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Clinical Communications

Safety and allergic reaction profiles of children undergoing baked milk and egg challenges: a 6-year experience from a pediatric tertiary referral center

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Clinical Implications

- Significantly different allergic reaction profiles may accompany positive baked milk and egg challenges, with baked milk potentially inducing respiratory symptoms and more severe anaphylactic reactions and baked egg resulting in gastrointestinal symptoms and less severe anaphylactic reactions.

TO THE EDITOR:

Both milk and egg allergy are common in childhood, and their prevalence is increasing. A recent Australian study reported an 8.9% prevalence of challenge-proven egg allergy,¹ whereas a rate of 1.9% to 3% has been reported for milk allergy.² Studies suggest that up to 70% of milk- and egg-allergic children can tolerate baked milk and egg, respectively.³ This allows for a more liberated diet, nutritional benefits, less social restrictions, and, ultimately, better quality of life. Regular ingestion of baked milk/egg may be associated with a faster development of tolerance to fresh milk/raw egg.⁴ There are currently no universally accepted cutoffs for the skin prick test (SPT) or specific IgE that may predict which children can tolerate the baked form of milk or egg. Therefore, a baked milk/egg challenge remains the gold standard diagnostic tool for baked milk/egg tolerance. Concerns have been raised previously regarding the safety of baked milk and egg challenges, and episodes of anaphylaxis have been reported during these in various studies.^{5,6}

We investigated the symptoms and severity of allergic reactions occurring during positive, open, baked milk/egg challenges over a 6-year period in a tertiary center in the United Kingdom. We also compared differences between the groups (baked milk challenge group vs baked egg challenge group).

We included all pediatric patients who experienced a positive baked milk/egg challenge between 2010 and 2016. All data were collected prospectively. Patients were referred for a baked challenge, after consultation with an allergist, based on their clinical history and family preferences. Children with a recent reaction (last 12 months) to baked milk/egg were not offered a baked challenge. There was no cutoff SPT level that would dictate who should be referred for a baked challenge; the decision was made by the consulting physician.

All challenges were performed in a dedicated area within our hospital (day unit), by a trained nurse or physician. The parents prepared the challenge material (cupcakes) at home, based on the recipe provided by the dietitians. Each cupcake contained the equivalent of 1.3 g of milk protein or 1.875 g of egg protein. Five

incremental doses of cupcake were administered every 15 to 20 minutes until a full serving size was ingested (2 cupcakes). The challenges were discontinued once objective symptoms of an allergic reaction occurred. After a positive challenge, the parents were provided with advice to avoid all forms of milk or egg in their child's diet. Training in recognizing allergic reactions, including anaphylaxis and use of epinephrine autoinjectors, was also provided. Anaphylaxis was defined in accordance with the NIAID criteria.

During the above 6-year period, a total of 90 children experienced a positive reaction during their baked challenge, 24 while undergoing a baked milk challenge and 66 a baked egg challenge. The demographics and clinical characteristics of our patient groups are shown in Table I. (We have also included the same information on our negative challenge cohort, for comparison.) There was no difference in age, sex, other food allergy, or history of asthma/rhinitis between the 2 groups. A history of eczema was more common in the baked milk group.

The time to onset of allergic symptoms was between 15 and 60 minutes for the majority of children; 1 delayed reaction was reported. When comparing symptoms of allergic reactions between the groups (Table II), the most common symptom experienced by both groups was urticaria. Interestingly, there was a significant difference between the percentages of children experiencing respiratory versus gastrointestinal symptoms depending on the food allergen. Specifically, 29% of children in the baked milk group experienced cough (odds ratio [OR] 5 [1.4-17.8]) and 29% experienced wheeze (OR 13.1 [2.5-69.2]), compared with only 8% and 3%, respectively, for the baked egg group. Gastrointestinal symptoms were observed much more often in the baked egg group, with 39% experiencing abdominal pain (OR 14.9 [1.9-117.5]) and 23% vomiting (OR 6.7 [0.8-54.3]) as part of their allergic reaction, compared with only 4% and 4%, respectively, in the baked milk group. In terms of severity, the rate of anaphylaxis treated with epinephrine was similar in both groups; 8% (baked milk) versus 6% (baked egg), but both children in the baked milk group required 2 doses of epinephrine to be administered, whereas none of the 4 children who experienced anaphylaxis in the baked egg group required a second epinephrine dose. There was a significant difference in bronchodilators use, with over a third of children in the baked milk group receiving this, compared with only 4% in the baked egg group. This is consistent with the increased incidence of respiratory symptoms in the baked milk group. Most episodes of wheeze responded promptly to bronchodilators (used as first line treatment for mild, transient, or isolated wheeze). Of note, 1 child in the baked milk and 2 in the baked egg group experienced isolated wheeze. Overall, there was no difference in the number of children with a history of asthma between the groups. All children underwent an asthma assessment before the challenge, to ensure good asthma control. Specifically, for those who experienced anaphylaxis, none in the baked milk group and only 1 of the 4 in the baked egg group had a history of asthma. Two previous studies have reported higher incidence of gastrointestinal symptoms in baked and non-baked egg challenges,^{7,8} whereas a study from Japan reported that non-baked egg challenges were associated with a reduced risk of severe reactions compared with other food, in a high-risk patient population.⁹

TABLE I. Demographics and characteristics of children with positive and negative baked milk and egg challenges

Food challenge	Positive baked milk (n = 24)	Positive baked egg (n = 66)	P value	Negative baked milk (n = 35)	Negative baked egg (n = 64)	P value
Age, y						
Median (range)	5 (1-17)	6 (1-17)	0.6	3 (1-9)	4 (1-17)	.56
IQR (range)	5 (2-7)	7 (2-9)		3 (2-5)	6 (2-8)	
Male subjects, n (%)	11 (46%)	33 (50%)	0.73	17 (44%)	40 (63%)	.2
SPT extract milk/egg, mm						
Median (range)	3 (0-15)	5 (0-15)	N/A	1 (0-8)	4.4 (0-12)	N/A
IQR (range)	3 (2-5)	4 (4-8)		3 (0-3)	2 (3-5)	
SPT fresh milk/raw egg, mm						
Median (range)	6 (2-20)	10.5 (3-23)	N/A	7 (1-19)	7 (3-18)	N/A
IQR (range)	4 (5-9)	8 (7-15)		5 (5-10)	6 (4-10)	
Other food allergy, n (%)	22 (92%)	58 (88%)	0.59	30 (86%)	54 (84%)	1
History of asthma/wheeze, n (%)	12 (50%)	25 (38%)	0.3	8 (23%)	11 (17%)	.59
History of rhinitis, n (%)	4 (17%)	12 (18%)	0.91	2 (6%)	9 (14%)	.31
History of eczema, n (%)	19 (79%)	33 (50%)	0.01	27 (77%)	31 (48%)	.0061

IQR, Interquartile range; N/A, not applicable; SPT, skin prick test.

P values were calculated by using the Mann-Whitney U test for comparison of medians between nonparametric groups and the Fisher exact test for categorical data.

TABLE II. Food challenge observations including time to onset of symptoms, percentage of amount ingested before symptom occurrence, recorded symptoms (by organ system), and treatment administered

Food challenge	Baked milk (n = 24) n (%)	Baked egg (n = 66) n (%)	P value
Time to onset of symptoms			
Immediate—up to 15 min	7 (29%)	11 (17%)	.21
>15 min up to 1 h	10 (42%)	31 (47%)	.67
>1 h up to 2 h	4 (17%)	13 (20%)	.75
>2 h	0 (0%)	1 (1.5%)	.54
Not recorded	3 (12%)	10 (15%)	.71
Percentage of total dose (2 cupcakes) ingested before symptom occurrence	26.4 (6-100)	30 (5-100)	.74
Symptoms during challenges			
Skin	17 (71%)	46 (70%)	
Urticaria	8 (33%)	17 (26%)	.5
Pruritus	6 (25%)	11 (17%)	.39
Erythema	2 (8%)	11 (17%)	.28
Angioedema	1 (4%)	7 (10%)	.36
Respiratory	23 (96%)	17 (26%)	
Sneezing	4 (17%)	5 (8%)	.21
Cough	7 (29%)	5 (8%)	.01
Rhinitis	4 (17%)	4 (6%)	.1
Wheeze	7 (29%)	2 (3%)	.0003
Shortness of breath/chest tightness	1 (4%)	1 (1.5%)	.47
Gastrointestinal	11 (46%)	65 (98%)	
Abdominal pain	1 (4%)	26 (39%)	.001
Vomiting	1 (4%)	15 (23%)	.03
Nausea	2 (8%)	12 (18%)	.24
Oral itching/sore throat	7 (29%)	11 (17%)	.21
Diarrhea	0 (0%)	1 (1.5%)	.54
Behavioral change	3 (12%)	9 (14%)	.8
Anaphylaxis	2 (8%)	4 (6%)	.73
Medications administered			
Antihistamines	23 (95%)	60 (90%)	.45
Bronchodilators	8 (33%)	3 (4%)	.0002
Steroids	3 (12%)	3 (4%)	.16
Adrenaline	3 (12%)	4 (6%)	.34

P values were calculated by using the Fisher exact test for categorical data.

In summary, we observed a significant difference in allergic reaction profiles between children undergoing baked milk versus baked egg challenges, with respiratory symptoms dominating the first group and gastrointestinal symptoms observed more commonly in the second. In addition, children who experienced anaphylaxis in our cohort required more than 1 dose of epinephrine for the treatment of their reaction in the baked milk group, compared with only 1 dose in the baked egg group. These differences may indicate that positive baked milk and egg challenges result in very different allergic reaction profiles, with baked milk potentially inducing respiratory symptoms and more severe anaphylactic reactions and baked egg resulting in gastrointestinal symptoms and less severe anaphylactic reactions. These findings will require validation in much larger populations and future research studies.

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