovalbumin (OVA, Gal d 2) and ovomucoid (OVM, Gal d 1). Other allergens in egg white are ovotransferrin (also called conalbumin, Gal d 3) and lysozyme (Gal d 4). Alpha-livetin (also called chicken serum albumin, Gal d 5) is the major allergen in egg yolk relevant in the egg-bird syndrome [32]. OVM is the dominant allergen in egg white [33], even though it is not the most abundant protein. OVM is heat stable while the other major allergens are all heat labile [32]. It is worth noting that brief heat treatment may not be enough to reduce the allergenicity of EW. The time of cooking has a larger effect on egg allergenicity than the temperature used, as measured in vitro [34]. A separate clinical study has also shown that brief heating is insufficient to reduce allergenicity. Forty patients were fed both raw EW and dehydrated EW, which is heated for 59 °C and then spray dried with hot air at 80 °C for 1 min. Ten patients reacted to both forms of EW and 30 reacted to neither [35]. Powdered EW was therefore stated to have the same clinical reactivity as raw EW.

The Milk and Egg Ladder and the Effect of the Matrix

The properties of the allergenic proteins are more complex than simply being heat labile or heat stable. There is an emerging understanding of the role of the matrix in which foods are

baked. The various levels of allergenicity of milk according to heat treatment and matrix incorporation have been referred to as the "ladder" for both milk [27, 36] and egg [37, 38]. For milk, the lowest level, or least likely to cause an allergic reaction in milk-allergic individuals, is a product which contains milk baked within a matrix such as wheat. The next level includes cooked cheese such as pizza, and then the most allergenic level includes uncooked cheese and liquid, non-cooked milk. These empirically defined categories can be further divided with milk products such as rice pudding being placed between cheese and liquid, non-cooked milk [39].

Eggs can be considered to be in various states of cooking from raw egg, to lightly cooked egg, well-cooked egg, and baked egg [37, 38]. Raw egg (RE) is the form of egg in foods such as salad dressings, icing, and mayonnaise. Lightly cooked egg (LCE) would include scrambled eggs, quiche, and meringue. Similar to milk, the antigenicity of egg white is also altered by wheat flour. For example, EW heated for 30 min in the presence of wheat flour has less antigenic activity as assessed by an inhibition ELISA assay after protein separation with SDS-PAGE [40]. According to one published egg ladder [37, 38], the well-cooked egg category includes egg noodles, egg in processed meats such as sausages, and BE in a matrix such as it would be found in muffins, waffles, and cakes. These designations are partly based on in vitro studies and partly empirical.

Throughout the literature, the terminology of BE and BM differs, with some authors using the term extensively heated, some using well-cooked, and others using baked for the same product. In this review, we will use BM or BE to mean a bakery good-style product such as a waffle, muffin, cookie, or brownie, unless otherwise noted.

There may be differential effects on allergenicity in baked goods with wheat versus non-wheat flours. A retrospective review of 104 children reported that after adjusting for gender, the odds ratio of reacting to BE in a muffin-containing wheat replacer was 3.56 (95% CI 1.16, 11.69; $p = 0.0264$) compared to BE in a muffin made with wheat flour [41]. This study is observational and did not directly challenge wheat flour BM-tolerant patients to muffins made with rice flour, and so further evidence is needed as to whether there is a difference in tolerance to milk made in these two matrices.

The Baked Diet Is Not Just Simply Underdosing the Antigen

BM and BE diets are tolerated not simply because of underdosing the antigen. A BM muffin prepared according to standard directions contains about 1.3 g of milk protein whereas a glass of milk contains about 8–9 g of milk protein. In the original Nowak-Wegrzyn et al. paper [16], the BM-tolerant children could tolerate 1.3 g of BM protein in a muffin and then a few hours later tolerate a waffle with 1.3 g of BM protein, and yet when they were exposed to regular milk the median eliciting dose was 0.4 g milk protein. Furthermore, a study of milk desensitization in children allergic to both BM and LM showed that 8/13 children had a BM dose eliciting a dose threshold more than double their individual eliciting dose threshold to LM [42]. Therefore, in children allergic to both forms, some may be able to tolerate more BM than LM.

The cautions required about avoiding undercooked milk have been addressed in a few publications on how to practically include BM in diets [19, 43]. It is known that some BM-tolerant individuals will react to the exact same amount of milk they have tolerated when it is not as fully baked. This observation supports that the milk allergenicity is changed by the baking process in the muffin.

For egg, it has also been reported that children can eat more egg in the baked form than in the regular form [44, 45]. A very recent study examined the thresholds for clinical reactivity in children who had undergone clinical BM or LM or BE or lightly cooked egg challenges. The data were collected from different children having a BM or LM challenge, not individual children reacting to the baked form who then had a LM challenge. The ED50, the eliciting dose predicted to cause a clinical reaction in 50% of the population, was calculated. The eliciting dose for positive challenges for cow's milk were found to be ED50 of 103-157mg to LM and the baked was 148-177mg. Similarly, in egg, the predicted ED50 for lightly cooked egg was 296–360 mg and for BE was 332–384 mg egg protein [46]. There are some limitations to using routinely collected data for threshold analysis; for example, many children reacted to the first dose, so the lowest threshold is not possible to derive from these data. Overall, the conclusions supported the prior studies that tolerance to baked goods is not likely to be due simply to underdosing the antigen, but rather to a thermal modification of the protein allergenicity.

Tolerance and Reactivity to Baked Milk Informs Severity Prediction

Importantly, cow's milk has been reported to be the most likely food to cause anaphylactic death in children under 16 years old in the UK [47] as well as in Israel [48]. Biological markers are imperfect to predict who is at risk of fatal allergic reactions [49], and therefore, all anaphylaxis is considered potentially fatal with the advice to administer epinephrine as first line [6, 50]. It has been shown that the children who tolerate BM were far less likely to have anaphylaxis requiring epinephrine when challenged with regular milk [16]. A recent review included an allergy to extensively heated (baked) milk as a potential predictor of severe food allergy [51]. There had been no reported fatality from clinical oral food challenges until 2017 at which time a 3-year-old boy

was reported to have died following a BM challenge [52]. Significant caution is required for all oral food challenges (OFCs). For individuals found to be allergic to BM, they are at risk of severe anaphylaxis upon milk exposure.

BE oral challenges have not shown this same ability to predict severity [45]. Both BE-reactive and BE-tolerant individuals experienced anaphylaxis at similar rates (18.5 versus 23%). The pros and cons of a baked challenge are summarized in Table 1.

How Do We Know Who Can Tolerate Baked Milk and Baked Egg?

Some families have introduced BM or BE first and then later discovered allergy to the raw or lightly cooked form. If tolerance to the baked form is clear from the history, then the individual should continue eating the food as part of their regular diet [53]. If the reactivity is unknown, the gold standard to diagnose food allergy is the double-blind, placebo-controlled (DBPC) oral food challenge (OFC). However, this procedure is time consuming and expensive and has a risk of inducing anaphylaxis. Open challenges are often an acceptable way to perform OFC but are still expensive and carry risk [54, 55]. OFCs require precautions and procedures to ensure the highest level of safety [56]. Laboratory testing can help identify who may or may not tolerate baked goods, and for whom to offer oral food challenges. Studies on BM or BE have not found consistent historical clinical or laboratory indicators of who will be able to tolerate BM or BE, as was recently reviewed [17], although some trends have emerged.

The Role of Skin Prick and Laboratory Testing in Predicting Baked Milk Tolerance

Multiple studies have found the size of the commercial cow's milk (CM) skin prick test (SPT) to be predictive of passing an OFC to BM including the prospective study of 100 children reported by Nowak-Wegrzyn et al. [16], and the retrospective study of 35 children reported by Bartnikas et al. [57]. Both of these studies found a good negative predictive value (NPV) for the CM SPT with a NPV of 100% to 5 and 7 mm, respectively. Uncuoglu et al. [23] and Ford et al. [58] also found the size of the CM SPT to be predictive of BM tolerance. However, the size of the CM SPT had no statistical difference between BM-reactive or tolerant individuals in Agyemang et al. [59] and Mehr et al. [60].

The specific IgE (sIgE) to milk has been reported to be predictive of passing a challenge. Caubet et al. [61] had a total of 225 prospectively enrolled children, including 100 patients from Nowak-Wegrzyn et al. [16], aged 2.1–17.3 years, and suggested a cutoff of 10 kU_A/L for CM sIgE. A low sIgE, less than 1.21 kU_A/L, had high NPV (95% sensitivity). They also suggested an optimal cutoff using molecular allergen analysis: 5 kU_A/L for casein sIgE. In other studies, both sIgE to milk and sIgE to casein have had discriminatory utility including in Ford et al. [58], Bartnikas et al. [57], Caubet et al. [61], Kwan et al. [62], Agyemang et al. [59], and Uncuoglu et al. [23]. Casein sIgE was also discriminatory in the study of Barbosa et al. [63]. Furthermore, using a peptide microarray, Wang et al. [64] showed that children with less IgE epitope diversity and lower affinity were more likely to tolerate BM and that these changes were similar to those who had outgrown their milk allergy. The diagnosis of milk allergy using the molecular components of milk has recently been reviewed [65]. Other allergens examined for predictive value include β-lactoglobulin and α-lactalbumin, but these have not been found to discriminate BM reactivity.

Ford et al. [58] described 132 children who were grouped into BM-reactive, BM-tolerant, or outgrown milk allergy and then further assessed the BM-tolerant group by whether they could tolerate muffins, pizza, or rice pudding. They reported that in addition to CM SPT and sIgE to casein and milk, the milk-specific basophil reactivity and spontaneous basophil activation could discriminate between phenotypes of milk-allergic children. Interestingly, this study highlighted that some measures, such as casein IgE/IgG4 and the ratio of milk-specific basophil reactivity to non-specific (anti-IgE) basophil activation, did not discriminate between milk-allergic children who have outgrown their milk allergy and those who are BM-tolerant, suggesting that the immune response to milk in BM-tolerant individuals is progressing toward resolution of their allergy. The basophil findings support an earlier work by Wanich et al. [66] which showed that basophils from BM-tolerant children were less responsive to milk allergen stimulation than from BM-reactive children.

Differences in T regulatory cells (Tregs) have been described between BM-tolerant and BM-reactive children.

Table 1 Pros and cons for a baked challenge

Pros	Cons
Discover severity of milk allergy	Risk of reaction to the challenge
Discover prognosis	May have trouble following the diet
Reduce dietary restrictions	May have mild reactions after known to tolerate
Possibly hasten tolerance for milk	

Shreffler et al. [67] showed that Tregs were present in a higher frequency in the circulation in children with BM-tolerance than in children reactive to BM.

In recognition of the importance of the matrix to BM reactivity, a few studies have utilized skin prick testing with a muffin slurry to predict BM OFC results. In a retrospective analysis of children with positive (≥ 3 mm) CM SPT milk tests, a negative muffin slurry was predictive of BM tolerance [68]; however, the prevalence of BM allergy in this population was unknown because these patients were not offered challenges unless the muffin test was negative. Kwan et al. [62] enrolled 30 children with milk SPT between 8 and 14 mm to enrich the group for BM-reactive children and offered OFC to all children. They found that a negative muffin slurry test (< 3 mm) was predictive of passing the OFC. However, Mehr et al. [60] did not find a muffin slurry to be predictive of BM-tolerance.

In summary, children with BM-tolerance versus reactivity may have smaller CM SPT, lower sIgE to milk and casein, less basophil reactivity, and more peripheral Treg cells. Additionally, the immunological parameters in patients with BM-tolerance approach the parameters seen when naturally outgrowing milk allergy, and in some cases are indistinguishable from those seen when outgrowing milk allergy. Despite these trends, the testing to predict BM reactivity is imperfect and not consistent across the studies, which are not directly comparable due to different populations and methodology. As an example, low casein sIgE is statistically predictive of BM tolerance and yet it has been documented that a child even with < 0.35 kU_A/L casein sIgE can react to BM [57]. Given that the testing for BM tolerance is variable and because reactions to BM can be so severe, the most prudent approach is for medically supervised challenges to BM [17].

The Role of Skin Prick and Laboratory Testing in Predicting Baked Egg Tolerance

The studies using laboratory testing to predict BE tolerance have had varying results, as was recently extensively reviewed [17, 32]. Multiple studies have attempted to define predictors for BE reactivity [44, 45, 68–76]. The commercial EW SPT has been reported to have good NPV in some studies. For example, in a retrospective study of 52 egg-allergic children reported by Cortot et al. [69], all 9 children with an EW SPT less than 10 mm passed the BE OFC. In Bartnikas et al. [70], a retrospective review of 169 OFC to BE, the > 90% predictive value for passing the challenge was an 11-mm wheal [70]. In 95 children undergoing OFC to BE reported by Clark et al. [76], BE OFCs were usually successful when the SPT was less than 5 mm. The EW SPT to consider excluding a challenge has been high. For example, in Cortot et al. two thirds of the children passed the BE OFC even with an EW SPT > 30 mm [69], although in another study 25 mm was reported to have 95% specificity [70].

The decision points suggested for sIgE to EW have also varied. For example, for sIgE to EW, Caubet et al. [73] found the > 95% specificity for predicting BE reactivity to be 26.2 kU_A/L, whereas Bartnikas et al. [70] found > 95% specificity for predicting BE reactivity to be 9.65 kU_A/L, and Lieberman et al. [71] reported that an EW sIgE of 10.0 kU_A/L had a specificity of 94% and showed that the EW sIgE was superior to the EW SPT to predict the outcome of BE challenges.

The sIgE to OVM also differs between BE-reactive and BE-tolerant individuals; however, a consistent decision point has not been found and the OVM sIgE does not offer diagnostic utility above SPT and sIgE to EW [32]. The > 95% specificity for sIgE to OVM has been reported as 3.38 kU_A/L [70], and Lemon-Mule et al. [45] found that OVM sIgE at high levels (> 50 kU_A/L) had a high positive predictive value (PPV). Caubet et al. also found OVM to be predictive of BM reactivity: OVM sIgE of 12.8 kU_A/L had a sensitivity of > 95%. Tan et al. [77] found OVM SPT > 11 mm wheal to have a high PPV. The PPV will change with the prevalence of allergy in the study, and they are not directly comparable.

OVM may have better ability to discriminate RE-allergic children who can tolerate cooked egg products than children who can tolerate BE products. It is postulated that the wheat matrix in BE products reduces the allergenicity of OVM to the point that OVM is not more informative than regular EW SPT and sIgE [32]. Overall, it is difficult to rule in or out who will be BE reactive or BE-tolerant, and therefore, OFC to BE may be best suited to a medically observed setting.

How Is BM or BE Introduced?

The interpretation of how to introduce a baked diet varies. In the original descriptions of the BM diet, the patients had undergone OFC to full servings of BM prior to including BM in their diets. The research participants ate both a muffin containing 1.3 g of milk protein followed by a waffle, also containing 1.3 g milk protein [16]. Current suggestions for clinical use from the Jaffe Food Allergy Institute suggests one muffin (1.3 g of milk protein) to be used for a physician-supervised BM oral food challenges and then, if there is no reaction to the whole muffin, to incorporate BM goods at home [17].

However, these recommendations of the challenge material and dichotomous assignment to a status of BM-tolerant or BM-reactive are not universal. The British Society guidelines recommend that a BM challenge can be performed with a malted biscuit containing 1 g of milk [36]. If the individual is deemed appropriate for a home challenge (young children who have had a previous mild reaction to milk [e.g., mild rash, gastroesophageal reflux]) with no concerning features

(previous cow's milk allergy which affected breathing, the gut, or circulation, asthma requiring a preventative inhaler or uncontrolled asthma, multiple or complex allergy, no significant reduction in SPT wheal since diagnosis, high milk sIgE levels without any previous milk exposure, parents who are unable to comprehend or adhere to the protocol), they suggest that a milk-allergic individual start with the small biscuit and then slowly build the dose over 5 weeks before moving up the next step of the ladder. If a few days are missed, they recommend going back down to a smaller amount and not to increase the amount when the child is unwell and, if symptoms are seen then, to reduce the dose to a previous dose which was well tolerated. Once eating BM in the form of a biscuit, the recommendations are that each step up the ladder be introduced in trace amounts and, if there is a reaction, to go down to a previous stage on the ladder. Whether graded introductions up the milk ladder are performed at home or in the office is decided by prior severity of reaction and co-morbidities.

For baked egg challenges, it has been recommended to use a muffin containing 2.2 g of egg protein [19] under medical supervision. The British Society recommends home challenges for children without asthma and, if their prior reaction was very mild (such as just redness around the mouth), to a significant exposure (for example, a mouthful of scrambled egg) and no ongoing asthma. The protocol suggests a fairy cake made with one egg and 4 oz. of flour to be introduced at home over days and, if there is any reaction, to stop and try again 6 months later after a discussion with their physician [37]. Both of these approaches aim to have only individuals who tolerate a serving of BE include it in their diet.

In summary, the British methods for BM and BE introduction triage some BM and BE introductions to home. Their BM protocol is likely to have many more children eating small amounts of BM, even those who may react at higher amounts and who would be considered BM-reactive to a full muffin, versus the method of ensuring that a full serving is tolerated in a medically observed setting. These two approaches differ significantly clinically and potentially immunologically. A very slow OFC, such as one recommended over days at home, may act as a form of desensitization and not prove tolerance to an entire serving [54, 55]. Considering the range of practices, when studying whether baked diets have an immunological effect, it is important to distinguish baked diets in those who can tolerate the product from baked diets in those who cannot. Finally, in view of the recent fatality caused by an OFC to BM, triaging for home introduction is associated with considerable risk. Therefore, studies to define the very mild phenotype of milk allergy on the basis of clinical characteristics and laboratory test results are necessary to validate the proposed criteria for home introduction. In the authors' opinion, an initial assessment of reactivity to BM is best suited for a supervised setting, e.g., office under the physician supervision.

Tolerability of Baked Diets

Once BM and BE are introduced, they tend to be well tolerated as has been reviewed previously [17, 53]. Children eating baked diets have had no negative effect on growth parameters and intestinal permeability and for atopic conditions such as atopic dermatitis. EoE was reported in a BM study in one child with strict avoidance of milk and in one eating BM [78]. The BM-tolerant child initially stopped and then re-introduced BM after it was demonstrated that avoidance of BM lead to no clinical improvement in their EoE. One child in the strict avoidance group of the Netting et al. trial of BE OIT developed EoE [79]. Therefore, there has not been a strong association with baked diets and the development of EoE.

Not all children introduced to the baked foods have continued the diet. In a follow-up questionnaire (median 12 months after OFC) of their patients having undergone BM and BE challenges, Lee et al. [80] reported that 8/75 (10.7%) of children stopped eating any BM and 2/23 (8.7%) stopped eating any BE. More recently, Weinbrand-Goichberg et al. [81] described that 51/70 (81%) who passed a BM OFC were still eating BM. Both studies noted that some children had mild reactions and gastrointestinal symptoms and some disliked the taste of BM and BE. In many of these patients, mild symptoms can be attributed to mistakes during baking, e.g., not adhering to the temperature and time of baking. Another common mistake is not baking individual servings, e.g., muffins versus cake or bread rolls versus a loaf of bread. The original recipes for BM and BE have been developed in individual servings to ensure baking throughout, and baking a larger amount increases the risk of not sufficiently baked and soggy middle parts of the product. In the author's experience (ANW), the development of reactivity to BM or BE is an uncommon phenomenon that has been seen in less than 5% of the patients participating in clinical trials of baked diets at Mount Sinai. However, baked diets add layers of complexity to the avoidance of the allergenic food and require detailed instructions and possibly a consultation with a registered dietician to facilitate adherence. Additionally, there has been a patient who was eating BE and developed food protein enterocolitis (FPIES)-like symptoms after eating RE [82].

Immunotherapy

The Merriam-Webster definition of immunotherapy is the treatment or prevention of disease that involves the stimulation, enhancement, suppression, or desensitization of the immune system.

Food OIT has had multiple successes and clearly causes an immune change to the food in many people. The remaining controversies about food immunotherapy with the intact food are predominantly concerning the safety and the longevity of

Table 2 Differences between baked diet and OIT for milk and egg allergy

Property	Baked milk diet	Baked egg diet	OIT to milk	OIT to egg
Allergic reactivity to the form of food consumed	Not allergic OR allergic (BM has been introduced in BM-allergic individuals, see text)	Not allergic OR allergic (BE has been introduced in BE-allergic individuals, see text)	Allergic	Allergic
Clinical applicability	Wide and accepted as clinical care	Wide and accepted as clinical care	Predominantly research	Predominantly research
Risk of reaction once tolerating a full dose	Low	Low	Present	Present
Number of medical visits required to include serving sizes of food in the diet	One	One	Multiple	Multiple
Expected success to eat a serving size	High, 70–80% of proven liquid milk-allergic tolerate BM	High, 70–80% of proven egg-allergic tolerate BE	Varies, 50–90%	Varies, 27–93.5%
Expected long-term outlook	Excellent for those who tolerate full servings, most will outgrow milk allergy	Excellent for those who tolerate full servings, most will outgrow egg allergy	Dropouts may continue over time in some studies	Dropouts may continue over time
Advice/label reading	If tolerate a full serving, may eat "may contain" as well as BM products according to the ladder	If tolerate a full serving, may eat "may contain" as well as BE products according to the ladder	Depends on the study/physician	Depends on the study/physician
Effect of avoidance once known to tolerate ("sustained unresponsiveness")	Unknown	Unknown	Allergy may return to level of natural history	Allergy may return to level of natural history
Expected immune results	Toward tolerance	Toward tolerance	Toward tolerance	Toward tolerance
Advised to carry epinephrine autoinjector	Yes	Yes	Yes	Yes

the response [13]. Given that most milk- or egg-allergic children can eat BM and BE respectively without allergic reactions, it would be safe and convenient to use as OIT.

Immunotherapy to Milk and Egg

Before considering the immunotherapy effect of the baked diets, it is helpful to consider the immunotherapy effect of other forms of OIT to milk and egg. Table 2 compares and contrasts the baked diets to regular OIT. In OIT, there are characteristic immune changes [30] of an increase in sIgG4, an initial increase and then decrease in sIgE, basophil signaling changes, and a reduction of the T cell proliferative response to the food allergen. However, there are marked variations in OIT protocols for native foods, which result in different levels of efficacy, safety, tolerability, and long-term results [83].

Milk

A meta-analysis of randomized controlled trials (RCTs) for milk OIT [84] summarized that desensitization was 10.3 times more likely in children undergoing milk OIT versus those who are not. The success if measured as the percent of patients achieving desensitization has ranged from about 50% up to 90%. The safety, as measured by the use of epinephrine, ranged from 6.7 to 30.8%. The immune changes showed an increase in sIgG4, although sIgE was not statistically different in treated and untreated groups. The form of milk used for OIT has varied. Non-fat powdered milk [85] has been used, as has pasteurized milk. The long-term result [13] for the Skripak et al. trial [85] showed that the long-term efficacy may be poor with only 31% of subjects tolerating a full serving of milk after a median of 4.5 years from the start of OIT.

Egg

As was recently reviewed for egg OIT [86–88], the success rate in terms of desensitization ranged from 27 to 92.5%. The use of epinephrine ranged from none in some studies to 18 uses in 13 of 50 children during the buildup phase of OIT. There is enormous variability in egg OIT protocols. The substance used for desensitization has varied markedly across studies and has included lyophilized egg, dehydrated egg white, pasteurized raw egg white, or various forms of the natural egg such as RE white, scrambled eggs, or hard-boiled egg. Most egg OITs have been performed with some form of RE [86]. However, there are some other forms which have been used which may help to inform whether immune changes could occur with BE. A study of egg OIT in children aged 1–8 years showed that a 3-month OIT protocol with hard-boiled egg, a form of egg some consider "lightly cooked" on the egg ladder [37, 38], followed by 3 months of daily intake of creamy deserts and flans desensitized 69% of participants to 7 g of RE white, versus 51% of control participants [89]. There has also been a pilot study of a placebo-controlled protocol with a hypoallergenic egg product, hydrolyzed egg powder [90], in which 29 children 1–5.5 years old were given up to 9 g of hydrolyzed egg powder over a 6-month period and then had an OFC with one boiled egg. The children in the interventional group passed the OFC at a rate of 36 versus 21% in the placebo group, which was not statistically significant. There were significant immunological findings. Specific IgG4 levels increased, and the CD203c+ and CD63+ basophils decreased more in the treatment versus the placebo group. These studies are illustrative because they demonstrate that a protocol with one form of egg may have some effect on the immune system response to another form of egg. These marked protocol variations also mean that there is not a clear comparator to BE OIT.

Sustained Unresponsiveness to Milk and Egg OIT

A recent review [91] evaluated the studies evaluating whether OIT can alter the disease course and allow a person to eat the food after a period of avoidance, called "sustained unresponsiveness (SU)." For milk and egg, Staden et al. [92] described 45 children who had a median of 21 months of OIT or an elimination diet and then another OFC was performed after 2 months of stopping therapy, and there was no difference in the rate of SU between the groups at 36 and 35%, respectively. This study is consistent with Buchanan et al. [93] for egg OIT and Keet et al. [13] for milk OIT. However, other studies have found higher rates of SU, such as Vickery et al. [94] who reported that six out of six children had SU after 1 month of discontinuing an individually dosed egg OIT regimen for a median time of 33 months.

Baked Milk Diets: Immunotherapy or a Marker of Spontaneous Resolution of Milk Allergy

Baked Milk Diet

Murine Model

Murine models of food allergy have recently been reviewed [95]. Mouse models of casein and whey allergy have contributed to our understanding of allergenicity of proteins.

Human Studies

Studies on BM have looked for clinical and laboratory changes during the BM diet as summarized in Table 3. When compared to historical controls who were avoiding milk, the children eating BM became LM-tolerant at a much higher rate

Table 3 Clinical and immunological changes observed on a BM diet of at least 3 months

Population	Methodology	Clinical outcome	Immunological changes	Conclusion
BM non-reactive, LM-allergic				
Nowak-Wegrzyn et al. [16] 100 children (mean age 7.5) recruited from tertiary center BM OFC followed by LM OFC unless highly predictive test results	Prospective cohort for 3 months Intervention: BM-tolerant advised to eat BM daily for 3 mo (open), BM-reactive avoided BM. Comparator: BM-tolerant, baseline Clinical Outcome: Tolerability	68/100 were BM-tolerant During 3 mo follow-up 1/68 BM-tolerant had oral pruruitis with undercooked BM 5/68 did not eat BM at home due to anxiety	Compared baseline in BM-tolerant to 3 month in BM-tolerant eating BM Milk SPT and Casein IgG4 significantly changed from baseline	Two distinct groups of milk allergic children Unclear if eating BM will lead to tolerance
Kim et al. [78] 89 children aged 2.1–17.3 (median age 6.6) recruited from a tertiary center BM OFC followed by baked cheese OFC followed by LM OFC	Prospective cohort followed for a median of 37 months Intervention: BM-tolerant advised to eat BM daily for 6+ months (open); BM-reactive avoided all milk. Comparator:BM-reactive, and also an observational group with usual care avoiding all forms of milk Clinical outcome: BM OFC	60% of BM-tolerant children became LM-tolerant 2% BM-reactive became LM-tolerant Observational group, 22% became LM-tolerant	Casein and β-lactoglobulin sIgE decreased and casein sIgG4 increased significantly in subjects ingesting BM versus those avoiding	Dietary BM appeared to accelerate the resolution of milk allergy in children
Nowak-Wegrzyn et al. [96] (abstract) 100 children followed following a BM OFC 52 were initially BM-tolerant, 23 BM-reactive 15 lost to FU	Prospective cohort followed for a median of 83 months Intervention: BM-tolerant advised to eat BM daily (1–3 servings) for 6+ months (open); BM-reactive avoided. Comparator: Between groups of milk tolerance Clinical outcome: periodic OFC to BM or LM	Of the initially BM-tolerant group, 37/52 (72%) became LM-tolerant, 10 (19%) had BM only and 5 (9%) avoided all milk 38 children had unrestricted milk intake: 2 (5%) developed EoE, 2 had exercise symptoms after milk Of 23 BM-reactive children at enrollment, 18 (78%) continued to avoid all milk, 3 became BM-tolerant and 2 LM-tolerant	In BM-tolerant children, no difference in any initial immunological outcome with respect to final milk tolerance	BM diet is safe and well tolerated in most BM-tolerant children
Nowak-Wegrzyn et al. [39] (abstract) 136 children (median age 7 years) were phenotyped at baseline with sequential OFC to place their reactivity on the milk ladder: 41 muffin allergic 31 pizza allergic 11 rice pudding allergic 10 tolerated LM	Prospective cohort for 366 months Intervention: sequential OFC with milk ladder (muffin/pizza/rice pudding/LM) q6 months in 41 children (open) Comparator: Sequential OFC to the milk ladder q12 months in 44 children and 34 control children avoiding milk Clinical outcome: tolerance of increasingly allergenic forms of milk (progression up the milk ladder)	61% children in 6 M and 73% in 12 M progressed to tolerating a more allergenic form of milk 49% in 6 M and 39% in 12 M tolerated LM LM tolerance unrelated to the baked food tolerated at baseline 20% of BM-reactive progressed up the milk ladder $p < 0.01$ versus randomized subjects. No control subjects became tolerant to LM; $p < 0.01$ versus randomized subjects.	None reported	For BM-tolerant children, progressive OFC up the milk ladder q6 months versus q12 months did not accelerate tolerance of the next form on the milk ladder or LM

Table 3 (continued)

Population	Methodology	Clinical outcome	Immunological changes	Conclusion
BM-reactive, LM-allergic				
Goldberg et al. [42]. 14 BM- and LM-allergic children who failed milk OIT	Prospective cohort for 12 months Intervention: BM OIT with muffin made from low-fat dried milk powder Baseline LM challenge and at 6 and 12 months Comparator: baseline: Clinical outcome: achieving maintenance to BM, OFC to LM	3/14 patients tolerated 1.3 g milk protein/day in BM, and a small increase in the threshold to LM was attained in these patients	Decreases in IgE reactivity to casein and α-lactalbumin in children reaching maintenance and increase in some others BAT: mean difference between heated milk-and unheated milk-driven CD203c percentage expression was lower for successfully completed BM OIT than in those who did not (211 versus 4.4%, $p = 0.0002$)	These BM-reactive patients who failed milk OIT were very difficult to desensitize Anti-IgE may help The BM may have had some effect on unheated milk thresholds
Amat et al. [97] 41 children > 3 years old (average 6 years old) with casein sIgE > 0.35 kU/L and DBPCFC-proven LM allergy	Prospective cohort followed for 5 months ("high-risk")–9 months ("low-risk") Intervention: "Low-risk arm": OIT starting with BM (commercially available shortbread cookie) until 210 mg milk protein, then to half-heated BM (commercially available milk-chocolate bar) until 1970 mg milk protein, and then LM until target of 2720 mg milk protein/day Comparator: "high-risk arm": LM OIT up to 2720 mg Clinical outcome: daily tolerated dose of milk protein at home and safety	Average daily tolerated dose of milk protein was 714 mg (106–2720) in the BM OIT arm and 1258 mg (476–2720) in the LM OIT arm ($p = .24$). 3 children (14.3%) in BM OIT and 2 (11.8%) in LM OIT required epinephrine at home ($p = 1$)	No difference in immune parameters between groups (casein-sIgE, sIgG4, sIgE/sIgG ratio, a-lactalbumin sIgE, B-lactoglobulin sIgE)	There is a risk of severe events in milk OIT even with BM Children with a severe milk allergy phenotype should be carefully evaluated in specialized centers

[78]. BM-tolerant patients consuming BM show immune changes of decreased casein and α-lactoglobulin sIgE and increased casein sIgG4 versus their own baseline [16] and versus individuals avoiding milk [78]. Criticisms of these studies include that they were all undertaken at a tertiary children's hospital without a randomized control group, without blinding, and the historical controls were treated differently in terms of phenotyping of their milk allergy and in terms of access to OFC [98]. Therefore, the favorable outcomes seen for BM-tolerant children may be because they have a better prognosis than BM-reactive children, not because they are eating BM. A long-term follow-up of the children ingesting BM has been reported in abstract form by Nowak-Wegrzyn et al. [96]. Over a median of 83 months, more than 70% of BM-tolerant children became LM-tolerant versus < 10% BM-reactive children.

Given the difficulty in recruiting BM-tolerant children to enter trials of avoidance of BM, a different study design was undertaken. In Nowak-Wegrzyn et al. [39], the children were allocated to q6-month or q12-month sequential OFC progressing up the milk ladder from muffin to pizza to rice pudding and finally to LM. There was no evidence that the every 6-month challenges helped the children to acquire tolerance any earlier than the every 12-month challenges.

A systematic review was recently published analyzing the studies on the immunological effect of BM and BE diets which concluded that without a randomized controlled trial (RCT), distinguishing between tolerance of BM as a marker of being more likely to outgrow their milk allergy versus a clinical and immunological effect of ingesting BM will not be possible [98]. There has been no RCT for the BM diet.

It is important to note that most of these studies are in LM-allergic children who could clearly tolerate BM. There is a study assessing BM OIT in BM-reactive individuals. A cohort of 15 patients who failed LM OIT underwent open-label BM OIT as reported by Goldberg et al. [42]. This trial showed that the introduction of BM to BM-allergic individuals might slightly increase the threshold at which they react to LM; however, there was no comparison group so it is not possible to say if these patients would have had those changes with avoidance. It is important to note that only three patients were able to reach 1.3 g of BM and side effects were common. The patients in this trial likely represent the most severe milk allergy phenotype, given that they failed LM OIT. This trial is also important to think about when considering how to convey advice about progressing up the milk ladder. According to this study, in terms of achieving LM tolerance, a BM-allergic person may have limited results by increasing the amount of BM in their diet.

A very recent study compared a milk OIT protocol starting with BM to a milk OIT protocol starting with LM. Forty-one children over 3 years old (average 6 years old) with DBPCFC-proven LM allergy were randomized to a typical milk OIT protocol with LM with a goal to reach maintenance (2720 mg of milk protein) in 5 months, or an OIT protocol starting with commercially available BM cookie followed by a commercially available milk chocolate bar and then LM OIT, with a goal to reach maintenance in 9 months. The rationale was that starting with BM may be safer [97]. There were no differences in clinical or immunological outcomes between the groups. The authors noted that the highly sensitive children, those with a threshold of reactivity to milk protein ranging from 3.4 to 17 mg, experienced the least increase in reactivity with the highly sensitive children achieving only 104 versus 1802 mg for the others ($p = 0.02$). It was concluded that severe events can occur in milk OIT even with slow protocols with BM, and therefore, highly sensitive children need careful evaluation and supervised updosing even with BM.

Overall, the studies for BM are quite persuasive that the ability to eat BM without an allergic reaction is an excellent prognostic sign for the subsequent development of tolerance to LM. Whether the BM itself is having an immune effect is not clear from these studies. Additionally, there are no studies addressing outcomes for SU to BM after a period of avoidance.

Baked Egg Diets: Immunotherapy or a Marker of Spontaneous Resolution of Milk Allergy

Murine Models

Murine models have examined the effect of heated OVA in OIT. A murine model of anaphylaxis has shown that heated OVA and heated OVM do not cause anaphylaxis when fed to sensitized mice orally; however, these heated antigens still cause anaphylaxis when given systemically [99]. Subsequently, the same group demonstrated that heated OVM was as efficacious as native OVM [100]. After OIT with heated OVM, the sensitized mice were protected more to an OFC than to a systemic challenge (intraperitoneal injection). The investigators did not demonstrate any changes in peripheral blood basophil activation or on peritoneal mast cell activation. Instead, they reported that protection was localized to the gastrointestinal tract and was associated with gene expression changes in the jejunum. These results suggest that the heated form of egg could retain the ability to cause immune changes and yet have less systemic side effects when used for OIT. It also suggests that evidence of successful immunotherapy may need to be sought locally in the GI tract, rather than by systemic markers.

Jimenez-Saiz et al. [101] have described a murine model of egg OIT using heated and ovomucoid-depleted egg white (HOMEW). HOMEW was the precipitate prepared from pH-adjusted EW heated to 95 °C for 30 min and centrifuged. The OVM was removed by centrifuge due to the property that OVM is retained in the supernatant. Mice were sensitized to EW and then treated with HOMEW in two different doses or

placebo three times a week for 6 weeks and then underwent food challenge with EW at week 13. The outcomes were histamine release on food challenge and immunological parameters. The HOMEW-treated mice had significantly less histamine release on EW challenge, lower EW sIgE, and lower IL-4 levels, as well as higher IL-10 and IFN-γ, than the untreated mice. Treated mice also demonstrated increased fecal IgA than did untreated mice. This study showed that the HOMEW OIT resulted in many immunological changes suggestive of successful OIT and that HOMEW may have potential to be used for OIT.

Human Studies

Studies of BE immunotherapy are summarized in Table 4. Some observational trials have shown the speed of resolution of egg allergy after BE introduction has been remarkable. For example, in the report of their clinic patients by Konstantinou et al. [102] in which they challenged the children referred to their clinic for egg allergy, they found that most of the referred patients could tolerate 0.63 mg of BE protein in cake, and after 6 months of gradual increase to 1.5 g of egg protein in BE, almost all of their patients could tolerate RE. These patients were very young with a median age of 24 months and they were not challenged to RE at baseline, so this population may have had many children who were not allergic to RE at baseline. Allen et al. [103] performed a retrospective questionnaire study of their clinic patients to discover their dietary advice (from allergy specialists, dieticians, pediatricians, and general practitioners) and whether the advice or diet influenced the prevalence of egg allergy years after they were initially seen in clinic. There was no statistical difference in the rate of egg allergy resolution by dietary exposure to egg, although more children eating BE than not outgrew their allergy. The studies by Lemon-Mule et al. [45] and Leonard et al. [82] are the initial and long-term follow-up, respectively, of a prospective cohort of RE-allergic children in whom BE was introduced to their diets after passing a BE OFC, or avoided if they were reactive to BE. The children had serial OFC to RE if they were BE-tolerant, and to BE if they were BE reactive. BE-tolerant group were evaluated for multiple outcomes including changes in their own immune evaluation, as well as a comparison to the BE-reactive group and historical controls in rates of passing OFC to LCE. Overall, these prospective studies showed that the BE-tolerant participants tolerated LCE at a much higher rate than BE-reactive participants or the historical controls and that there were significant immune changes from baseline. These studies suggested that the ingestion of BE may be hastening tolerance.

Immunological changes with ingestion of BE including increases in sIgG4 and decreases in sIgE [45, 82] have been documented in observational cohorts. However, a study by Tey et al. [104] reported that eating BE did not appear to cause immunological changes. In this retrospective cohort of 125 children who were OFC positive to RE, the EW SPT was examined for children grouped by their BE exposure. There was no difference in the rate of decline of the size of the EW SPT based on BE ingestion.

The study by Netting et al. [79] is notable because they performed a RCT with a double-blind, placebo-controlled (DBPC) methodology of BE introduction in BE-tolerant, likely RE-allergic children. In this study, the eligibility was children aged 6 month to 5 years who had a recent clinical reaction to egg (within 12 months) and positive SPT to EW, or high likelihood SPT tests (SPT ≥ 5 mm if 6 months–2 years old or ≥ 8 mm if 2–5 years old). They performed BE OFC with 10 g of egg baked in a muffin (1.3 g egg protein). An OFC with RE confirmed RE allergy in those children whose SPT to egg was small (SPT < 5 mm if 6 months–2 years old or < 8 mm if 2–5 years old) if they did not have a clinical history of reaction to raw egg in the last 12 months. The study investigators supplied the baked products containing 1.3 g egg protein or placebo for home consumption two to three times a week for 6 months. The children then had an OFC to RE unless there was a recent clear accidental exposure with a resulting allergic reaction. They had to screen more than 200 children for eligibility to offer 83 children BE OFC, 43 of whom passed. These children were randomized to the intervention (21) or placebo (22). The enrolled children had a median age of 2 years. Two children withdrew from both groups due to failure to eat the study product or illness. One was lost to follow-up in the control group, and three (two in intervention and one in control) did not have a RE OFC. Therefore, 35 had open OFC 1 month after stopping interventional diet. There was no difference between groups in the rate of passing the RE OFC (4/17 (23%) intervention and 6/18 (33%) placebo) or in terms of immunological outcomes. One child in the control group was diagnosed with EoE; the method of diagnosis not specified. The authors concluded that there was no evidence that short-term, regular consumption of BE products in this selected population of BE-tolerant young children modified tolerance acquisition.

Overall, although the initial retrospective and prospective cohort studies suggested that the introduction of BE quickly results in immune changes and tolerance acquisition, the DBPC RCT [79] did not support that BE has a clinical effect as measured by OFC to pasteurized RE. Although the numbers were small, there did not appear to be any reduction in severity of egg allergy in the BE group either, as evidenced by the epinephrine use in two of the intervention group versus one in placebo. This study used a very small amount of BE in the diet when compared to the Lemon-Mule et al. [45] and the Leonard et al. [82] studies which recommended a daily intake of one to three servings of baked egg, a dose of 2.2 g of egg protein per serving. It is not known if a higher dose or longer duration of treatment may have had more efficacy in

Table 4 Clinical and immunological changes observed on a BE diet of at least 3 months

Population	Methodology	Clinical outcome	Immunological outcome	Conclusion
BE in BE-tolerant patients				
Konstantinou et al. [102] 94 children with suspected egg allergy (clinical history plus sensitized (positive EW SPT or EW sIgE ≥ 0.35) (55), or just sensitized (39)) Median age 24 months	Retrospective analysis of egg allergy consults who passed OFC with BE cake containing 0.63 mg egg protein Intervention: Ate up to 1.5 g of egg protein in BE (cake) for 6 months (open) Comparator: none Clinical Outcome: OFC at 6 months of eating BE	87/94 (93%) could eat BE 83/87 (95%) children eating BE passed RE OFC after 6 months of BE	Not reported for baseline versus 6 months of BE	Consumption of BE may be helpful for tolerance acquisition and should be evaluated in controlled trials
Lemon-Mule et al. [45] 117 likely RE0-allergic, all challenged to BE resulting in 64 BE-tolerant, who were presumed (25) or proven (39) RE-reactive aged 0.5–25 years	Prospective, open label Intervention: BE (containing 2.2 g egg protein) 1–3 times a day for 12 months (open) Comparator: to baseline Clinical Outcome: immune changes	64/117 were BE-tolerant RE tolerance not assessed 18/64 BE-tolerant withdrew from the study (16 for inconvenience, but continued to eat BE, 1 did not like BE, and 1 parental concerns re AD)	EW SPT decreased, OVA IgE decreased, OVA and OVM IgG4 increased, OVA and OVM IgE/IgG4 ratio decreased	Ingestion of BE was well tolerated and associated with immune changes which are similar to those seen with development of tolerance to RE
Allen et al. [103] 261 children diagnosed with egg allergy, mean age 6.6 years old	Retrospective survey of dietary advice and dietary habit since egg allergy diagnosis Comparator: grouped by dietary advice Clinical Outcome: outgrew egg allergy	32% of children eating cooked egg versus 22% of children avoiding egg outgrew their egg allergy (not statistically significant)	Not reported	Strict avoidance of egg and accidental ingestion of egg did not appear to influence the acquisition of tolerance
Leonard et al. [82] 79 presumed or proven RE-allergic subjects recruited from Mount Sinai, median age 5.8 years old, all challenged to BE (56/79 BE-tolerant)	Follow-up study to Lemon-Mule et al. [45] Prospective, observational study Intervention: eat BE (containing 2.2 g egg protein) 1–3 servings a day followed up to 6 years (open) Comparators: to their baseline, to BE-reactive/RE-allergic and compared to a retrospective historical control of 47 non-phenotyped egg--allergic patients (median age 4.6) Clinical Outcome: For BE-tolerant: OFC q6 months to LCE and immune changes For BE-reactive: OFC to LCE q12 months	1 child developed atypical FPIES 36/56 (64%) baseline BE-tolerant became RE tolerant 14/23 (61%) baseline BE-reactive became BE-tolerant, 6/23 (26%) baseline BE-tolerant became RE-tolerant Comparison group: 13/47 tolerated RE, 6/47 tolerated BE after a median of 67.3 months	EW SPT EW OVA OVM sIgE OVA and OVM IgE/IgG4 all significantly decreased from baseline in subjects ingesting BE	Initiation of a BE diet accelerates the development of RE tolerance compared to strict avoidance
Tey et al. [104] 125 children with OFC-proven raw egg allergy, median age at OFC 5.1 years old	Retrospective cohort study Intervention: none Comparator: groups compared by egg ingestion (frequent, regular, or strict avoidance) Clinical Outcome: size of the EW SPT	Tolerance not assessed	Mean rate of decline in egg skin prick test size in all children was 0.7 mm/year (95% CI 0.5–1.0 mm/year). There was no difference between groups.	Rate of decline of SPT was unrelated to BE ingestion
Peters et al. [105] A subgroup of 117 RE-allergic infants from the HealthNuts study, BE-tolerant	A subgroup analysis of a prospective, observational study Intervention: none	6/117 were not eating BE, 29/117 eating BE 1–4×/month and 82/117 eating 5 or more times/month	Not reported	Frequent ingestion of BE (≥ 5×/month) was associated with RE tolerance acquisition, but not clear if

Table 4 (continued)

Population	Methodology	Clinical outcome	Immunological outcome	Conclusion
at 1 year by OFC or parental report	Comparator: ingestion of BE Clinical Outcome: RE-tolerant at 1 year by OFC or parental report			ingestion is accelerating tolerance or just a marker of better prognosis
Netting et al. [79] 43 BE-tolerant and presumed or proven RE-allergic children aged 1–5 years, median age 2 years old	Prospective, randomized, double-blind, placebo-controlled Intervention: 1.3 g BE protein ingestion 2–3 times a week for 6 months (blinded) Comparator: placebo baked product Clinical outcome: open OFC to pasteurized RE 1 month after stopping interventional diet and immune changes	35 had open OFC No difference between groups: 4/17 (23%) intervention passed and 6/18 (33%) placebo At RE OFC, 2/17 in the intervention group needed epinephrine and 1/18 in placebo	No differences between groups Both groups had significant reductions in median sIgE to WE, EW, OVA, or WE IgE/IgG4 ratio. No significant differences in Th1/Th2 cytokines or T cell phenotypes	Development of tolerance to raw egg was unrelated to ingestion of BE
BE in BE-reactive patients				
Saifi et al. [106] (abstract) 12 BE-allergic or OVM IgE > 50 kU/L	Prospective cohort Intervention: 125 mg BE with home updosing at 2 and 4 weeks and 3, 6, and 9 months (open) up to 3.8 g Comparator: baseline Clinical outcome: complete OIT, OFC at 12 months to 3.8 g BE	7/12 subjects completed therapy and 6/7 passed the OFC	EW SPT and IgE decreased	BE ingestion is possible for the most severely allergic
Dorman et al. [107] (abstract)	Prospective cohort Intervention: as in Saifi et al. [106] Comparator: baseline Clinical outcome: withdrawals, 24 months RE OFC	6/12 withdrew due to non-compliance 4/12 (33.3%) passed RE at 24 months at the time of publication, 2 awaiting challenge	Mean EW sIgE decreased from 38.0 to 17.6 ($p = 0.003$) Ovomucoid and ovalbumin sIgE and EW-SPT showed no change	BE OIT desensitizes severely egg-allergic children to RE
Bravin and Luyt [108] Fifteen children, median age 11, with persistent egg allergy as defined as a positive EW SPT and a reaction to an accidental exposure to BE in the last 6 months or a positive OFC to BE	Prospective cohort Intervention: BE (125 μg of egg protein) in a wheat biscuit increased daily at home over 60 days to a target of 6.25 g of egg protein Comparator: none Clinical Outcome: reach OIT target, open OFC to boiled egg.	4/15 children completed the OIT protocol within 60 days; 4/15 completed the OIT between 80 and 270 days. 5/15 could tolerate some BE and remained on a lower dose; 2/15 could not tolerate the initial dose and remained on an egg-free diet. All of the children who completed the BE OIT were able to eat whole boiled egg.	None reported	BE might have potential to be used as OIT

promoting tolerance to RE. Additionally, this study does not address whether there could be local immune changes in the GI tract.

The studies above are in BE-tolerant, RE-allergic children. Reported only in abstract form currently, there is a study of using BE OIT in BE-allergic individuals [106]. This open, observational study suggested that BE was well tolerated in BE allergy and may help to achieve BE-tolerance. They reported that 7/12 (58%) children who were BE-allergic by OFC or presumed BE-allergic by OVM > 50 kU_A/L were able to complete BE OIT and 6/7 passed an OFC to BE at 12 months. Additionally, Dorman et al. [107] further reported that after 24 months of BE OIT, four children passed a RE challenge and two more were awaiting challenge. Therefore, in the overall cohort 4/12 (33.3%) had passed RE at 24 months at the time of publication. Another study of BE OIT in BE-allergic children was recently published [108]. Fifteen children, median age 11, who had persistent egg allergy defined as a positive EW SPT and a reaction to an accidental exposure to BE in the last 6 months or a positive OFC to BE were recruited. They were given a dose of BE (125 μg of egg protein) in a wheat biscuit which was then increased daily at home over 60 days to a target maximum dose of 6.25 g of egg protein, at which point the subjects had an open OFC to boiled egg. They found that 4/15 children easily completed the OIT protocol within 60 days and another 4/15 completed the OIT between 80 and 270 days. Five out of 15 could tolerate some but not all doses of OIT, and 2/15 could not tolerate the initial dose and remained on an egg-free diet. All of the children who completed the BE OIT were able to eat whole cooked egg. RE-tolerance was not assessed, and there was no comparator group.

There is an ongoing CoFAR7 study (NCT01846208) on BE or RE OIT in children with egg allergy. In this study, children who are BE-tolerant and RE-allergic have been randomized to the ingestion of BE or OIT with commercially available egg white solid, and children who are BE-allergic have been allocated to OIT with EW solid. The primary outcome is sustained unresponsiveness as assessed by the ability to tolerate a 10-g egg OFC and open feeding of egg 8–10 weeks after OIT. The number of children who can achieve desensitization to 5 g or more of egg white solid at 1 and 2 years of treatment, side effects, and safety will also be evaluated. The study has completed recruitment and is ongoing with results expected in 2018.

It is possible that the observational results suggesting BE introduction is tolerogenic was reflective of the better prognosis of BE-tolerant individuals. OVM is the dominant heat-stable antigen in egg, and it has been established in multiple studies that the children who react to OVM are more likely to have persistent egg allergy. In Urisu et al. [109], 30 children underwent OFC to EW challenges and those who were reactive were challenged again at mean intervals of 32 months. They found that the children with high IgE binding to pepsin-treated OVM were the least likely to outgrow their allergy. Additionally, children with persistent egg allergy were found to have sIgE to sequential epitopes of OVM [110, 111].

A recent review highlighted the challenges of clinical studies of baked diet immunotherapy [98]. People who know they are tolerant to baked forms may not want to enter a study to continue to avoid the food. So far, the Netting et al. RCT [79] provides the highest level of evidence and it supports that BE does not have an effect on tolerance acquisition in young children. Additionally, currently there are no studies formally assessing whether SU will be achieved after avoidance for BE.

Prevention of Allergy to Milk and Egg with Baked Milk and Baked Egg Diets

The strict avoidance of milk in non-IgE conditions has been reported to be followed by new-onset milk allergy in some patients. The avoidance of milk due to atopic dermatitis and the subsequent development of IgE-mediated allergy were reported back in 1984 [112] and then in retrospective case series [113, 114]. These reports warned of the dangers of an elimination diet with respect to the development of IgE-mediated allergy. This concern was recently evaluated in a retrospective chart review of 298 children from 2002 to 2010 with atopic dermatitis suspected to be food-triggered [115]. It was reported that the risk of developing an IgE-mediated allergy in this population is 18.9% with a strict elimination diet and that most common foods to which the children became allergic were milk and egg.

The LEAP trial [116] has been transformative in the way we think about the relationship of foods to allergies. The introduction of peanut to the diets of infants at risk for peanut allergy (severe eczema and or egg allergy) markedly reduced the subsequent development of peanut allergy at 5 years of age (86.1% relative risk reduction in the group of infants with negative peanut SPT and 70% relative risk reduction in the infants with positive peanut SPT). Currently, it is not clear if the early introduction of LM is preventative toward milk allergy [117], as was recently reviewed. The early introduction of BM as prevention for milk allergy has not been formally studied.

For egg allergy prevention, the results of early introduction have recently been reviewed [117, 118] and an additional study has been published [119]. These trials differed in their patient populations and in the results of prevention. One notable issue, which arose from these early introduction egg trials, is that infants can already be allergic to raw egg at 4–6 months of age. Therefore, it is worth considering whether BE may be a safer and efficacious way to prevent egg allergy.

There is a retrospective analysis of the HealthNuts study in which Koplin et al. [120] categorized infants into age of introduction of egg and whether the egg was cooked (boiled,

scrambled, fried, or poached) or BE. The definition of egg allergy in this cohort was by OFC or parental-confirmed allergy at age 1 year. They reported that the infants who had been introduced cooked egg at 4–6 months had the lowest risk of egg allergy, and that this risk was significantly lower than the infants who had BE introduced at the same age.

There is one study evaluating a heated egg powder (Kewpie corporation, Japan), which is stated to be equivalent to a whole egg boiled for 15 min [121]. In this study, 100 infants aged 4–5 months with eczema were enrolled in a placebo-controlled RCT of 50 mg of heated whole egg powder (25 mg egg protein) from 6 to 9 months, with a medically supervised up-dose at 9 months to 250 mg a day. Then 250 mg/day continued until 12 months, with aggressive eczema control for all participants. The outcome was an open OFC to 7 g heated whole egg powder with a blinded assessor. They found that 43/47 passed OFC from the intervention group and only 29/47 passed OFC from the control group with a risk ratio of 0.222 (95% CI 0·081–0·607, $p = 0·0012$). The immune evaluation found that the ovomucoid sIgE was lower and IgG1, IgG4, and IgA were higher in the intervention group. The study was stopped early due to the high degree of allergy prevention in the intervention group. They concluded that a stepwise intervention of heated egg white powder, in the context of aggressive eczema control, was safe and efficacious to reduce egg allergy in infants.

Non-IgE-Mediated Allergy and Baked Milk and Baked Egg Diets

There is limited information about the tolerability or the therapeutic value of baked diets in the non-IgE-mediated allergies. It is generally assumed that in food-allergic disorders of mixed and cell-mediated pathophysiology, the reactivity is directed predominantly against sequential epitopes. Therefore, the expected rates of tolerance to baked proteins are lower than in IgE-mediated food allergy and the current standard of care for mixed and cell-mediated food-allergic disorders is that of strict dietary elimination of all forms of milk and egg. In eosinophilic esophagitis (EoE), strict milk avoidance is commonly recommended for its therapeutic effect [122, 123]. However, there are now multiple reports of strict milk avoidance for EoE followed by development of IgE-mediated allergic reactions [124–126]. It is known that some children with EoE can tolerate BM diets. Leung et al. [22] reported the endoscopy results of 15 children (age 6–17 years) with milk-implicated EoE who had ingested sufficient BM products for at least 6 weeks. Eleven patients had maintained disease remission, and four had disease recurrence as defined by histological criteria of > 10 eosinophils per high-powered field. It is not known if continuing BM in the diet could prevent the development of IgE-mediated allergy seen in some children with EoE on a milk-restricted diet.

A study of young children [23] with non-IgE-mediated cow's milk protein allergy (CMPA) as defined by the DRACMA guidelines [127] showed that of 16 children under 2 years old with challenge-proven non-IgE-mediated allergy to milk, 11 were able to tolerate fermented milk and all 16 could tolerate BM in the form of a muffin with 1.3 g of milk protein. This study suggested that milk avoidance may not need to be absolute in FPIES, although there are case reports of marked sensitivity and the current expert advice is for strict avoidance [128]. There is evidence that some individuals with FPIES to milk and other foods may develop IgE-mediated allergy [129]. It has not been studied if keeping BM in the diet would prevent this development of potentially anaphylactic allergy.

Conclusions

The BM and BE diets are mostly well tolerated in milk- and egg-allergic children and allow dietary restrictions to be relaxed. The methods of BM and BE diet introduction vary widely. Reactions can be very severe to baked milk and egg proteins, and medical supervision for OFC evaluating BM and BE tolerance is recommended. At this time, the evidence for BM and BE diets as a form of immunomodulation is derived from murine models and observational trials which support that children eating baked diets have faster resolution of their allergy and immune changes similar to outgrowing allergy and similar to those seen in OIT. The single-center 6-month RCT of a BE diet of two to three small serving sizes/week in BE-tolerant children did not support the observational findings. Another study of BE immunotherapy is expected to be completed in 2018. There is currently no evidence for prevention of allergy with the baked diets. There may be a future role for BM and BE in liberating the diets in a subset of individuals with non-IgE-mediated food allergy.

Compliance with Ethical Standards

Conflict of Interest Author JU has received research funding from SickKids Foundation and the Department of Pediatrics, Hospital for Sick Children, speaker honorarium from Food Allergy Canada, research support from DBV, Aimmune, and ALLEVIATE, and is the Anaphylaxis and Food Allergy Section Chair for the Canadian Society of Allergy and Clinical Immunology. Author ANW has received research funding from NIH NIAID, FARE, DBV, Nutricia, and Nestle. She serves as the DMC chair for the trial of sublingual dust mite immunotherapy for Merck, and she is a member of the Advisory Council for the Gerber Nutrition Institute and has received honoraria from Nestle, Nutricia, and Thermo Fisher Scientific. She serves as the vice chair of the Food Allergy, Dermatitis, Drug Allergy and Anaphylaxis Section of the American Academy of Allergy, Asthma and Immunology. She is the medical chair for the International FPIES Association.

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