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DIAGNOSTIC ORAL FOOD CHALLENGES IN THE TERTIARY PAEDIATRIC ALLERGY CLINIC IN THE UK

Aida SEMIC-JUSUFAGIC, Philip CHETCUTI, Douglas GILLIES, Brenda DEWITT, Donald HODGE

Leeds Teaching Hospitals NHS Trust
The University of Leeds, Leeds
United Kingdom

Correspondence:
aida.semic@nhs.net
Tel.: + 44 113 392 5041
Fax.: + 44 113 392 8617

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Objective – To assess outcomes of oral food challenges (OFC) and to investigate food reintroduction success among children who had negative OFC within single UK tertiary paediatric allergy centre. **Methods –** This study was a retrospective audit of OFC conducted over a 1 year period among children aged 0 to 18 years at Leeds's Children's Hospital who were referred for assessment of their food allergy. Data were collected on demographics, clinical history, challenge outcome and success of reintroduction **Results –** Out of 363 challenges conducted 282 (77.7%) had a negative outcome. Of 70 positive challenges, 2 were anaphylaxis due to cow's milk. Positive challenge outcome was more common in children with a history of atopic eczema (23.4% vs 13.2%, p=0.03) and those who avoided multiple food allergens (p=0.007). The majority of nut challenges (93.9%) tended to be negative. Following negative challenge, data on reintroduction was available on 188/282 children. The majority of children (82.4.2%) were successful in reintroducing allergen into diet. The most common reason for failure of reintroduction of allergen among 33 (17.6%) children with negative challenge was food aversion and delayed reactions. **Conclusion –** The majority of OFC conducted for assessment of food allergy in children are negative. Although a significant proportion of children experience reaction during challenge, systemic reactions during the challenge are relatively rare. Timely recognition of resolution of allergy is important due to its impact on overall health. The majority of children with negative challenge outcome have successfully reintroduced the allergen back in their diets. Clinicians need to discuss and proactively manage patient and families' expectations before and after negative challenge.

Introduction

Food allergy in childhood is common in westernised societies (1). Recent data from the UK birth cohort study has found that 5% of children under the age of 2 years have food hypersensitivity. The most common allergens for IgE and non-IgE mediated allergy were hen's egg (2.1%) and cow's milk (1.7%) (2). The prognosis of food allergy to cow's milk and egg is relatively good with the majority of children growing out of it by adolescence (3). A significant proportion of children are allergic to multiple foods or avoid a number of allergenic foods due to a perceived risk of allergic reaction. As a consequence, strict

allergen avoidance and elimination diet regimes are implemented that often have a significant negative impact on economic, emotional and social wellbeing of patients and their families (4). Early life avoidances of food allergens have also been associated with reduced growth (5), bone mineralisation (6) and reduced variety of foods in diet (7) which could lead to fussy eating habits later in childhood. Therefore, timely assessment of possible tolerance attainment or exclusion of allergy diagnosis particularly where foods have been avoided for precautionary reasons is essential.

Oral food challenge (OFC) is the gold standard diagnostic procedure both for establishing diagnosis, proving oral tolerance and for assessment of resolution of food allergy. Although there is a risk of inducing anaphylaxis, oral food challenge is a relatively safe procedure with a small number of challenge induced anaphylaxis compared to reactions in real life situations (8). A negative oral food challenge has been shown to cause significant improvement in patient and family's quality of life with direct reduction in food related anxiety and social and dietary restrictions(9). It has been well recognised that failure to reintroduce food into the diet after a negative challenge, might be associated with the length of avoidance contributing to feeding difficulties due to learnt behaviour whilst avoiding foods.

In this audit we aimed to assess the safety and efficacy of OFC in the management of food allergy and the factors that predicted successful reintroduction of avoided food after a negative challenge.

Methods

This study was a retrospective audit of children aged 0 to 18 years who underwent OFC in a tertiary paediatric allergy service at Leeds Children's Hospital, Leeds, United Kingdom over a one year period (30 September 2015 - 30 September 2016). The challenges were conducted as part of a diagnostic work up to confirm or refute allergy or to establish if a child has developed tolerance to foods that have been avoided. The audit was approved and registered with Leeds Teaching Hospital NHS Trust's clinical governance team. The objectives of audit were to assess current practice in our centre by determining median waiting time to undergo OFC, current rate of positive and negative OFCs and to assess success rate of food reintroduction after negative challenge.

All children were initially referred to the service by their primary care physician or paediatric specialist for assessment of food allergy. An experienced paediatric allergist (ASJ and DH) or paediatrician with allergy experience (PC and DG) took a detailed allergy focused clinical history including history of eczema, asthma and allergic rhinoconjunctivitis. As a part of assessment all children had skin prick testing (SPT) and/or measurement of serum allergen-specific IgE (sIgE) using ImmunoCAP® (Thermofisher, Uppsala, Sweden) antibody to suspected foods during their initial and follow up assessments. Skin prick test results that were ≥ 3mm greater than the negative control and specific IgE > 0.35 kU_A/L were considered positive.

The ultimate decision to request OFC was made by the reviewing paediatric allergist or paediatrician with experience in allergy. The most common indications for challenge referral were: 1) clinical history suggestive of IgE-mediated, type I immediate allergy but negative SPT or sIgE results, 2) assessment of tolerance development where recent SPT or sIgE results suggested resolution of food allergy, 3) allergic sensitisation to food allergen where tolerance was not known or 4) avoidance and lack of prior exposure to food due to personal or family history of food allergy. Children who had significant clinical history of recent immediate allergic reaction (<1 hour after food ingestion) in presence

of positive SPT or sIgE to culprit food had their diagnosis confirmed and were not challenged.

Oral food challenges

All challenges were conducted as an open OFC using established protocols described elsewhere (1, 12-14). Challenges were conducted on the day when the child was feeling well in the absence of infection or asthma symptoms for at least one week and off oral antihistamines for required period. Children were invited to attend hospital as a day case admission to undergo an OFC to test food. Parents/guardians were given written information prior to the challenge and had an opportunity to discuss the procedure with a member of the clinical team. All parents/guardians gave written consent prior to the start of the procedure. Challenges were conducted to either food in natural or heat processed form, with or without use of food matrix (e.g. fresh milk and milk in a baked cake) based on patient's clinical history of reaction and most recent SPT or sIgE results. Children who were on complete milk or egg avoidance due to previously diagnosed allergy to milk or egg were offered to undergo highly- baked milk or egg challenges (in muffin or cake) unless their SPT result was <3mm in which case they were offered straightforward milk or egg challenge. The total challenge dose for given allergen was based on standard portion size for the child's age (e.g. milk- 100ml or 200 ml skimmed milk, egg- 1 scrambled egg, nuts- 8 g of nut tested, wheat- 1 weetabix biscuit, fish- 90 g, soya- 100 ml of soya milk etc.) divided in incremental doses. Examples of most commonly performed challenge protocols are given in Appendix. The doses were administered in 15-30 minute intervals until the dosing was completed or a child developed ≥1 objective sign or a subjective symptom that persisted for 2 dose levels. Following completion of the challenge children were observed for a minimum of 2 hours in case of negative outcome before being discharged home. Challenge outcome was graded according to the modified grading system proposed recently that classifies reactions into three grades of local (redness, swelling pruritus), mild-moderate systemic (skin and/or gastrointestinal tract) and severe systemic reaction-anaphylaxis (respiratory and/or cardiovascular) (15) . Children who had a positive challenge were advised to continue with allergen avoidance. Those who had a negative challenge were advised to freely introduce the allergen into their regular diet. The success of allergen reintroduction was checked at the next follow up visit or in case of discharge from service, by follow up phone call.

Data collection and statistical analysis

Eligible patients were identified from the allergy service's oral challenge database. Relevant data was collected from child's electronic medical record and extracted into Excel sheet. Statistical analysis was conducted using IBM SPSS Statistic 24 (IBM, New York, USA). Chi square analysis was used to investigate differences between children who had positive and negative challenge results. Inconclusive challenges were excluded from the analysis. Further analysis was performed using univariate and where necessary multivariate logistic regression.

Results

Characteristics of study population

Overall 363 oral food challenges in 303 children were conducted over a 1 year period (Table 1). Of those children, 179 were male (59.1%). Median age at challenge was 4.9 years (0.8-18.3 years). An average waiting time for challenge from referral was 4 months. Two hundred and fifty two children underwent a single challenge and 51 children

had two or more food challenges. A significant proportion of challenges (36.4%) were conducted in children who had never consumed the challenge allergen, either because of empirical avoidance due to a history of food allergy to another allergen, family history of allergy to the index allergen or fear of introducing allergen into the diet of a child with atopic eczema with or without detectable positive allergen specific antibodies. Another 10.7% of children reported delayed symptoms such as flare up of their atopic eczema after consumption of allergen. More than half of the children (59%) were avoiding 2 or more major allergens in their diet.

Table 1 Characteristics

Oral food challenges, n=363	
Age, median ± SD (range)	4.9 years ± 4.5 (0.8-18.3)
Waiting time for challenge median (range)	4 months (0-13)
Number of patients challenged	n=303
Male gender	179 (59.1%)
Number of major allergens avoided (n=303)	
0	3 (1.0%)
1	121 (39.9%)
2	81 (26.7%)
3	98 (32.3%)
Number of challenges per patient	
1	252 (83.3%)
2	45 (14.9%)
3	4 (1.3%)
4	2 (0.7%)
Allergic disease comorbidity (n=303)	
Any allergic disease	232 (76.4%)
Eczema	193 (63.7%)
Asthma	94 (31%)
Allergic rhinoconjunctivitis	83 (27.4%)
Non-IgE mediated milk allergy	24 (7.9%)
History of immediate reaction (n=363)	
No	39 (10.7%)
Yes	192 (52.9%)
Not known	132 (36.4%)

Other than food allergy, a high proportion of children had allergic disease comorbidity with 63.1% of children having a history of atopic eczema, 31% asthma and 27.4% allergic rhinoconjunctivitis. One third of children (32.8%) received dietetic support prior to challenge. Egg (n=120), nuts (n=114) and milk (n=61) accounted for 81% of all challenges.

Challenge outcomes

Of 363 challenges performed (Table 2), 282 (77.7%) were negative, 70 (19.3%) positive and 11 (3%) were inconclusive. The inconclusive outcome was recorded if child refused to eat sufficient quantity of the challenge food (n=9) or had developed subjective symptoms in the absence of objective signs of allergic reaction (1 with abdominal pain and 1 with oral pruritus). There was no association between a positive challenge outcome and gender (male vs female, 20.6% vs 18.8%, p=0.7). Of 70 positive challenges two were anaphylaxis, one of which was in a 10 year old boy who required treatment with intramuscular adrenaline. Both of these challenges were to cow's milk, one to milk in highly- baked (muffin) form which required adrenaline and one to fresh milk. According to the grading system, 10 children (14.3%) had local, Grade I reaction (e.g. redness, swelling, pruritus), 58 (82.9%) had mild to moderate systemic, Grade II reaction (skin, e.g. urticaria, angioedema, erythema and/or GI tract, e.g. abdominal pain, vomiting, diarrhoea) and 2 (2.8%) had severe systemic Grade III allergic reaction (respiratory and/or cardiovascular) (Table 2). Isolated cutaneous manifestations such as urticaria, pruritus, flushing and angioedema were the most common reason (47.1%) for stopping the challenge, followed by gastrointestinal symptoms such as vomiting or abdominal pain (20.0%). The remainder were stopped due to

Table 2 Challenge outcome and reaction severity

Challenge outcome and reaction severity	n (%)	HIR		
		Yes	No	Not known
Challenge outcome (n=363)				
Negative	282 (77.7)	134	31	117
Positive	70 (19.3)	50	8	12
Inconclusive	11 (3)	8	0	3
Allergic reaction grading system (n=70)				
Grade I (local reaction - redness, swelling, pruritus)	10 (14.3)	-		
Grade II (mild to moderate systemic reaction)				
II A (skin or GI tract)	55 (78.6)	-		
II B (skin and GI tract)	3 (4.3)	-		
Grade III (severe systemic reaction=anaphylaxis)				
III A (respiratory or cardiovascular)	1 (1.4)	-		
III B (severe respiratory and/or severe cardiovascular)	1 (1.4)	-		
III C	-	-		
Allergen reintroduced (n=188)				
Yes	155 (82.4)	-		
No	33 (17.6)	-		
Allergen reintroduced not known (n=94)				

HIR=History of immediate reaction.

upper respiratory and/or conjunctival symptoms (12.9%) or a combination of the above symptoms (17.1%). Respiratory or cardiovascular involvement was noted in 2.9% of positive challenges. The likelihood of positive challenge was significantly higher for cow's milk compared to other allergens (37.7%, p=0.01, OR 5.18, 95% CI 1.40-19.12, Table 3). Although it did not reach statistical significance, the highest proportion of negative challenges was recorded for nuts (93.9% were negative).

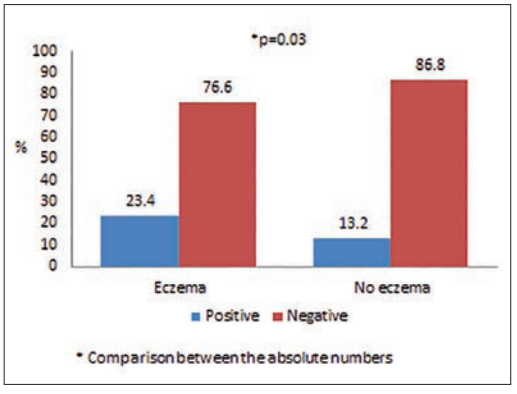

Fig. 1 *Eczema and challenge outcome.*

Predictors of positive challenge

Inconclusive challenges (n=11) were excluded from the association analysis. The odds of positive challenge outcome decreased with increasing age (p=0.002, OR 0.99, 95% CI 0.98-0.99). The outcome of challenge was more likely to be negative in those who had no history of immediate reaction or who have never consumed the culprit allergen (p=0.001). Those with a history of eczema were two times more likely to have a positive challenge outcome (23.4% vs. 13.2 %, p=0.03, OR 2.02, 95%CI 1.0919-3.67, Fig. 1). In a multivariate analysis this association

was independent of gender. Children who had a positive challenge were more likely to require support from an allergy dietician than those who had negative challenge (47.1% vs. 30.1%, p=0.007). The likelihood of having a positive challenge outcome increased with the number of major allergens that the child was avoiding (p=0.001, OR 1.40, 95%CI 1.15-1.70).

Allergen reintroduction

Out of 282 children who had a negative challenge 188 (66.6%) had information available on reintroduction of allergen (Table 2 and 3). Of these, 155 (82.4%) children were successful in introducing the allergen. There was no statistically significant difference in reintroduction rates between different allergens (p=0.3). Thirty three (17.6%) children did not introduce allergen back into their diet. Boys were more likely not to introduce food after the negative challenge (22.3% of boys vs. 10.5% of girls, p=0.04). Among 28 patients who gave reason for failure of introducing allergen, 10 children had food aversion (7 were to nuts), 6 had gastrointestinal symptoms (abdominal pain, diarrhoea or vomiting), 4 had worsening of eczema (3 were to soya), 5 had delayed symptoms after challenge, one was not reintroduced due to parental anxiety, one due to problem with swallowing solids and one due to allergen not being a part of family's diet. Food reintroduction rate was neither associated with receipt of dietetic support (p=0.4) nor the age of child at the challenge (p=0.4). Of 70 children that had positive food challenge, two have successfully reintroduced allergen to their diet on their own incentive against the advice (peanut and egg).

Discussion

Data from this audit has demonstrated that OFC is a safe and effective method of assessing food allergy as evidenced by high proportion of negative OFCs (77.7%) with positive OFC rate (19.3%) and severity of reactions comparable to reported figures from other centres in industrialised societies. The rate of negative challenges in our study was comparable to rates reported in another tertiary allergy centre with high prevalence of childhood food allergy (11). The majority of

Table 3 Allergens and challenge outcome

Allergens	(n=363)	Challenge outcome			
		Negative n=282	Positive n=70	Inconclusive n=11	IR (n=188/282)
	Number and percentage				I/IA
Milk	61 (16.8)	37 (60.7)	23 (37.7)	1 (1.6)	22/27
Egg	120 (33.1)	82 (68.3)	31 (25.8)	7 (5.8)	47/53
Wheat	11 (3)	8 (72.7)	3 (27.3)	-	7/8
Nuts	114 (31.4)	107 (93.9)	5 (4.4)	2 (1.8)	48/59
Soya	10 (2.8)	9 (90)	1 (10)	-	5/9
Fish	12 (3.3)	9 (75)	2 (16.7)	1 (8.3)	7/8
Shellfish	2 (0.6)	1 (50)	1 (50)	-	1/1
Sesame	5 (1.4)	4 (80)	1 (20)	-	3/3
Other*	28 (7.7)	25 (89.3)	3 (10.7)	-	15/20

IR=Information on reintroduction; I/IA=Introduced/information available; *Legumes, Oats, Locust gum bean, Lactose, Potato, Coconut, Strawberry, Tomato, Pineapple, Apple, Avocado, Garlic, Citrus Fruit and Chocolate.

children who reacted during the challenge experienced mild to moderate allergic reactions that responded to antihistamine. The rate of anaphylaxis in this audit was similar to the 2.8% anaphylaxis rate (5 out of 177) reported in an Australian population-based cohort HealthNuts study among 4 year old children who were investigated for suspected food allergy, although the HealthNuts study only performed challenges to egg, peanut and sesame (8).

Anaphylaxis was experienced by 2 out of 70 children (2.869%) who had a positive challenge result, one of whom needed intramuscular adrenaline treatment. Both of these children reacted to milk. Severe allergic reactions to milk have been previously reported in older children (9-12 years of age) who required intensive care treatment (16). With milk related allergic reactions being potentially life threatening, this highlights the importance of considering possible intervention with oral immunotherapy in older milk allergic children.

There was a slightly greater majority of male children (59.1%) who underwent OFC which is in concordance with reported figures in other paediatric allergy outpatient studies (11, 17). Our patient population did have a large burden of allergic disease comorbidity. Almost two thirds of children did have a history of atopic eczema which was more commonly associated with a positive challenge outcome. In this study we did not collect data on current eczema and its severity to investigate whether this was a determinant of confirmed food allergy or its persistence. Atopic eczema is a known risk factor for the development of food allergy due to a defective skin barrier in early life, allowing cutaneous allergic sensitisation to foods to occur before there is a chance for oral tolerance development(18). Flohr at al. in their population based study have shown a direct link between early-onset severe atopic eczema and increased risk of food sensitisation at age 3 months (19). A similar study among 1260 newborns looked at transepidermal water loss (TEWL) as a measure of effectiveness of skin barrier at 3 time points until the age of 2 years, found that children who had higher TEWL at birth were 4 times more likely to have food allergy at age 2 years (20). A recent genetic association study has identified a novel single nucleotide polymorphism in SPINK5 gene that is associated both with increased TEWL and challenge proven food allergy (21). Improvement of the skin barrier through use of emollients has been explored as a possible primary prevention strategy for food sensitisation and food allergy in small studies with more data expected to be published from a large scale BEEP study (22, 23).

The majority of children in our study (59%) were on multiple allergen elimination diets with a high proportion of children avoiding foods in the absence of clinical history (36.4%). Multiple staple food avoidance is known to have a negative impact on a child and family's quality of life (24, 25). Therefore, timely intervention and regular assessment of allergy is important for long term health and eating habits.

A large proportion of OFC to nuts (93.9%) were negative. For the purpose of our analysis we did not differentiate between challenges to different nuts as we did not aim to assess differences in that respect. Our data indicate that nut challenges in some circumstances may be performed in cases where likelihood of reaction is lower such as in cases with a negative clinical history but high parental anxiety due to personal or family history of nut allergy. A proportion of peanut or tree nut allergic children would have undergone challenges to other nuts to which they tested negative to assess possible cross-reactivity. Similar to some other larger centres in the UK (12), our centre serves a population

of mixed ethnic background with large proportion of south Asian families whose diet frequently incorporates nuts. In such families children may be under greater risk of accidental exposures and accurate assessment of nut allergy and cross-reactivity is important part of risk management.

A review of OFC to nuts in another tertiary centre in the UK, concluded that children with isolated peanut allergy who have negative SPT to tree nuts may not require confirmatory OFC to other nuts as all of 72 children in the study who went on to have tree nut challenge tested negative (12). However, those who were tree nut allergic who went on to be challenged to peanut and/or other tree nuts 7.9% of those who had negative SPT had positive challenge.

One of our aims was to assess the food reintroduction rate following negative OFC. Of 188/282 (66.6%) children for whom data on reintroduction was available 82.4% had successfully reintroduced the culprit allergen into their diet with 17.6% still avoiding the allergen. These figures are similar to those reports from other tertiary allergy centres ranging from 20% to 28% (11, 26, 27). Unlike in other studies, we did not find an association between failure of food reintroduction and the age of child. This could be possible explained by differences in populations between centres and on average 1.5- 2 years younger age of our study population compared to two other studies (10, 11). Although there was no statistically significant difference among allergens, the highest proportion of failed reintroductions was seen for nuts due to food aversion and for soya due to worsening of eczema. Other studies have also found the highest failure rates with peanut and tree nuts (11, 26) which is possibly due to greater awareness and publicity of peanut allergy in the media. This study was limited in investigating factors that might influence successful reintroduction due to its retrospective nature. We have not investigated behavioural and nutritional factors that could predict success of reintroduction. Polloni et al. have published recently that pre challenge low interest in tasting new foods and monotony of the diet were associated with failure to introduce foods (10). The same study found higher pre-challenge maternal anxiety levels were associated with failure of allergen reintroduction after negative challenge. Similar to our findings other reasons quoted in a number of studies were fear of reaction, food aversion and allergen not being part of the family's regular diet (26-28). On the other side, unfamiliarity of taste due to lifelong avoidance, fear of possible reaction or ease of continuing with old habits due to other family member's allergen avoidance are common reasons for not introducing the allergen (29).In addition, our relatively long waiting times for children to undergo OFC may have contributed to failure of reintroduction of allergen in some cases due to lifelong avoidance. As successful reintroduction of allergen after negative challenge seems to be influenced by many behavioural and nutritional factors, clinicians need to be actively managing patients' and families' expectations and seeking multiprofessional support from dieticians and where necessary psychologists in cases where failure of allergen introduction is anticipated.

Conclusion

In summary, this audit has shown that OFC is a safe tool for diagnosing and managing food allergy. History of atopic eczema and number of food avoidances are strong predictors of positive challenge outcome demonstrating a high disease burden in those children. Following negative challenge about 18% of children have failed to reintroduce challenge food into their diets. Clinicians and wider multidisciplinary team need to

proactively manage expectations before and after challenge to prevent or minimise reintroduction failures.

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Appendix
Examples of portion sizes, protein content and protocols

Food	Cow's Milk	Hen's Egg	Peanut/Tree nuts
Portion size	100-200 ml skimmed milk	1 scrambled egg	8 g
Protein content	3.6 g/ 7.2 g	6.1 g	2 g
Step 1	0.5 ml	1/4 of teaspoon	¼ of peanut/ tree nut
Step 2	1.0 ml	1/2 of teaspoon	½ of peanut/ tree nut
Step 3	2.5 ml	1 teaspoon	1 peanut/ tree nut
Step 4	5.0 ml	2 teaspoons	2 peanuts/ tree nuts
Step 5	10 ml	4 teaspoons	4 peanuts/tree nuts
Step 6	20 ml	give remaining amount (if any)	8 peanuts/ tree nuts
Step 7	50 ml	-	-
Step 8	100 ml (If >10 years old)	-	-