Published in final edited form as:

Ann Allergy Asthma Immunol. 2012 November ; 109(5): 309–313.e1. doi:10.1016/j.anai.2012.07.026.

Predicting Food Challenge Outcomes for Baked Milk: Role of Specific IgE and Skin Prick Testing

Lisa M. Bartnikas, MD^{1,2}, William J. Sheehan, MD^{1,2}, Elaine B. Hoffman, PhD³, Perdita Permaul, MD^{2,4}, Anahita F. Dioun, MD^{1,2}, James Friedlander, MD^{1,2}, Sachin N. Baxi, MD^{1,2}, Lynda C. Schneider, MD^{1,2}, and Wanda Phipatanakul, MD, MS^{1,2}

¹Boston Children's Hospital, Boston, MA, USA

²Harvard Medical School, Boston, MA, USA

³Harvard School of Public Health, Department of Biostatistics, Boston, MA, USA

⁴Massachusetts General Hospital, Division of Pediatric Pulmonary, Allergy, and Immunology, Boston, MA, USA

Introduction

Cow's milk allergy is the most common childhood food allergy, affecting 2–3% of children.^{1, 2} Although most children will develop tolerance to cow's milk, recent studies demonstrate that children are outgrowing their cow's milk allergy at a later age than previously reported.^{2, 3} With food allergies on the rise⁴ and children outgrowing cow's milk allergies later in life,^{2, 3} there is a growing population of patients avoiding cow's milk. Recent evidence suggests that 70–80% of children with IgE-mediated cow's milk allergy will tolerate baked milk products.⁵ Furthermore, children with milk allergy who tolerate baked milk products may outgrow their milk allergies faster than those who cannot tolerate baked milk,¹ possibly via the induction of milk-specific regulatory T cells.⁶

Cow's milk proteins can be divided into two broad groups based on their solubility at pH 4.6: whey and casein.⁷ Whey proteins, which account for 20% of the total milk protein, include α -lactalbumin and β -lactoglobulin. Caseins, which consist of α_{S1} -, α_{S2} -, β -, and κ -caseins, comprise the remaining 80% of milk proteins. Caseins and α -lactalbumin are more heat stable than β -lactoglobulin.⁸ Exposing milk proteins to high temperatures through baking reduces allergenicity by destroying the conformational epitopes.^{9, 10} Analysis of serum samples of children with persistent cow's milk allergy demonstrates significantly higher ratio of sIgE to linear versus conformational epitopes compared to children who have achieved tolerance.¹¹ In addition to heating, milk protein allergenicity may also be decreased through interaction with other food proteins in a complex food, such as in a wheat matrix in a baked muffin or cupcake.¹²

Strict avoidance of cow's milk results in significant stress for patients and families.¹³ Identifying milk allergic children who might tolerate baked milk products would not only increase dietary choices and potential for maintaining adequate nutrition and decrease stress, but may also hasten resolution of milk allergy.¹ Few studies have evaluated predictive factors for passing food challenges to baked milk. In this study, we sought to determine whether SPT wheal size and/or serum sIgE levels to milk proteins could be used to predict successfully passing a baked milk challenge.

Methods

Study Design

A retrospective chart review was performed of all patients who underwent oral challenges to baked milk at Boston Children's Hospital from September 2009 through September 2011. All subjects had a history of prior allergic reactions to milk (either baked or unheated) documented in the medical record by an allergist and detectable milk protein sIgE, as determined by a positive SPT or elevated serum sIgE. The study was approved by the Institutional Review Board of Boston Children's Hospital.

Allergy Evaluation

SPT were performed according to previously published methods¹⁴ using the Multi-Test II device (Alk-Abello, Round Rock, TX) and commercially prepared extracts (Greer Laboratories, Lenoir, NC). Control tests for SPT were performed with histamine (positive control) and normal saline (negative control). Wheal diameters were measured 15 minutes after the skin test was placed, in a standard fashion.¹⁴ A SPT wheal diameter at least 3 mm larger than the negative control was considered positive.¹⁵

All children had SPT to milk and 34 (97.1%) had SPT to casein documented in the medical record prior to oral food challenge (median time prior to challenge 3.0 months, range 0.82–32.0 months). All children had serum sIgE testing to milk and 33 (94.3%) also had sIgE to casein, α -lactalbumin, and/or β -lactoglobulin performed prior to oral food challenge (median time prior to challenge 3.1 months, range 1.15–34.6 months). All subjects had either SPT or sIgE obtained within 1 year of the food challenge, and 29 (83%) had both performed within 1 year of the food challenge. Serum samples were analyzed for sIgE using an ImmunoCAP fluorescence enzyme immunoassay (Phadia AB, Portage, MI). The lowest limit of detection of the assay was 0.35 kU/L. For analysis, we evaluated the most recent SPT and sIgE testing documented prior to the food challenge.

Oral Challenge

Baked milk challenges were performed as open challenges under physician supervision at Boston Children's Hospital, in a standard fashion based on previously published methods.⁸ Parents were instructed to prepare muffins or cupcakes at home according to a specific protocol that our clinic provided. Each muffin or cupcake contained 1.3 grams of milk protein from non-fat dry milk powder. The muffins or cupcakes were baked at 350°F in an oven for 30 minutes. A standard graded open food challenge consisted of increasing increments every 15 minutes of 1/4 (325 mg), 1/2 (650 mg), and 1 1/4 (1,625 mg) muffin or cupcake, totaling 2.6 grams of milk protein. Subjects were monitored throughout and for 30–60 minutes after the completion of the challenge. Challenges were discontinued at the first objective sign of reaction,¹⁵ and treatment was initiated at the discretion of the supervising physician.

Statistical Analysis

Median values were calculated for subject ages at the time of oral challenge, as well as for milk protein sIgE and SPT wheal sizes. Prevalence rates of baseline characteristics were calculated, and differences were compared between those who passed or failed baked milk challenges. The Wilcoxon rank sum test was used to compare baseline characteristics between individuals who passed or failed baked milk challenges including age, serum sIgE, and SPT wheal sizes. Dichotomous variables were analyzed using the Fisher's exact test. A *P* value <0.05 was considered statistically significant.

Oral food challenge outcome was used as the gold standard by which performance characteristics (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) were calculated. The PPV refers to a level above which it is a given percentage likely that a patient will react and therefore have a failed food challenge outcome. The NPV refers to a level below which it is a given percentage likely that a patient will not react and therefore have a passed food challenge outcome.¹⁶ Receiver operator characteristic (ROC) curve analysis was used to determine a threshold that would differentiate subjects who were allergic or tolerant to baked milk. The relationship between SPT or sIgE and food challenge outcome was analyzed using logistic regression. Fitted predicted probability curves were plotted using results from the logistic regression.

Results

Study Population

Thirty-five children (median age 8.1 years, range 3.1–18.1 years) underwent food challenges to baked milk (Table 1). Twenty-nine children (83%) passed a baked milk challenge and six children (17%) failed. This pass rate is consistent with what is reported in the literature.^{5, 8} Compared to those who passed, children who failed the baked milk challenges were younger (median 8.9 years and 3.7 years, respectively; $P = 0.02$). Gender was not a factor in passing a baked milk challenge. Atopic conditions including diagnoses of asthma, allergic rhinoconjunctivitis, and other food allergies were not associated with higher risk of failing a baked milk challenge. Children with atopic dermatitis were more likely to fail a baked milk challenge, although this finding did not reach statistical significance ($P = 0.06$). Symptoms at first reported milk reaction did not differ among the groups (Table 2).

Oral Food Challenge Failures

Children failed baked milk challenges for a variety of reasons, as described in Table 3. No child who failed the challenge in our clinic developed anaphylaxis or required epinephrine. Subjects 1–3 reacted to 2.6 grams, 325 mg, and 1.7 grams of milk protein, respectively. Interestingly, 50% ($N = 3$) of the children who reacted to baked milk (Subjects 4–6) passed the initial physician-supervised challenge but reacted to ongoing baked milk ingestion at home. One child who reacted at home required epinephrine (Subject 4). None of the children who failed at home returned to our clinic to undergo repeat baked milk challenges. The clinical courses of the subjects with delayed reactions are subsequently described. Since these reactions occurred at home, details regarding amount of milk protein ingested, degree of baking, and frequency of baked milk consumption are limited.

Ten months after passing the initial clinic challenge, Subject 4 reacted to cake containing yogurt baked at 350°F for 30–35 minutes. Subject 4 immediately developed anaphylaxis with hives, lip swelling, and vomiting, and was treated with epinephrine.

Subject 5 complained of oral pruritus during the clinic challenge with a baked milk cupcake but the symptoms resolved and the subject ultimately passed the challenge. Several days later, Subject 5 refused to eat a baked milk cupcake made from the same recipe. However, while consuming a brownie containing baked milk, the subject again complained oral pruritus.

Subject 6 passed the initial clinic challenge to a baked milk muffin and continued consuming baked milk daily at home. However, three weeks later, Subject 6 was given a muffin made from the same recipe but instead of plain muffin mix it was made with the same brand's blueberry muffin mix. The subject did not have a documented blueberry allergy, and had consumed blueberry multiple times previously without reactions. While eating the muffin, this subject developed immediate hives.

Predictive Value of Allergy Testing for the Outcome of Baked Milk Challenge

There was no significant difference in milk protein skin or blood test results among the groups who passed or failed baked milk challenges (Table 4). All subjects had either SPT or sIgE obtained within 1 year of the food challenge, and the majority within 3 months of the food challenge.

Casein SPT had 66.7% sensitivity, 85.7% specificity, and 92.3% NPV using a cutoff of 9 mm. In other words, if a patient has a casein SPT <9 mm, it is 92.3% likely that the patient will not react and will pass a baked milk challenge. No child with a casein wheal >15 mm passed the food challenge (Table 4 and Supplemental Figure 1 A, B). Milk SPT had 66.7% sensitivity, 72.4% specificity, and 91.3% NPV using a cutoff of 13 mm (Figure 1). A >90% NPV was also achieved for milk SPT using a cutoff of 17 mm; however, at that level sensitivity decreased and PPV increased to 75%. Notably, all subjects with milk SPT wheal <7 mm passed the challenge. No child with casein SPT >15 mm, casein sIgE >10.3 kU/L, or milk sIgE > 20.6 kU/L passed the challenge. ROC curve analysis for casein and milk SPT revealed an area under the curve (AUC) of 0.64 and 0.70, respectively.

Sensitivity, specificity, and PPV, for α -lactoalbumin and β -lactoglobulin were poor. A >90% NPV was established for α -lactoalbumin using a cutoff of 0.35 kU/L. A β -lactoglobulin sIgE 0.35 kU/L had an 84.2% NPV and a >90% NPV could not be established. Casein sIgE had poor sensitivity and specificity in predicting oral food challenge outcomes and a >90% NPV was established using a cutoff of 0.9 kU/L (Supplemental figure 1 C, D). Milk sIgE also had poor sensitivity and specificity, and a >90% NPV was established using a cutoff of 1.0 kU/L (Supplemental figure 1 E, F). ROC curve analysis for casein and milk sIgE revealed an AUC of 0.56 and 0.60, respectively.

Discussion

Cow's milk allergy is the most common food allergy among children.¹ However, 70–80% of children with cow's milk allergy may tolerate milk in well-baked goods, and these children may outgrow their milk allergies faster than those excluding milk completely.⁵ For these reasons, it is critically important to identify milk allergic children who may be able to consume baked milk products. To date, reliable markers for selecting subjects for baked milk challenge have not been clearly established. Therefore, oral food challenge to baked milk remains the gold standard. The aim of this study was to determine whether milk protein sIgE levels or SPT wheal sizes were predictors of passing a baked milk challenge. We addressed this question by examining these parameters in a retrospective review of patients who underwent baked milk challenges in our allergy clinics. Our study is one of the largest evaluating baked milk challenges. Furthermore, this study reports on the largest number of milk proteins and is the first study evaluating the relationship of casein SPT and α -lactoalbumin sIgE, the heat stable milk proteins,⁸ with baked milk challenge outcome.

We found that 83% of milk allergic children in our study population passed baked milk food challenges, which is consistent with the rate reported in the literature.⁸ Younger children were more likely to fail a baked milk challenge, and this may be reflective of the natural history of baked milk allergy.²

We found that α -lactoalbumin and β -lactoglobulin sIgE were poor predictors of baked milk challenge outcome. Casein and milk sIgE performed slightly better, with >90% NPVs established at decision points of 0.9 kU/L and 1.0 kU/L, respectively. However, the milk sIgE decision point is unlikely to be of additional clinical utility, since it is the same decision point reported by Sampson and Ho¹⁶ as the >90% NPV in differentiating unheated milk allergic from tolerant subjects. One subject who reacted to baked milk in our study had a

milk sIgE of <0.35 kU/L. This is in contrast to the results of Nowak-Węgrzyn et al.⁸, who reported that no subject with a milk sIgE of <0.35 kU/L reacted to baked milk. Casein SPT had a >90% NPV at a decision point of 9 mm. However, two subjects failed baked milk challenges with negative casein SPT, suggesting that milk proteins other than casein are important in determining tolerance to baked milk. No subject with milk SPT <7 mm failed baked milk challenge in our study. This is similar to the results of Nowak-Węgrzyn et al.⁸, who found that no subject with a milk SPT <5 mm reacted to baked milk.

Three of the subjects who reacted to baked milk in our study passed the initial physician-supervised clinic challenges but reacted to ongoing exposure at home. Reactions to ongoing exposure at home have been reported by other groups. In one recent study,⁸ one of the 68 subjects who passed the supervised baked milk challenge developed oral pruritus with homemade bread and Belgian waffles at home. The subject tolerated a repeat supervised baked milk challenge without symptoms. It was thus determined that the homemade products were not sufficiently baked. In another study,¹ one of the 65 subjects who passed the supervised baked milk challenge reacted to a waffle that the authors deemed “unintentionally undercooked.” However, the family declined to undergo a repeat baked milk challenge to confirm non-reactivity. Interestingly, this phenomenon of late reactions has not been reported in patients who underwent challenges to baked egg.^{18, 19}

Among the subjects in our study that reacted to ongoing baked milk exposure at home, it is possible that they also reacted to unintentionally undercooked products. A key intervention is to stress to families the importance of adequately cooking the baked milk products so that no residual unheated protein remains, which could potentially trigger an allergic reaction. It is also possible that the milk protein quantity used during the food challenge was not large enough to confirm tolerance and larger amounts of protein may have been ingested in the products prepared at home. The source of milk protein used in baking may also be important. In the case of Subject 4, it is possible that using yogurt as a milk source, rather than non-fat dry milk powder, may have caused the severe reaction that required epinephrine. Different forms of milk (e.g., non-fat dry milk powder, liquid milk, yogurt) may contain different conformational epitopes, some of which may be more resistant to heat denaturation and therefore more likely to trigger an allergic reaction. These possibilities will be important to address in future studies.

Several limitations exist in our study. Children were identified as milk allergic based on history and suggestive laboratory studies and not confirmed by failed unheated milk food challenges. Therefore, it is possible that some of the subjects who passed the baked milk challenges may be tolerant to unheated milk as well. While the majority of subjects had both sIgE and SPT performed within 1 year of the baked milk challenge, and most within 3 months, it is possible that obtaining sIgE and SPT results closer to the time of challenge could improve reliability. Among subjects who failed baked milk challenges at home, it would have been beneficial to repeat a physician-supervised baked milk challenge to determine whether they reacted because the milk was inadequately baked or because they were indeed intolerant to baked milk. Given the retrospective nature of this study, we did not have longitudinal data on patients after passing the baked milk challenge, subsequent intake of baked milk at home, or progression to tolerance of unheated milk products. A future, longitudinal prospective study may further our understanding of such patients. Furthermore, we acknowledge that the predictability of outcomes for sIgE and SPT may be enhanced by a larger sample size and future larger studies are needed to confirm these findings.

Despite these limitations, our study is important because it is one of the few studies evaluating predictors of baked milk challenge outcomes and reports on the largest number of milk proteins in association with baked milk challenges to date. Our study provides

practical, real-world implications and evidence that patients who pass these challenges may tolerate products with baked milk that are ubiquitous in various foods, even if they may not tolerate unheated milk. Our food challenge protocol was conducted in a fashion that other practicing allergists may adapt into their practices. Our study also raises the important point that passing a baked milk challenge may not guarantee prolonged tolerance to baked milk products, possibly due to inconsistencies in baking of milk products at home, which is a key consideration when this type of protocol is to be continued in a less highly controlled home setting.

In summary, we defined novel decision points based on serum sIgE and SPT that may be useful in predicting outcomes to baked milk challenges. We found that milk SPT wheal size was a better marker for food challenge outcome to baked milk, compared to casein SPT and milk protein sIgE levels. We identified >90% NPVs for baked milk challenge outcomes for milk and casein SPT wheal sizes and sIgE levels. Furthermore, a milk SPT wheal size <7 mm was predictive of passing the baked milk challenge in 100% of cases. Based on our findings, we propose using a milk SPT wheal of <12 mm to identify those who would pass a baked milk challenge (approximately 90% rate of passing baked milk challenge). Further, a milk SPT wheal of <7 mm could identify patients who may be candidates for home introduction of baked milk (100% rate of passing baked milk challenge). We did identify SPT and sIgE levels above which no subject passed a challenge, but we recognize that our sample size is small, and since the majority of milk-allergic children tolerate baked milk, perhaps higher cutoffs will be identified once more patients are challenged. Future studies will be needed to validate our findings in a larger patient population. Our study also demonstrates the need to caution families and healthcare providers of the possibility of late reactions to ongoing baked milk exposure and to monitor patients over time to verify that clinical tolerance to baked milk is maintained, with hopeful progression towards tolerance of all forms of cow's milk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Dr. Lisa Bartnikas is supported by the 2010 AAAAI/Food Allergy Initiative Howard Gittis Memorial Third/Fourth Year Fellowship/Junior Faculty Research Award. Dr. Wanda Phipatanakul is supported by grants R01 AI 073964 and R01 AI 073964-02S1 from the National Institutes of Health.

References

1. Kim JS, Nowak-Wegrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. *J Allergy Clin Immunol*. 2011; 128:125–131. e2. [PubMed: 21601913]
2. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol*. 2007; 120:1172–1177. [PubMed: 17935766]
3. Saarinen KM, Pelkonen AS, Makela MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol*. 2005; 116:869–875. [PubMed: 16210063]
4. Allen KJ, Koplin JJ. The Epidemiology of IgE-Mediated Food Allergy and Anaphylaxis. *Immunol Allergy Clin North Am*. 2012; 32:35–50. [PubMed: 22244231]
5. Nowak-Wegrzyn A, Sampson HA. Future therapies for food allergies. *J Allergy Clin Immunol*. 2011; 127:558–573. quiz 74-5. [PubMed: 21277625]

6. Shreffler WG, Wanich N, Moloney M, Nowak-Wegrzyn A, Sampson HA. Association of allergen-specific regulatory T cells with the onset of clinical tolerance to milk protein. *J Allergy Clin Immunol*. 2009; 123:43–52. e7. [PubMed: 19130927]
7. Downs ML, Taylor SL. Effects of thermal processing on the enzyme-linked immunosorbent assay (ELISA) detection of milk residues in a model food matrix. *J Agric Food Chem*. 2010; 58:10085–10091. [PubMed: 20735137]
8. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N, et al. Tolerance to extensively heated milk in children with cow's milk allergy. *J Allergy Clin Immunol*. 2008; 122:342–347. 7, e1–e2. [PubMed: 18620743]
9. Taheri-Kafrani A, Gaudin JC, Rabesona H, Nioi C, Agarwal D, Drouet M, et al. Effects of heating and glycation of beta-lactoglobulin on its recognition by IgE of sera from cow milk allergy patients. *J Agric Food Chem*. 2009; 57:4974–4982. [PubMed: 19489627]
10. Thomas K, Herouet-Guicheney C, Ladics G, Bannon G, Cockburn A, Crevel R, et al. Evaluating the effect of food processing on the potential human allergenicity of novel proteins: international workshop report. *Food Chem Toxicol*. 2007; 45:1116–1122. [PubMed: 17395354]
11. Vila L, Beyer K, Jarvinen KM, Chatchatee P, Bardina L, Sampson HA. Role of conformational and linear epitopes in the achievement of tolerance in cow's milk allergy. *Clin Exp Allergy*. 2001; 31:1599–1606. [PubMed: 11678861]
12. Nowak-Wegrzyn A, Fiocchi A. Rare, medium, or well done? The effect of heating and food matrix on food protein allergenicity. *Curr Opin Allergy Clin Immunol*. 2009; 9:234–237. [PubMed: 19444093]
13. Lebovidge JS, Strauch H, Kalish LA, Schneider LC. Assessment of psychological distress among children and adolescents with food allergy. *J Allergy Clin Immunol*. 2009; 124:1282–1288. [PubMed: 19910035]
14. Bernstein IL, Li JT, Bernstein DI, Hamilton R, Spector SL, Tan R, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2008; 100:S1–S148.
15. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010; 126:S1–S58. [PubMed: 21134576]
16. Sampson HA, Ho DG. Relationship between 46 food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol*. 1997; 100:444–451. [PubMed: 9338535]
17. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006; 117:391–397. [PubMed: 16461139]
18. Clark A, Islam S, King Y, Deighton J, Szun S, Anagnostou K, et al. A longitudinal study of resolution of allergy to well-cooked and uncooked egg. *Clin Exp Allergy*. 2011; 41:706–712. [PubMed: 21488997]
19. Lemon-Mule H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Wegrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. *J Allergy Clin Immunol*. 2008; 122:977–83. e1. [PubMed: 18851876]

Figure 1. Performance characteristics of milk SPT

(A) Milk SPT wheal sizes grouped by baked milk challenge outcome. Each data point represents an individual patient and medians are indicated by horizontal lines (N = 35). *P* value determined using the Wilcoxon rank sum test. (B) Estimated probability curve for failing oral baked milk challenge at a given milk SPT wheal size derived from logistic regression. Open circles represent individual subjects. Shaded regions indicate 95% confidence limits. (C) Performance characteristics of milk SPT wheal size at various cutoff values.

Table 1

Characteristics of study population.

	Passed baked milk (N=29)	Failed baked milk (N=6)	Pvalue
Age			
Years, median (range)	8.9 (3.9–18.1)	3.7 (3.1–11.0)	0.02
Gender			
Male, % (N)	69.0% (20)	83.3% (5)	0.65
Other Atopic Conditions			
Asthma, % (N)	55.2% (16)	33.3% (2)	0.40
Atopic dermatitis, % (N)	51.7% (15)	100% (6)	0.06
ARC, % (N)	51.7% (15)	66.7% (4)	0.68
Other food allergies, % (N)	82.8% (24)	100% (6)	0.56

ARC, allergic rhinoconjunctivitis.

Statistical significance for age was calculated using the Wilcoxon rank sum test.

Statistical significance for the remaining parameters was calculated using the Fisher's exact test. A *P* value <0.05 was considered statistically significant.

Table 2

Symptoms at first reported milk reaction.

	Passed baked milk	Failed baked milk
Atopic dermatitis, % (N)	24.1% (7)	33.3% (2)
Cutaneous, % (N)	58.6% (17)	66.7% (4)
Gastrointestinal, % (N)	34.5% (10)	16.7% (1)
Upper airway, % (N)	10.3% (3)	16.7% (1)
Lower airway, % (N)	10.3% (3)	16.7% (1)
Cardiovascular, % (N)	3.4% (1)	0% (0)
Anaphylaxis, % (N)	31.0% (9)	33.3% (2)

Atopic dermatitis: Either in relation to milk ingestion or milk allergy evaluated and milk exclusion recommended in the setting of atopic dermatitis.

Cutaneous: Hives, angioedema, rash, or pruritus.

Gastrointestinal: Abdominal pain, vomiting, or diarrhea.

Upper airway: Rhinoconjunctivitis, oral pruritus, tongue swelling, or stridor.

Lower airway: Wheezing or coughing.

Cardiovascular: Hypotension or lethargy.

Anaphylaxis: Defined by the clinical criteria from the Second Symposium on Anaphylaxis.¹⁷

Table 3

Failed baked milk challenge data.

Subject	SPT wheal (mm)		Serum antigen-specific IgE (kU/L)				Prior reaction	Reason for failure	Treatment
	casein	milk	α -lactalbumin	β -lactoglobulin	casein	milk			
1	22	20	0.36	<0.35	1.56	2.63	Hives, periorbital swelling	Rhinorrhea, hives	Diphenhydramine
2	0	7	<0.35	<0.35	<0.35	<0.35	Atopic dermatitis	Hives	Diphenhydramine
3	9	7	2.15	<0.35	1.11	2.15	Atopic dermatitis	Tongue itching, cough	None
4	9	13	0.40	0.91	0.91	1.16	Hives	Passed clinic challenge. 10 months later, hives, lip swelling, and vomiting with cake baked with yogurt.	Epinephrine, diphenhydramine, steroids
5	20	20	4.67	2.07	31.5	31.0	Hives, vomiting	Oral pruritus but symptoms resolved and passed clinic challenge. Several days later, oral pruritus with baked milk brownie.	None
6	0	17	0.82	1.66	1.03	2.80	Cough, tongue swelling, hives	Passed clinic challenge. 3 weeks later, hives with baked milk muffin.	Diphenhydramine

Table 4

Immunologic responses to milk proteins.

	Passed baked milk	Failed baked milk	<i>P</i> value
Casein SPT, wheal (mm), median (range)	5 (0–15)	9 (0–22)	0.26
Milk SPT, wheal (mm), median (range)	10 (0–20)	15 (7–20)	0.12
α -lactalbumin sIgE (kU/L), median (range)	0.73 (<0.35–8.63)	0.61 (<0.35–4.67)	0.50
β -lactoglobulin sIgE (kU/L), median (range)	<0.35 (<0.35–15.4)	0.63 (<0.35–2.07)	0.62
Casein sIgE (kU/L), median (range)	1.05 (<0.35–10.3)	1.07 (<0.35–31.5)	0.69
Milk sIgE (kU/L), median (range)	1.93 (<0.35–20.6)	2.39 (<0.35–31.0)	0.50

Statistical significance was calculated using the Wilcoxon rank sum test. A *P* value <0.05 was considered statistically significant.