Clinical Communications

Adherence to extensively heated egg and cow's milk after successful oral food challenge

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Clinical Implication

- Two-thirds of children with egg and/or cow's milk allergies and who tolerate extensively heated allergen on in-hospital challenge maintain regular dietary consumption. Symptoms with ongoing allergen exposure were common but did not always prompt dietary cessation. Dietary liberalization was helpful for parents.

TO THE EDITOR:

Up to 70% of children with IgE-mediated allergy to hen's egg (HE) and cow's milk (CM) tolerate the allergen in an extensively heated (EH) form. Regular dietary incorporation of modified allergens may accelerate natural tolerance to HE and CM.[1,2] Liberalizing dietary restrictions may improve patients' and parents' quality of life and anxiety about strict allergen avoidance. Most experts recommend oral food challenges (OFC) to extensively heated HE and CM take place under medical supervision due to the lack of highly predictive parameters to predict challenge outcome[3,4] and the potential for anaphylaxis. At the Children's Hospital Westmead, a large tertiary children's hospital in Australia, baked HE and CM OFC account for 25% of in-hospital OFC. However, it is unclear whether the effort expended by parents, health care facilities, and allergists on liberalizing diets by incorporation of EH CM and HE outside the research setting is worthwhile in terms of long-term dietary adherence. We sought to examine this question.

A postal questionnaire (see Supplement E1 in this article's Online Repository at www.jaci-inpractice.org) was sent to parents of all children with HE and CM allergies who had undergone a successful baked muffin (CM or HE) OFC at least 4 months earlier, within the period February 2012 to September 2013 at Children's Hospital Westmead in the inpatient day unit and in the outpatient setting. Our baked muffin protocol was previously published[5] (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). All the children with a history of clinical reactivity to allergen (in any form, including baked) and current sensitization or an allergist recommendation to avoid allergen based upon serum specific IgE and/or allergy skin prick test (SPT) to HE and/or CM and with no history of clinical tolerance to EH allergen (EHA) were strictly avoiding all forms of HE and CM at the time of the OFC. On successful OFC (no symptoms for 2 hours after the last dose of muffin, with a total cumulative protein dose: HI 1 g, CM 0.5 g), all the children were advised to have no further EHA for 24 hours and to then incorporate baked muffin HE and/or CM into their diet on an at-least weekly basis. SPT wheal size and age were compared by using the Mann-Whitney *U* test, whereas categorical data were analyzed by using the χ^2 test or the Fisher exact test (cell numbers, <5). A *P* value of <.05 was considered statistically significant. The study was approved by the ethics committee at the Children's Hospital at Westmead.

TABLE I. Patient characteristics at challenge

	Baked HE (n = 75)	Baked CM (n = 23)
Boys, no. (%)	50 (67)	15 (65)
Age (y), median (IQR)	3.2 (1.8-6.5)	4.8 (1.8-9.1)
SPT wheal size at OFC (mm), median (IQR)	8 (6-10.5)	7.5 (6-9.5)
Asthma, no. (%)	23 (31)	12 (52)
Eczema, no. (%)	51 (68)	17 (74)
History of reaction to allergen, no. (%)*	43 (57)	21 (91)
Sensitized only: allergen SPT >95% PPV†	24 (32)	2 (9)
History of anaphylaxis to allergen, no. (%)	8 (11)	4 (17)

IQR, Interquartile range; *PPV*, positive predictive value.
*Allergen in any form, including baked.
†95% PPV->7mm (Aged 2 years and over), >4mm (aged less than 2 years).

Ninety-eight of 126 of questionnaires (78%) were returned (75/97 HE, 23/29 CM). The median time between OFC and the return of the questionnaire was 12 months (range, 8 to 15 months). There was no difference in responders compared with nonresponders in terms of child's age, size of SPT, timing of last allergic reaction to HE and/or CM, and history of anaphylaxis to HE and/or CM. The characteristics of the responders are shown in Table I. Overall, 72% of children were still eating muffin that contained EHA and 68% continued to eat EHA (in some form) at least weekly. In total, 27 children (28%) had stopped muffin ingestion: 17 (17%) were eating biscuit only (with reduced amounts of EHA), and 10 children (10%) stopped all forms of EHA (Table II). Forty-one children (42%) reported symptoms attributed to EHA allergy that occurred either within 24 hours of successful challenge (n = 23) and/or on allergen reexposure in the weeks after OFC (n = 26); 8 children had symptoms both within 24 hours of OFC and in the weeks and months thereafter (Table II).

Despite experiencing symptoms after OFC due to muffin, 19 of 41 children (46%) continued to eat muffin with the same amount of EHA. Of those who experienced symptoms within 24 hours of OFC, only 8 of 23 children (35%) stopped eating muffin. A further 4 children stopped eating muffin because of symptoms on muffin reexposure. Symptoms at either time point were predominantly mild gastrointestinal in nature (Table II). Only 3 children had a dislike of the muffin as their sole symptom. Most parents reported being motivated to keep EHA in the diet on the premise that it may assist their child in outgrowing HE and/or CM allergy (Table II). We sought to determine if preexisting characteristics were predictive of whether children continued to have EH CM or EH HE in their diets on a frequent (weekly or more) basis compared with those who completely stopped ingestion. We found no significant difference between the 2 groups with respect to age; sex; asthma; eczema; degree of skin prick sensitization at OFC; and history, duration since, and severity of a prior clinical reaction to HE and/or CM.

Of children who reported any symptoms after successful EHA OFC (either within the first 24 hours or on reexposure), only

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TABLE II. Questionnaire responses

	Baked HE, no. (%) (n = 75)	Baked CM, no. (%) (n = 23)	All subjects, no. (%) (n = 98)
Frequency and type of EHA ingestion			
Still eating muffins	55 (73)	16 (70)	71 (72)
Eating any EHA frequently (at least weekly)	52 (69)	15 (65)	67 (68)
Eating any EHA infrequently (every few weeks or monthly)	16 (21)	4 (18)	20 (20)
Stopped eating EHA altogether	8 (11)	2 (9)	10 (10)
Changed to only eating biscuits with EHA	12 (16)	5 (22)	17 (17)
Symptoms			
Children with symptoms attributed to muffin	29 (39)*	12 (52)*	41 (42)
Within 24 h of OFC	15 (20)	8 (35)	23 (23)
On EHA reexposure	21 (28)	5 (22)	26 (26)
Children stopped eating muffin due to symptoms	6 (8)	6 (35)	12 (12)
Within 24 h of OFC	3 (4)	5 (22)	8 (8)
On EHA reexposure	3 (4)	1 (4)	4 (4)
Continued with the same amount of EHA in muffin despite symptoms	15 (20)*	4 (18)*	19 (20)
Within 24 h of OFC	6 (8)	2 (9)	8 (8)
On EHA reexposure	11 (15)	3 (13)	14 (14)
Stopped eating muffin within I mo of OFC	13 (17)	7 (30)	20 (20)
Reported symptoms			
Gastrointestinal			
Abdominal pain, vomit, diarrhea	16 (21)	7 (30)	23(23)
Itchy mouth	6 (8)	5 (22)	11 (11)
Skin			
Hives	4 (5)	2 (9)	6 (6)
Worsening eczema	11 (15)	3 (13)	14 (14)
Respiratory			
Cough and/or wheeze	3 (4)	0	3 (3)
Dislike taste	8 (11)	3 (13)	11 (11)
Current diet			
Eating the same amount or more muffin than at OFC	47 (63)	13 (56)	60 (61)
Eating other foods with allergen in diet (pancakes, butter, quiche)	45 (60)	13 (57)	58 (59)
Now eating allergen in all forms	11 (15)	3 (13)	14 (14)
Parental perceptions			
Parents kept in the diet to help with tolerance	55 (80)	12 (63)	67 (68)
OFC was helpful in relieving concerns about allergy	61 (81)	21 (91)	82 (84)
OFC was useful for dietary management	61 (85)	16 (84)	77 (79)

EHA, Extensively heated allergen (includes children eating only biscuits).
*Some children reported symptoms at both time points, hence, these are not mutually exclusive categories.

known asthma ($P = .05$) was potentially associated with symptoms. Children with HE allergy who reported symptoms on EHA reexposure in weeks or months after their successful OFC were more likely to have asthma ($P = .02$). No predictive factors were identified for those with symptoms within the first 24 hours after initial "successful" OFC. No other factors, including a history of a recent reaction or anaphylaxis to CM and/or HE were associated with symptoms at any time. The majority of parents reported that the challenges had been useful or very useful in relieving concerns about their child's allergy and in dietary management (Table II).

We achieved a reasonably high questionnaire response rate of almost 80%. Although we found no difference in characteristics between responders and nonresponders, we cannot exclude the possibility that parents whose children stopped regular dietary exposure or those with ongoing symptoms may have been more likely to respond to the questionnaire. Because the children did not undergo OFC to naive allergen immediately before the EH OFC, it is possible that some children who tolerated EHA were not clinically allergic to the allergen at EH OFC; however, we found no difference between SPT at OFC between these groups. It is possible that children who had ongoing symptoms represented a more-severe "allergic phenotype," with asthma as well as food allergy at this relatively young age (median age, 3 to 5 years). Moreover, our cohort reflects a highly atopic tertiary hospital population and may not be readily applicable to children with less complex atopic disease.

Dietary restrictions in children with food allergy are associated with reduced quality of life; however, adherence to dietary advice regarding allergen avoidance of egg[6] and parental recall about regular peanut ingestion after successful challenge[7] is reported to be poor. Continued food avoidance after successful OFC of approximately 25% has previously been reported in the context of OFC to non-EHA, particularly in girls and

individuals with peanut allergy.[8] There also may be risks associated with regular dietary allergen exposure and "quasi-tolerance" in the context of known IgE-mediated food allergy. Eosinophilic esophagitis has been noted as an adverse event in several recent oral immunotherapy trials (reviewed in Sampson[9]). Although we did not identify any children with symptoms suggestive of eosinophilic esophagitis in this cohort, we are mindful of this potential risk.

We report that, in our tertiary HE and/or CM allergic cohort, ongoing symptoms and cessation of consumption of EHA occurs in a significant proportion of children after a baked muffin OFC, although the two are not always related. The majority of children in our cohort continued with regular consumption, and cessation of dietary EHA occurred most often within a month of the OFC and was not predicted by prechallenge characteristics. However, children with symptoms after EH-HE OFC were more likely to have asthma, perhaps indicative of a more severely atopic phenotype. We suggest that after a successful EHA OFC that it is important to educate parents and children about the likelihood of ongoing symptoms and to be mindful that children with asthma may be at greater risk of ongoing allergic symptoms.

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No funding was received for this work.
Conflicts of interest: P. J. Turner has received research support from the UK Medical Research Council and the UK National Institute for Health Research. D. E. Campbell has received research support from Ilhan Food Allergy Foundation, NHRMC; and has received travel support from Allergy Society of South Africa, Australasian Society for Clinical Immunology and Allergy, International Congress of Pediatrics. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication June 16, 2014; revised August 25, 2014; accepted for publication August 28, 2014.
Available online ■ ■
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2213-2198
© 2014 American Academy of Allergy, Asthma & Immunology
http://dx.doi.org/10.1016/j.jaip.2014.08.013

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SUPPLEMENT E1

Follow-up questionnaire: baked egg allergy challenge

Thank you for taking the time to complete this questionnaire. Your participation helps improve the care of children with food allergies. We are interested to know how useful the muffin (baked egg) challenge was for your child, and whether your child has continued to eat the muffin or other foods that contained baked or cooked egg after successfully passing his or her challenge here with us at Children's Hospital Westmead.

BACKGROUND INFORMATION

Q1. How long has it been since your child underwent his or her last medically supervised baked egg in muffin challenge
☐ <6 months
☐ 6-12 months
☐ >12 months

Q2. Can your child now eat egg in all forms and has outgrown his or her egg allergy?
☐ Yes; eating whole egg (eg, scrambled or boiled) and baked egg (muffins or cakes)
☐ No; still avoiding whole egg but eating baked egg (muffins or cakes)
☐ No; avoiding whole egg but eating baked egg in biscuits only
☐ No; avoiding all egg, including baked in muffins, cakes, and biscuits

Q3. How often does your child now eat baked egg?
☐ Once a day
☐ Once a week
☐ Once every couple of weeks
☐ Less than once a month
☐ Not at all

Q4. How long after the last muffin challenge did your child continue to have baked egg (cakes, muffins) in his or her diet? (mark all that apply)
☐ Stopped directly after the challenge
☐ <1 month
☐ >1 to <6 months
☐ ≥ 6 months
☐ Still eating baked egg in cakes or muffins

Q5. On average, does your child still eat approximately the same amount of muffin as he or she consumed during challenge?
☐ Yes
☐ No, he or she eats less
☐ No, her or she eats more
☐ No, her or she does not eat muffin at all

DIRECTLY AFTER THE LAST BAKED EGG HALLENGE

Q6. Did your child have any symptoms that you thought might have been caused by the challenge after you got home from the challenge or on the following day?
☐ Yes
☐ No

Q7. If yes to Q6: what were these symptoms? (mark all that apply)

☐ Itchy mouth or tingling mouth or throat	☐ 2-8 hours	☐ >8 hours
☐ Hives	☐ 2-8 hours	☐ >8 hours
☐ Worsening of eczema	☐ 2-8 hours	☐ >8 hours
☐ Abdominal pain	☐ 2-8 hours	☐ >8 hours
☐ Vomiting	☐ 2-8 hours	☐ >8 hours
☐ Diarrhea	☐ 2-8 hours	☐ >8 hours
☐ Cough or wheeze	☐ 2-8 hours	☐ >8 hours
☐ Other (please specify)	☐ 2-8 hours	☐ >8 hours

Q8. If yes to Q7: did these symptoms stop you from continuing with baked egg into your child's diet at the time?
☐ Yes; I completely stopped giving baked egg in muffins or cakes
☐ No; I continued with approximately the same amount of muffin as the challenge
☐ No; but I reduced the amount of egg in the mixture or the amount of muffin
☐ No; but I changed to egg in biscuits

IN THE WEEKS AND MONTHS AFTER THE LAST BAKED EGG CHALLENGE

Q9. Did your child have any ongoing problems in the weeks or months after you continued baked egg in his or her diet that you thought were related to the baked egg?
☐ Yes
☐ No
☐ I did not continue with baked egg in his or her diet

Q10. If yes to Q9: what were these symptoms and how long after eating the baked egg did they occur? (mark all that apply)
☐ Dislike of the food

☐ Itchy mouth or tingling mouth or throat	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours
☐ Hives	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours
☐ Worsening of eczema	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours
☐ Abdominal pain	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours
☐ Vomiting	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours
☐ Diarrhea	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours
☐ Cough or wheeze	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours
☐ Other (please specify)	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours

Q11. If yes to Q9: did these symptoms stop you from continuing with baked egg in your child's diet?
☐ Yes; I completely stopped giving baked egg in muffins or cakes
☐ No; I continued with approximately the same amount of muffin as the challenge
☐ No; but I reduced the amount of egg in the mixture or the amount of muffin
☐ No; but I changed to egg in biscuits

Q12. If no to Q11: what was the reason that you continued with the baked egg? (mark all that apply)
☐ Belief that it would help my child outgrow his or her egg allergy
☐ Symptoms were not very serious
☐ My child still wanted to eat it
☐ Other (please specify).....

OTHER FOODS WITH EGG IN THE CURRENT DIET

Q13. Is your child now eating other food with containing egg?
☐ Yes
☐ No
Q14. If yes, what sort of egg can they now eat? (mark all that apply)
☐ Baked egg in quiche or egg pie (oven cooked)
☐ Egg in a pancake
☐ Hard boiled egg
☐ Scrambled egg
☐ Raw egg (for example in ice cream, icing, mayonnaise)
☐ Other (please specify).....

USEFULNESS OF THE BAKED EGG CHALLENGE

Q15. How useful was the muffin challenge in relieving your concerns that relate to your child's egg allergy?
☐ Not at all
☐ A little bit
☐ Somewhat
☐ A lot
Q16. How useful was being able to add baked egg into your child's diet at the time that he or she was still allergic to whole egg?
☐ Not at all
☐ A little bit
☐ Somewhat
☐ A lot
☐ Was not able to introduce because of ongoing symptoms
Q17. Is there anything else you would like to tell us about the impact or outcome of your child's baked egg challenge?

Follow-up questionnaire: baked cow's milk allergy challenge

Thank you for taking the time to complete this questionnaire. Your participation helps improve the care of children with food allergies. We are interested to know how useful the muffin (baked cow's milk) challenge was for your child, and whether your child has continued to eat the muffin or other foods that contained baked or cooked cow's milk after successfully passing his or her challenge here with us at Children's Hospital Westmead.

BACKGROUND INFORMATION

Q1. How long has it been since your child underwent his or her last medically supervised baked cow's milk in muffin challenge
☐ < 6 months
☐ 6-12 months
☐ >12 months

Q2. Can your child now eat dairy in all forms and has outgrown his or her milk allergy?
☐ Yes; drinking fresh cow's milk
☐ No; not drinking fresh cow's milk but tolerating other forms of dairy (eg, cheese, yogurt)
☐ No; still avoiding dairy except baked in cakes or muffins
☐ No; avoiding dairy except baked in biscuits
☐ No; avoiding all forms of dairy, including baked into muffins or cakes
Q3. How often does your child now eat baked cow's milk?
☐ Once a day
☐ Once a week
☐ Once every couple of weeks
☐ Less than once a month
☐ Not at all
Q4. How long after the last muffin challenge did your child continue to have baked cow's milk (cakes, muffins) in his or her diet? (mark all that apply)
☐ Stopped directly after the challenge
☐ <1 month
☐ >1 to <6 months
☐ ≥ 6 months
☐ Still eating baked cow's milk in cakes or muffins
Q5. On average, does your child still eat approximately the same amount of muffin as he or she consumed during his or her challenge?
☐ Yes
☐ No; he or she eats less
☐ No; he or she eats more
☐ No; he or she does not eat muffin at all

DIRECTLY AFTER THE LAST BAKED COW'S MILK CHALLENGE

Q6. Did your child have any symptoms that you thought might have been caused by the challenge after you got home from the challenge or on the following day?
☐ Yes
☐ No
Q7. If yes to Q6: what were these symptoms? (mark all that apply)

☐ Itchy mouth or tingling mouth or throat	☐ 2-8 hours	☐ >8 hours
☐ Hives	☐ 2-8 hours	☐ >8 hours
☐ Worsening of eczema	☐ 2-8 hours	☐ >8 hours
☐ Abdominal pain	☐ 2-8 hours	☐ >8 hours
☐ Vomiting	☐ 2-8 hours	☐ >8 hours
☐ Diarrhea	☐ 2-8 hours	☐ >8 hours
☐ Cough or wheeze	☐ 2-8 hours	☐ >8 hours
☐ Other (please specify)	☐ 2-8 hours	☐ >8 hours

Q8. If yes to Q7: did these symptoms stop you from continuing with baked cow's milk in your child's diet at the time?
☐ Yes; I completely stopped giving baked cow's milk in muffins or cakes
☐ No; I continued with approximately the same amount of muffin as the challenge

☐ No; but I reduced the amount of cow's milk in the mixture or the amount of muffin
☐ No; but I changed to cow's milk in biscuits

IN THE WEEKS AND MONTHS AFTER THE LAST BAKED COW'S MILK CHALLENGE

Q9. Did your child have any ongoing problems in the weeks and/or months after you continued baked cow's milk in his or her diet that you thought were related to the baked cow's milk?
☐ Yes
☐ No
☐ I did not continue with baked cow's milk in his or her diet

Q10. If yes to Q9: what were these symptoms and how long after eating the baked cow's milk did they occur? (mark all that apply)

☐ Dislike of the food				
☐ Itchy mouth or tingling mouth or throat	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours	
☐ Hives	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours	
☐ Worsening of eczema	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours	
☐ Abdominal pain	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours	
☐ Vomiting	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours	
☐ Diarrhea	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours	
☐ Cough or wheeze	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours	
☐ Other (please specify)	☐ within 2 hours	☐ 2-8 hours	☐ >8 hours	

Q11. If yes to Q9: did these symptoms stop you from continuing with baked cow's milk in your child's diet?
☐ Yes; I completely stopped giving baked cow's milk in muffins or cakes
☐ No; I continued with approximately the same amount of muffin as the challenge
☐ No; but I reduced the amount of cow's milk in the mixture or the amount of muffin
☐ No; but I changed to cow's milk in biscuits

Q12. If no to Q11: what was the reason that you continued with the baked cow's milk? (mark all that apply)
☐ Belief that it would help my child outgrow his or her cow's milk allergy
☐ Symptoms were not very serious
☐ My child still wanted to eat it
☐ Other (please specify)……

OTHER FOODS WITH COW'S MILK IN THE CURRENT DIET

Q13. Is your child now eating other food that contain cow's milk?
☐ Yes
☐ No

Q14. If yes, what sort of milk can he or she now consume? (mark all that apply)
☐ Milk in a pancake
☐ Cheese (dairy based)
☐ Butter
☐ Yogurt (dairy based)
☐ Ice cream (dairy based)
☐ Fresh milk
☐ Other (please specify)……

USEFULNESS OF THE BAKED COW'S MILK CHALLENGE

Q15. How useful was the muffin challenge in relieving your concerns relating to your child's cow's milk allergy?
☐ Not at all
☐ A little bit
☐ Somewhat
☐ A lot

Q16. How useful was being able to add baked cow's milk into your child's diet at the time he or she was still allergic to whole cow's milk?
☐ Not at all
☐ A little bit
☐ Somewhat
☐ A lot
☐ Was not able to introduce because of ongoing symptoms

Q17. Is there anything else you would like to tell us about the impact or outcome of your child's baked cow's milk challenge?

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BAKED MUFFIN CHALLENGE PROTOCOL

(Suitable for baked egg and baked milk)

CHALLENGE PROTOCOL

Note: A maximum total of one muffin should be consumed at challenge

Time	Amount of muffin	mg of milk protein	mg of egg protein
0	1/16 of a muffin	60mg	62mg
20 min	1/8 of a muffin	120mg	125mg
40 min	1/4 of a muffin	240mg	250mg
60 min	1/4 of a muffin	240mg	250mg
80 min	Remainder of a muffin	270mg	312mg
Total		930mg	1000mg

OBSERVATION POST-CHALLENGE

2 hours

HOME CONTINUATION

- No further muffin for 24 hours after challenge (to detect any delayed reactions).
- If no reaction 24 hours after challenge, child can continue to have baked muffin as per recipe at least once a week

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Food challenges are primarily used to determine if positive food allergy tests are associated with current clinical allergy.

ASCIA Food Challenge Protocols were developed to standardise protocols used by Immunology and Allergy specialists in Australia and New Zealand. They are peer reviewed, based on expert opinion and published literature, and not funded by, nor influenced by any commercial organisations. ASCIA takes no responsibility for any adverse outcomes that may occur using these protocols.

Precautions:

- Food challenges should only be undertaken in carefully selected patients by Immunology and Allergy specialists or appropriately qualified and experienced medical practitioners, in consultation with Immunology and Allergy specialists.
- Food challenges may provoke an allergic reaction in sensitised individuals and should therefore only be performed under medical supervision with immediate access to emergency treatment for anaphylaxis.

FIGURE E1. Baked Muffin Challenge protocol.