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Jennifer R. Yonkof, MD, Irene J. Mikhail, MD, Benjamin T. Prince, MD, MSCI, David Stukus, MD



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Delayed and Severe Reactions to Baked Egg and Baked Milk Challenges

Jennifer R. Yonkof MD^{1,2}, Irene J. Mikhail MD¹, Benjamin T. Prince MD, MSCI¹, David Stukus MD¹

¹Nationwide Children's Hospital Department of Pediatrics, Division of Allergy and Immunology, Columbus, OH.

²The Ohio State University Wexner Medical Center, Division of Otolaryngology, Division of Allergy and Immunology, Columbus, OH.

Corresponding Author: Jennifer R. Yonkof MD, 567-585-0480

Contact Information Following Publication: Jennifer R. Yonkof MD

ProMedica Physicians Allergy and Immunology

4041 W. Sylvania Ave.

Suite 204

Toledo, OH 43623

Author Email Addresses:

Jennifer.Yonkof@promedica.org

Irene.Mikhail@nationwidechildrens.org

Benjamin.Prince@nationwidechildrens.org

David.Stukus@nationwidechildrens.org

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ABSTRACT

Background: While many egg and milk-allergic children tolerate baked egg (BE) and milk (BM), reactions elicited by these oral food challenges (OFCs) can be severe. Previous studies comparing BE and BM reactions to other OFC reactions are limited.

Objective: Compare the clinical features of reactions to BE and BM with other OFCs to promote challenge safety.

Methods: Retrospective review of OFCs eliciting objective reactions to BE, BM, lightly-cooked egg (CE), fresh cow's milk (CM), peanut (PN), and tree nuts (TN) performed at a tertiary-referral-center from 6/1/2017-6/1/2019.

Results: We identified 174 OFCs conducted in 158 subjects, age 6-187 months (34 BE, 19 BM, 14 CE, 25 CM, 52 PN, 30 TN). TN reactors were older than BE ($p=0.049$) and PN ($p<0.01$) reactors and had a higher frequency of persistent asthma than PN-reactive subjects ($p=0.02$). Mucocutaneous symptoms occurred less frequently during BE (56%) and BM (42%) OFCs compared to other OFCs ($p<0.05$). Lower respiratory reactions were increased during BM (37%) vs. BE, CM, and PN OFCs ($p<0.05$). Epinephrine was administered to more BE (44%) and TN (50%) than PN (17%) OFCs ($p<0.01$). New reaction manifestations developed ≥ 60 min. after OFC termination during 29% BE and 21% BM vs. 0% PN OFCs ($p<0.05$). One-third of anaphylactic reactions to BE began >60 min. after OFC termination.

Conclusions: BE and BM challenge reactions differed phenotypically from other OFC reactions, including significantly increased frequencies of new symptoms beginning ≥ 60 min. after challenge termination. Consider amended dose-escalation and prolonged observation after BE and BM OFCs.

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54 **HIGHLIGHTS BOX**

55 **What is known? (15 words)**

56 Some children react to baked egg (BE) and baked milk (BM) oral food challenges (OFCs).

57

58 **What does the article add? (33 words)**

59 Compared to other OFC reactions, BE and BM reactions were characterized by increased frequencies
60 of epinephrine administration and lower respiratory reactions, respectively, as well as delayed reactions
61 ≥ 60 min. after the challenge ended.

62

63 **How does the study impact current management? (12 words)**

64 Consider amended dose-escalation protocols and prolonged observation after BE and BM challenges.

65

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66 **KEY WORDS**

67 Food allergy

68 Egg allergy

69 Milk allergy

70 Oral food challenge

71 Anaphylaxis

72 Allergen tolerance

73

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74 **ABBREVIATIONS**

75 Baked egg: BE

76 Baked milk: BM

77 Lightly-cooked egg: CE

78 Fresh cow's milk: CM

79 Peanut: PN

80 Tree nut: TN

81 Oral food challenge: OFC

82

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Introduction

Hen's egg and cow's milk allergies are the most common food allergies in young children.^{1,2} Regular ingestion of extensively-heated egg or milk may accelerate acquisition of tolerance, and the expanded diet can improve quality of life.³⁻¹⁴ Consequently, baked egg (BE) and baked milk (BM) oral food challenges (OFCs) have become a routine part of managing egg and milk-allergic patients. While approximately 75% of patients tolerate BE and BM,³⁻¹⁴ reactions which do occur can be severe. Neither clinical history nor degree of sensitization have been found to predict the severity of an allergic response to these foods.³⁻¹⁴ Reported rates of anaphylaxis during BE and BM OFCs are highly variable, and previous studies have not directly compared the frequency of anaphylaxis during BE and BM OFCs to other food challenges. Furthermore, additional characteristics of reactions to BE and BM OFCs compared to other food allergens have not been extensively described.

We aimed to study the differences between clinical reactions to BE and BM OFCs compared to lightly-cooked egg (CE), fresh cow's milk (CM), peanut (PN), and tree nut (TN) OFCs. Based on observational evidence from our clinic supported by limited previous reports,¹⁵⁻¹⁷ we hypothesized that the clinical manifestations of reactions to BE and BM OFCs were more likely to be severe, and in some cases delayed, compared to those elicited by other OFCs. The data presented herein confirm these hypotheses and describe patterns of reactivity that may help clinicians to optimize safety when conducting OFCs.

Methods

We performed a retrospective review of OFCs eliciting objective reactions to BE, BM, CE, CM, PN, and TN performed at Nationwide Children's Hospital (Columbus, OH) from 6/1/2017-6/1/2019. Institutional Review Board approval was obtained. Eligibility for OFC was determined on a clinical basis by the subject's allergist and included sensitization without previous ingestion, or a past reaction with evidence of declining sensitivity. Anaphylaxis to the food being challenged within the past 12 months was a

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contraindication to OFC. OFCs involved open administration of up to five doses every 10-20 minutes and were typically stopped if patients demonstrated objective signs of an IgE-mediated food reaction. The duration of observation thereafter was individualized based on clinician preferences and patient history, but was ≥ 60 min. after one of the following: administration of the last medication used to treat a reaction, resolution of mild symptoms that were not treated, or the last dose when no reaction occurred.

BE and BM challenges were performed with muffins baked at 400°F for 20 minutes (the recipe is in Table E1 of this article's Online Repository at www.jaci-inpractice.org). The target dose was 1.1g egg or milk protein for children <2 years, and 2.2g for children ≥ 2 years. Target doses for other foods were standardized for our division's clinical practice and are in Table E2 of the Online Repository. The cumulative ingested dose was recorded as a percentage of the target dose to facilitate comparison between foods.

Data regarding sensitization, dose escalation, the character and timing of allergic reactions, and medication administration were recorded in a systematic fashion by the performing clinician using an electronic medical record template. All available documentation was further reviewed by the study team. The National Institute of Allergy and Infectious Disease definitions of anaphylaxis and hypotension were used.¹⁸ Hypoxemia was defined as $SpO_2 < 90$ percent.

Skin prick test (SPT) wheal diameter and specific IgE (sIgE) (ImmunoCAP®, Thermofisher, Uppsala, Sweden) levels to the challenge food were recorded if they were obtained within 12 months of the OFC. Children were characterized as having multiple food sensitizations if SPT or serologic testing was positive to ≥ 1 additional food. Given our interest in comparing TN to other OFCs, we grouped the TNs into a single category. However, most (27 of 30) TN-allergic subjects were sensitized to ≥ 2 TNs.

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We recorded descriptive statistics, including medians (interquartile ranges [IQR]) for non-parametric continuous variables and percentages for categorical variables. For continuous variables, six-way comparison of BE, BM, CE, CM, PN, and TN was performed using the Kruskal-Wallis test, followed by Dunn's post-hoc analysis to identify significant pairwise differences. For categorical variables, each of the 15 pairwise comparisons were made by Pearson's chi-squared test, and multiplicity-adjusted p values were subsequently calculated using the Holm-Sidak method. We also replicated a prior analysis examining the likelihood of gastrointestinal or lower respiratory involvement during BE and BM OFCs¹⁵ using Fisher's exact test. Unless specified, adjusted p values calculated during post-hoc analyses are presented. P values <0.05 were considered statistically-significant. Analyses were performed using GraphPad Prism 8 (GraphPad Software Inc., La Jolla, CA).

Results

We identified 174 OFCs performed in 158 subjects which elicited objective reactions (34 BE, 19 BM, 14 CE, 25 CM, 52 PN, 30 TN). Children reacting to TN were significantly older than children reacting to BE (p 0.049), CE (p 0.03), and PN (p<0.01) and had a higher frequency of persistent asthma than PN-reactive subjects (p 0.02). Gender and frequencies of eczema, intermittent asthma, allergic rhinoconjunctivitis, and history of anaphylaxis or any prior IgE-mediated clinical reaction to the challenge food were not significantly different between the groups. The proportion of subjects with multiple food sensitizations was significantly higher for BE compared to PN (p 0.03) and for BM compared to CE (p 0.03). Median SPT and sIgE values were not directly compared because positive predictive values (PPV) used for interpretation vary for each food (Table I).

Significant differences in the clinical manifestations of allergic reactions to individual foods were observed (Fig.1). Objective mucocutaneous reactions were significantly less frequent during BE compared to CM (p 0.02) and PN (p 0.01) OFCs, and during BM compared to CE (p 0.04), CM (p <0.01), PN (p <0.01), and TN (p 0.01) OFCs. Vomiting occurred more frequently during BE vs. BM (p

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0.02), CM ($p < 0.01$), PN ($p < 0.01$), and TN ($p = 0.04$) OFCs, and during CE vs. CM OFCs ($p = 0.03$).

Reactions to TN had a higher proportion of laryngeal and pharyngeal involvement vs. BE ($p = 0.02$) and PN ($p = 0.01$), while lower respiratory manifestations occurred more often during BM compared to BE ($p = 0.03$), CM ($p = 0.02$), and PN ($p = 0.02$) reactions (Fig.1), although the frequency of asthma was not significantly higher in BM reactors (Table I).

Compared to PN reactions, epinephrine was administered to a significantly higher proportion of TN (50.0%, $p < 0.01$) and BE (44.1%, $p < 0.01$) reactors (Fig.1). Anaphylactic reactions lacking mucocutaneous abnormalities were enriched during BE OFCs (17.6% BE vs. 5.2% BM, 0% CE, 4.0% CM, 5.8% PN, 3.3% TN), but the difference did not achieve statistical significance. Hypoxemia and hypotension were observed exclusively during BE and BM OFCs, occurring in two and three subjects, respectively. The frequency of subjects requiring ≥ 2 doses of epinephrine did not differ significantly between the groups (5.9% BE, 10.5% BM, 0% CE, 8.0% CM, 1.9% PN, 3.3% TN). ED transfer (5.9% BE, 4.0% CM, 1.9% PN, 3.3% TN), hospital floor admission (4.0% CM), and intensive care admission (2.9% BE) were not significantly different. There was no record of intubation, long-term morbidity, or death.

Objective reactions to BE OFCs were delayed (Fig.2) and occurred after consuming a higher percentage of the target dose (Fig.3) compared to PN OFCs. The median durations of time from ingestion of the first dose to the first objective sign of reactivity (i.e., to the eliciting dose [ED]) (Fig.2a), to the end of the OFC (Fig.2b), and to epinephrine administration (Fig.2c) were significantly longer for BE vs. PN ($p < 0.01$). The median time from ingestion of the ED to the development of the last new objective manifestation of reactivity was also significantly longer for BE (25 min.) compared to CM (0 min., $p < 0.01$), PN (0 min., $p = 0.01$), and TN (0 min., $p = 0.02$) OFCs (Fig.2d). Most challenges were stopped upon ingestion of the ED (Fig.2e). There was no significant difference in median time from ED ingestion to epinephrine between any foods ($p = 0.35$) (Fig.2f). The median ED (Fig.3a) and total

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cumulative dose ingested (Fig.3b) were higher for BE compared to PN (35% vs. 5%, $p<0.01$ and 35% vs. 15%, $p=0.04$, respectively).

Subsets of BE, BM, CE, and TN reactors experienced delayed allergic reactions ≥ 1 hour after the end of the challenge. The proportion of subjects developing any new objective sign of reactivity ≥ 60 min. after OFC termination was significantly higher for BE compared to CM (0.04) and PN ($p<0.01$), and for BM vs. PN ($p<0.01$) challenges (Fig.4). Non-anaphylactic delayed reactions included emesis ($n=3$ BE, $n=1$ BM), urticaria ($n=2$ BE, $n=1$ BM), and cough responsive to albuterol ($n=1$ BM, $n=1$ TN).

Anaphylaxis occurred ≥ 60 min. after challenge conclusion in 14.7% BE, 5.3% BM, 7.1% CE, and 6.7% TN OFCs (Fig.4), at median 80 min. (range 60-115 min.) after the challenge ended. There was a trend towards a significantly higher frequency of delayed anaphylaxis during BE vs. PN OFCs ($p=0.07$). All cases of delayed anaphylaxis to BE and CE were originally stopped for gastrointestinal symptoms that were not treated. One child with persistent asthma developed wheezing responsive to albuterol after ingesting 33% of the BM target dose, but 65 min. later presented with anaphylaxis (diffuse urticaria and wheezing) requiring two doses of epinephrine. There was one case of biphasic anaphylaxis to pistachio that occurred 64 min. after the initial reaction to 5% of the target, and both reactions resolved rapidly with epinephrine. Another child developed anaphylaxis 85 min. after consuming 100% of the cashew OFC without any prior symptoms. No reactions after discharge from clinic or inpatient settings were documented.

Discussion

In our cohort, significant differences in the clinical characteristics of OFC reactions emerged for individual foods. Nearly half of BE and BM reactions lacked mucocutaneous abnormalities, and lower respiratory manifestations were significantly increased among BM reactors (Fig.1). Significantly higher proportions of patients reacting to BE and BM developed new symptoms ≥ 60 min. after the end of the

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OFC (Fig.4). Furthermore, approximately half of reactions to BE and TN were treated with epinephrine (Fig.1). To the best of our knowledge, this is the first study to systematically compare the characteristics of reactions to these food challenges.

The lack of mucocutaneous involvement during BE and BM challenges that we observed (Fig.1) has been reported in other cohorts. Al Enezi et al. compared objective reactions elicited by 66 BE and 24 BM OFCs and found low rates of urticaria (26% BE, 33% BM) and angioedema (10% BE, 4% BM).¹⁵ This profile of reactivity contrasts anaphylaxis to other causes, in which 72-90% of cases display mucocutaneous abnormalities,¹⁹⁻²⁰ and the incidence we observed in our other food challenges. Given the absence of cutaneous reactivity may be a risk factor for fatal anaphylaxis due to delayed treatment with epinephrine,²¹⁻²² clinicians should remain particularly vigilant for extra-cutaneous signs of reactions to BE and BM.

BE reactions were characterized by a high proportion of emesis, while lower respiratory involvement was significantly increased among BM reactors (Fig.1). A retrospective review of 100 BE OFCs also found that isolated gastrointestinal symptoms were the most common manifestation of BE reactivity, accounting for 39% of reactions.⁸ Al Enezi et al.'s comparison of BE to BM challenges demonstrated that gastrointestinal symptoms occurred more frequently during BE challenges (39% vs. 4%, odds ratio [OR] 14.9 [95% C.I. 1.9-117.5]), while wheezing was more common during BM OFCs (29% vs. 3%, OR 13.1 [2.5-69.2]).¹⁵ When we directly compared BE and BM OFCs, the odds of emesis was significantly elevated for BE reactions (OR 4.8 [1.3-14.9], p 0.02), and the odds of lower respiratory involvement was higher for BM reactions (OR 4.4 [1.1-14.9], p 0.04), despite no significant difference in asthma frequency between these groups (Table I).

The heightened potential for BM to provoke lower respiratory reactions may represent an extension of previous reports describing milk as a leading cause of fatal food-induced anaphylaxis, with the majority

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of subjects suffering respiratory failure.^{23,24,25} Furthermore, one fatality during a BM OFC was reported in the US, although details about this tragic case have not been published.²⁶ Collectively, these studies illustrate the potential for severe respiratory reactions to both baked and fresh cow's milk and underscore the importance of controlling asthma before offering OFCs. Clinicians may also consider deferring challenges if patients report a recent respiratory infection.

We observed a high frequency of anaphylactic reactions to BE, with 44% of reactors receiving epinephrine (Fig.1). Other studies of BE OFCs have reported 6%¹⁴-28.5%⁷ of reactions were treated with epinephrine.⁵⁻¹⁴ Differences in practice style regarding patient selection for challenges and epinephrine utilization are a potential source of variability. Target dose variability seems a less likely factor, as one cohort targeting 3.7g egg protein reported a low incidence of anaphylaxis (6% reactions)¹⁴, while another using 1g egg protein found that 28.5% of BE reactions were treated with epinephrine.⁷ Similar to other cohorts, we did not identify significant differences in age, gender, frequency of atopic comorbidities including asthma, or history of anaphylaxis to egg (Table E3 in the Online Repository) between patients treated with or without epinephrine.^{4,5,14} While the median egg IgE was higher in patients who developed anaphylaxis compared to those who had milder reactions (16.40 kU/L vs. 10.40 kU/L, p 0.03), the applicability of this finding is unclear, as degree of sensitization by SPT or sIgE has not previously been shown to predict food reaction severity.⁴

Delayed recognition of anaphylactic reactions lacking cutaneous manifestations was postulated to contribute to the severity of BE OFC reactions. However, when our patients with or without mucocutaneous reactions to BE were compared, neither the odds of epinephrine administration (OR 1.5 [95% CI 0.4-5.3], p 0.73), median time to epinephrine (142 min; IQR 62 min. vs. 86.5 min; IQR 116 min., p 0.19), nor the median cumulative dose ingested (35%; IQR 57 min. vs. 35%; IQR 46 min., p 0.52) were significantly different. Another hypothesis is that BE antigens have intrinsic potential for heightened allergenicity in patients sensitized to heat-strengthened or neoepitopes created by the

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Maillard reaction. The ability of heat to enhance food allergen immunogenicity by glycation has been demonstrated in studies of BE, BM, roasted PN, and cooked shrimp.²⁷

TNs have also been identified as potent immunogens implicated in severe food-induced anaphylaxis,^{21,23,24,25,28} and our results demonstrating epinephrine administration to 50% of positive OFCs support these findings (Fig.1). Only 3 subjects had a history of anaphylaxis to TN. Notably the frequency of persistent asthma, which is an independent risk factor for severe reactions,^{21,28,29} was increased in TN vs. PN reactors, and may partially reflect the older age of patients challenged to TN. TN reactors showed increased symptoms of dysphagia, throat itching, and throat closing (Fig.1), which could be affected by concurrent tree pollen sensitization (observed in 4 of 7 subjects with pharyngeal symptoms). Incomplete ability to differentiate laryngeal from pharyngeal symptoms in a subset of patients is one limitation of this report. Small sample size restricts our ability to comment on variability in reactions to different TNs.

The high frequency of anaphylaxis to BE and TN accentuates the importance of clinical preparedness to treat potentially-severe anaphylaxis. Three subjects (9%) who reacted to BE developed hypotension or hypoxemia requiring transfer for escalated care, so clinicians may consider performing these challenges at sites where emergency services can be easily accessed. The British Society of Allergy and Clinical Immunology guidelines offer the possibility of home BE introduction for children with mild egg allergy who have not reacted in the past 6 months and have no history of asthma.²⁹ In our cohort, 9 of 20 (45%) subjects eligible for home introduction by this definition were treated with epinephrine. Therefore, clinicians may consider in-office challenges even in such patients lacking obvious risk factors for severe reactions.

The potential for delayed reactions to BE and BM distinguished them from other OFC reactions (Fig.2, Fig.4). The delayed kinetics of BE relative to PN reactions when measuring time from ingestion of the

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first dose (Fig.2a-c) likely relates to the higher ED of BE (Fig.3a), as time from ED ingestion to OFC termination (Fig.2e) and epinephrine (Fig.2f) were not significantly different. Nearly 30% of BE and 20% of BM reactors developed new allergic manifestations ≥ 60 min. after the end of the OFC (Fig.4), and one-third of anaphylactic reactions to BE developed ≥ 60 min. after the end of the challenge. Delayed reactions to BE beginning up to 2 hours after asymptomatic ingestion of 100% of the target dose accounted for 16% of positive challenges in another cohort.⁸ One potential explanation is that the complex interactions between proteins, lipids, and carbohydrates rendered during baking modulate digestibility in a manner which delays immune exposure to specific allergenic epitopes.³⁰⁻³² Heating delays *in vitro* intestinal epithelial cell transport of ovalbumin and ovomucoid in forms capable of activating T-cells and basophils,³² which may explain the high frequency of delayed gastrointestinal symptoms to BE (Fig.1) and the increased median ED relative to PN (Fig.3a).

A Work Group report of the Adverse Reactions to Food Committee of the American Academy of Allergy, Asthma & Immunology (AAAAI) advises clinicians to individualize the duration of observation after OFC reactions, but states that discharge 1-2 hours after resolution of IgE-mediated symptoms is commonly practiced.³³ The latest reaction reported in our cohort occurred approximately 3 hours after the end of the challenge. Our findings advocate for consideration of prolonged monitoring after BE and BM OFCs and emphasize the importance of anticipatory guidance and epinephrine availability for reactions which could occur after discharge.

Clinicians should also consider extending the observation time between doses, particularly after one-quarter to one-third of the target dose has been ingested, given the median BE and BM EDs were 35% of the target dose (Fig.3a). Increasing the number of doses may further promote identification of mild reactions: for example, a six-dose series of 5%, 10%, 13%, 17%, 25%, and 30% of the target dose could be used. This differs from the six-dose schedule described in the AAAAI Work Group Report³³ by slowing the progression between 15% and 45% of the target dose, when the majority (55%) of our BE

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and BM-allergic patients first reacted. Table E4 of the Online Repository provides additional dose schedule information.

Limitations of this report include small sample sizes, selection bias in determining OFC candidates, and lack of blinding. Our study was not powered to detect significant differences between the experimental groups. We included children with known allergies to the foods being challenged (i.e., a history of clinical reactivity and demonstration of sensitization), and a relatively-high proportion of children with food sensitization of unclear clinical significance at the time of OFC (Table I). Because many children have not ingested BE or BM at the time of egg or milk allergy diagnosis, using a recent clinical reaction as an OFC exclusion criterion may impact baked products to a lesser degree than other foods. However, there was no significant difference between the proportions of patients with a previous IgE-mediated clinical reaction to any of the challenge foods (Table I). Our institution offers a robust early peanut introduction clinic for peanut-sensitive infants, which accounts in part for the younger age of our PN-allergic patients. While this contributes to cohort heterogeneity, our study design excluded subjects with asymptomatic sensitization. Furthermore, previous studies of BE and BM challenge outcomes have defined egg or milk allergies as either history of an IgE-mediated reaction or sensitization exceeding the 95% PPV,⁵⁻¹⁴ and our additional experimental groups are therefore matched in this regard.

We had limited ability to study a sufficient number of children who reacted to both the extensively-heated and frank versions of egg and milk to better control for individual confounding factors. In Norwak-Wegrzyn's landmark prospective trial, subjects were successively challenged to BM and if they were tolerant, to unheated milk.⁴ Congruent with our data, reactions to BM were more severe than reactions to unheated milk: 35% of BM reactions were treated with epinephrine, while no CM reactions required epinephrine.⁴ Longitudinal observation of this cohort suggested that the propensity toward severe allergic responses in BM reactors may be preserved over time: >6 months after the initial OFC,

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epinephrine was administered during CM challenges at a higher rate to BM-reactive than to BM-tolerant subjects (17% vs. 3%, p 0.04).³⁴ Another retrospective study found that BE tolerance was associated with milder reactions to CE, but that this phenomenon was not observed in children with milk allergy.¹⁶ Future studies aimed at analyzing OFC reactions to multiple foods within the same individual would mitigate confounding factors and generate additional hypotheses regarding mechanisms of phenotypic variability during IgE-mediated food reactions. Our study also highlights the need for biomarkers which can predict reaction severity in food-allergic patients.

In summary, we identified distinguishing characteristics of reactions to BE and BM OFCs, including significantly increased frequencies of anaphylaxis to BE (Fig.1), lower respiratory reactions to BM (Fig.1), and new reaction manifestations developing ≥ 60 min. after the end of the OFC to both foods (Fig.4). These challenges are an important component of treating patients with egg and milk allergies, not only to potentially modify the immunopathology, but to improve quality of life regardless of challenge outcome.³ Emergency preparedness is essential. Clinicians may consider amended dose-escalation schedules and prolonged observation after BE and BM OFCs to promote safety.

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Figure Legends

Fig.1) Objective clinical manifestations of allergic reactions to OFCs. Urticaria, angioedema, rash, flushing, and conjunctivitis were characterized as objective mucocutaneous findings. Dysphonia, stridor, and dysphagia were considered laryngeal and pharyngeal reactions, respectively. Lower respiratory symptoms included wheezing, coarse breath sounds, and decreased air exchange.

* $p < 0.05$

Fig.2) Time from: ingestion of the first dose to the first objective sign of reactivity (the eliciting dose [ED]) (A); first dose to OFC termination (B); first dose to epinephrine administration (C); ED ingestion to the last new symptom of reactivity (D); ED to OFC termination (E); ED to epinephrine administration (F). Medians and interquartile ranges are shown.

* $p \leq 0.01$, ** $p = 0.04$

Fig.3) Eliciting (A) and total (B) doses ingested during oral food challenges (OFCs). Eliciting dose was defined as the cumulative percentage of the target dose ingested before the first objective manifestation of an allergic reaction developed. Medians and interquartile ranges are shown.

* $p < 0.01$, ** $p < 0.05$

Fig.4) Proportion of patients developing any new symptom of an allergic reaction (A) or anaphylaxis (B) ≥ 60 min. after the end of the oral food challenge (OFC).

* $p \leq 0.01$, ** $p < 0.05$

Table I. Demographics

	BE N=34	BM N=19	CE N=14	CM N=25	PN N=52	TN N=30	P Value
Median age in months (IQR)	23 (14-55)	37 (15-55)	34 (13-71)	31 (9-187)	11 (6-37)	53 (28-88)	<0.05*
Male	24 (71%)	13 (68%)	7 (50%)	20 (80%)	31 (60%)	16 (53%)	NS
Atopic dermatitis	25 (74%)	16 (84%)	7 (50%)	15 (60%)	41 (79%)	19 (63%)	NS
Intermittent asthma	6 (18%)	5 (26%)	1 (7%)	9 (36%)	5 (10%)	5 (17%)	NS
Persistent asthma	8 (24%)	3 (16%)	4 (29%)	3 (12%)	3 (6%)	10 (33%)	0.02**
Allergic rhinoconjunctivitis	14 (41%)	10 (53%)	2 (14%)	5 (20%)	10 (19%)	10 (33%)	NS
Multiple food sensitizations	27 (79%)	15 (79%)	5 (36%)	19 (76%)	24 (46%)	15 (50%)	0.03 [†]
History of anaphylaxis to the challenge food	5 (15%)	2 (11%)	3 (21%)	2 (8%)	5 (10%)	3 (10%)	NS
History of any IgE-mediated clinical reaction to the challenge food	13 (38%)	9 (47%)	7 (50%)	17 (68%)	19 (37%)	15 (50%)	NS
Median SPT wheal diameter in mm (IQR)	6 (6-15)	11 (6-15)	5 (3-6)	4.5 (0-10)	5 (4-8)	7 (2-12)	-
Median sIgE in kU/L (IQR)	14.20 (7.88-25.75)	28.65 (11.63-100)	1.36 (1.25-2.50)	17.30 (0.38-26.63)	2.60 (1.37-3.75)	3.67 (0.63-4.00)	-

IQR: interquartile range. *SPT*: skin prick test. *sIgE*: specific IgE. *BE*: baked egg. *BM*: baked milk. *CE*: lightly-cooked egg. *CM*: fresh cow's milk. *PN*: peanut. *TN*: tree nut. *NS*: not significant for any pairwise comparisons. Median SPT and sIgE values were not directly compared because positive predictive values used for interpretation vary for each food.

*Significant pairwise differences between BE and PN (p 0.049), CE and PN (p 0.03), and TN and PN (p<0.01)

**Significant pairwise difference between PN and TN

[†]Significant pairwise difference between BE and PN, as well as BM and CE







