

Comparison of open and double-blind placebo-controlled food challenges in diagnosis of food hypersensitivity amongst children

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Abstract

Background Correct diagnosis of food hypersensitivity (FHS) is important to ensure appropriate patient care and to accurately establish the population prevalence and incidence. Food challenges play a very important role in the diagnosis of FHS, but it is unclear when open food challenges (OFCs) opposed to double-blind placebo-controlled food challenges (DBPCFCs) should be used. This study investigated the use of OFCs and DBPCFCs when diagnosing FHS.

Methods Children with a reported history of FHS or with sensitization to a food without known previous consumption were invited to undergo food challenges. Children of consenting parents underwent an OFC and those with a positive OFC were approached to undergo a DBPCFC. Food challenges were either performed as 1-day or 1-week challenges depending on sensitization status and clinical history.

Results Forty-one children underwent both OFCs and DBPCFCs. The positive predictive values for 1-day and 1-week OFCs were 73% (8/11; 95% CI: 39–94%) and 57% (20/35; 95% CI: 39–74%) respectively. There was no evidence to indicate that the younger children were more likely to have a positive OFC confirmed by a DBPCFC compared to older children (Fisher's exact $P = 0.53$). In the 1-day challenges parents indicated a preference for OFC rather than DBPCFC. By contrast, in the 1-week challenge parents indicated a preference for DBPCFC ($P = 0.0192$).

Conclusion Open food challenge may be suitable for diagnosing immediate objective symptoms, whereas DBPCFC may be needed for the diagnosis of delayed and mainly subjective symptoms, irrespective of the child's age.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflict of interests.

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All authors have critically reviewed the paper and have approved the final version. CV designed the food challenge protocols; she contributed to the analysis of the study and drafted the paper with TD. BP and KV carried out the medical assessment and clinical supervision of the food challenges. They also contributed to the interpretation of the results and commented on the drafts of the manuscript. JG and BC recruited the study participants and carried out the food challenges. They also contributed to the interpretation of the results and commented on the drafts of the manuscript. CG designed the food challenge protocols and commented on the drafts of the manuscript. BH contributed to the analysis of the study and commented on the manuscript draft. TD was the principal investigator and conceptualized and designed the study. She assisted with the analysis and interpretation of the data and drafted the paper with CV.

Introduction

Food hypersensitivity (FHS) is believed to affect 1.5% of adults and up to 8% of children (Bock, 1987; Fuglsang *et al.*, 1994; Jansen *et al.*, 1994; Zuberbier *et al.*, 2004; Pereira *et al.*, 2005; Venter *et al.*, 2006b). Correct diagnosis of FHS is important to ensure appropriate patient care and to accurately establish the population prevalence and incidence. Furthermore, false negative diagnoses can lead to the risk of ongoing symptoms with further (severe) reactions. False positive diagnoses on the other hand can lead to unnecessary restrictions on life style and possible disease from nutrient restriction (Eggesbo *et al.*, 2001; Sicherer *et al.*, 2001; Christie *et al.*, 2002). It has also been suggested that early identification of children with FHS and atopic dermatitis may provide opportunities to prevent the development of asthma (Bender *et al.*, 2003). The diagnosis of FHS starts with the clinical history alongside

diagnostic tests and symptom diaries when indicated. When these diagnostic measures are suggestive of FHS, an elimination diet is suggested. Upon improvement of symptoms, the patient may need to undergo a food challenge test.

Food challenges are the accepted standard in diagnosing FHS. A major issue is when to use open food challenges (OFC) as opposed to double-blind placebo-controlled food challenges (DBPCFC). Many studies have used either OFC or DBPCFC or a combination of both (Bock, 1987; Baehler *et al.*, 1996; Isolauri & Turjanmaa, 1996; Sicherer *et al.*, 2000; Hill *et al.*, 2001).

In general, the DBPCFC is the accepted gold standard in objectively diagnosing FHS (Bock *et al.*, 1988; Pastorello *et al.*, 1991; Sampson, 2001). However, some clinicians consider it far from a perfect test as it can be labour intensive and more unsafe to perform than the OFC, particularly in children, due to masked oral symptoms when using capsules (Hill & Hosking, 1991; Hide, 1994).

There is a consensus amongst many clinicians suggesting that OFC is acceptable in children under the age of three and the DBPCFC should be used in older children (Bahna, 1994; Muraro, 2001; Bindslev-Jensen *et al.*, 2004). However, there is no evidence to support this.

The aim of this study was to investigate the reliability of responses to OFC when compared to DBPCFC in a group of children aged between 1 and 15 years of age.

Materials and methods

Children participating in this study were recruited from a larger prospectively designed population based study which aimed to establish the prevalence of childhood FHS (Pereira *et al.*, 2005; Venter *et al.*, 2006a,b). Approval for the study was obtained from the Isle of Wight, Portsmouth and South East Hampshire Local Research Ethics Committee (Ref 09/01). Written informed consent was obtained from the parents.

All children were skin prick tested to a standard battery of food (milk, egg, wheat, peanut, sesame and cod fish), aero-allergens (house dust mite *Dermatophagoides pteronyssinus*, cat and grass) and other allergens as identified by history.

Skin prick tests (SPT) were conducted with commercial extracts of standard food and aeroallergens (Soluprick SQ allergens-ALK Allergologisk Laboratorium A/S, Horsholm, Denmark). Results were expressed as positive if mean diameter was 3 mm or more in the presence of a negative control and a positive histamine reaction after 15 min (Bock & Atkins, 1990; Eigenmann & Sampson, 1998).

Children were invited for a food challenge if they had never previously knowingly eaten a large amount of the food to which they had a positive SPT or if they had a previous adverse reaction to foods regardless of their SPT result.

Prior to the food challenges, children and parents were advised by the research dietitian regarding avoidance of the offending food or ingredient. Children were advised to avoid the offending food for at least 4 weeks prior to the challenge (Bock *et al.*, 1988). Challenges were performed following an algorithm (Figs 1–3) adhering to the history in terms of dose and timing where available. In other words, if there was a good clinical history available regarding dose of food eliciting the reaction and time to reaction, then this information was used to design the food challenge. All food for challenges was freshly prepared for each child, taking into consideration the range of food each child would prefer as a vehicle.

Challenge protocols were developed based on current available literature. As there are no agreed international protocols, the draft protocols were circulated to experts in the UK, Europe and USA. A consensus was reached and protocols established for the diagnosis of immediate (1-day challenge, Appendix A) and delayed (1-week challenge, Appendix B) symptoms (Baehler *et al.*, 1996; Isolaure & Turjanmaa, 1996; Majamaa *et al.*, 1999a,b). One-day challenge protocols were based on the consumption of a total of 8–10 g of dried food (Sampson, 2001), unless the history clearly indicated otherwise, i.e. the history clearly indicated that more or less food was needed to elicit a reaction. Food was used as consumed by the patient, e.g. boiled egg rather than dried egg white. The amount of food was calculated to provide 10 g of dried product, e.g. 100 mL of semi-skimmed milk = 89.8 g of water thus contains 10.1 g of

dried product (Holland *et al.*, 2000). At the end of a negative challenge (after a 2-h observation period), the child was expected to consume a normal portion of the food. If the child refused the food at this stage, the parents were asked to give a normal portion of this food to the child, at home, on the same day (Sampson, 1998). One-week challenges were based on normal daily consumption for the specific age group, unless the history clearly indicated otherwise. A normal portion was defined as an amount indicated by the history or as a normal portion for that age group calculated by means of the National Diet and Nutritional Survey (Gregory *et al.*, 1995, 2000) or portion sizes recommended for children by textbooks (Watling, 2001).

All 'eligible for challenge' children underwent open challenges and only those with a positive reaction were invited to participate in a DBPCFC. Those with a negative OFC, were not invited for a DBPCFC, as ethical permission was not obtained for this. Those with a history of immediate symptoms were invited to the Paediatric Day Unit. If children presented with a positive SPT without previous consumption of the food, the challenge was also performed in hospital. Challenges were performed at home when the history indicated delayed development of symptoms and the SPT was negative. Some of these challenges were started in hospital and were continued at home (see Appendices A and B for examples of challenge protocols). Foods used for the DBPCFC were tested for blindness by the study team and an independent group of parents and children. Blinding was particularly tested to prevent parents from guessing which foods contained the active ingredients. Foods for the DBPCFC at home were prepared by a chef, once the recipes were tried and tested by the allergy dietitian, and provided to the parents to give to the children at home. If upon open challenge a convincing positive reaction occurred corresponding to the history and/or sensitization, this was recorded as a positive outcome for that case. For the DBPCFCs, those children with severe reactions during the OFC or history of anaphylaxis were excluded. Reactions during home challenges were reported by parents on a symptoms diary. These diaries

Algorithm used for performing Open or Double Blind Placebo Controlled Oral Food Challenges

Immediate reactions after food has been eaten or a positive Skin Prick Test without knowingly eating the food before

All patients with a positive Skin Prick Test and/or history of previous immediate adverse reactions to a food will be challenged

STEP 1: Open food challenge

Follow the open challenge procedure for the specific food using either the amount indicated by a clear history or 8-10g of dried food

Positive outcome⁺
Continue to avoid offending food till Double Blind Placebo Controlled Food Challenge

Negative Outcome: **End of challenge**

STEP 2: Proceed to: Double Blind Placebo Controlled Food Challenge

Follow the double blind placebo controlled challenge procedure as described for this specific food, using both the active and placebo

Challenge need to be performed twice; Once with active and once with placebo⁺
After completion of the challenge

Break the code

If positive to placebo: Negative challenge
If positive to placebo and active: Negative challenge – possibly re-challenge
If positive to active: Avoid food as discussed with dietitian

To be reviewed after 1 month

⁺ If challenge positive and medication was given, the next challenge must not start as long as the medication is still active.
Also, if challenge positive, due to depletion of mediators (tachyphylaxis) the next challenge starting on the same day, or even the next day might be falsely negative.
THUS if medication is used or if a patient develops symptoms during challenge – an appropriate wash out period will be required before the next challenge.

Figure 1 Algorithm used for performing open or double-blind placebo-controlled oral food challenges – immediate reactions or positive skin prick test without knowingly eating the food before.

were reviewed by a blinded observer (research fellow, allergy nurse or paediatrician) and participants were invited to the Allergy Unit for

verification of symptoms when indicated. A wash-out period of 1–6 weeks was allowed between active and placebo challenges. This ensured

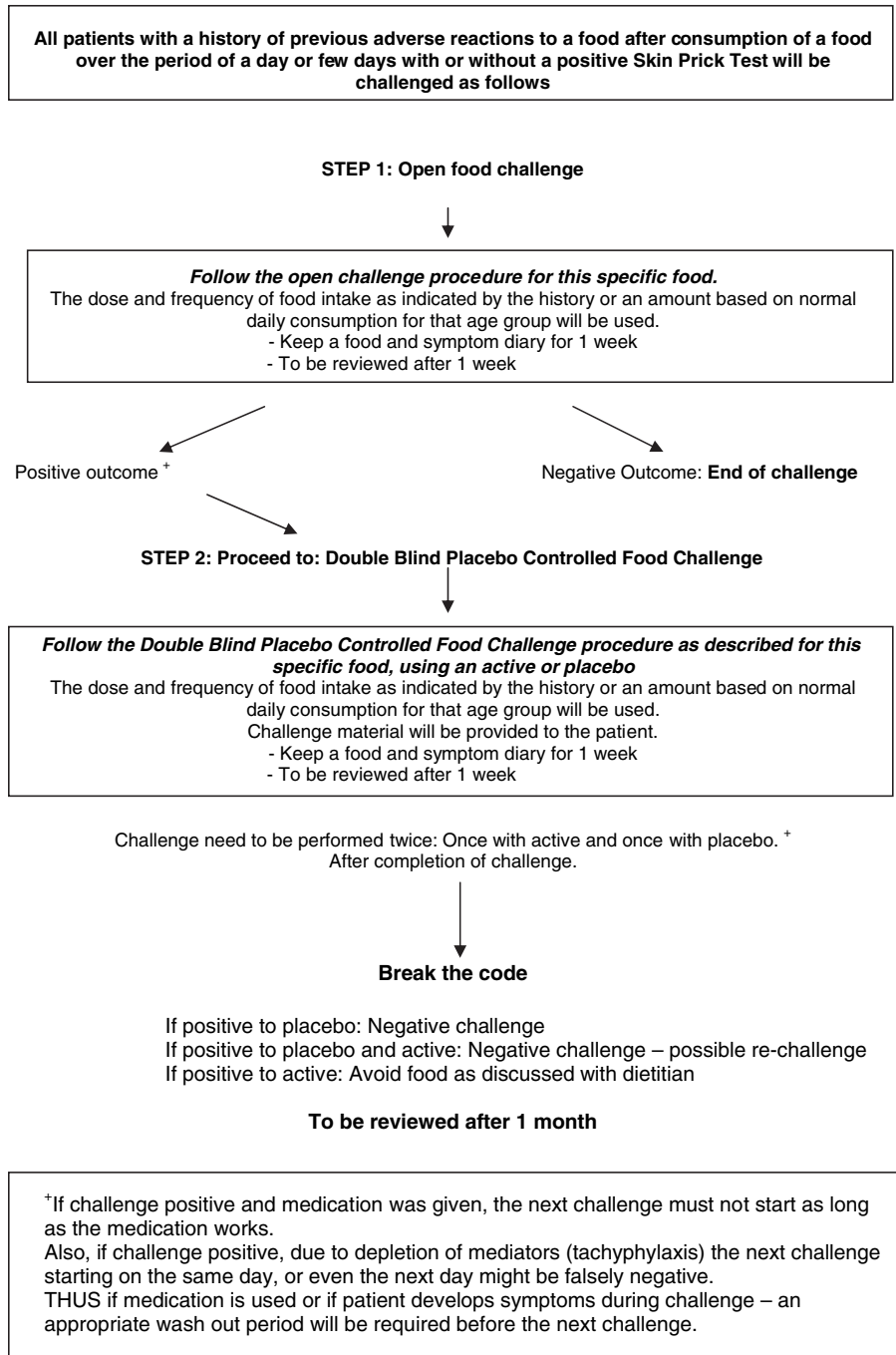
Algorithm used for performing Open or Double Blind Placebo Controlled Oral Food ChallengesDelayed reactions

Figure 2 Algorithm used for performing open or double-blind placebo-controlled oral food challenges – delayed reactions.

adequate time between challenges, but minimized the possibility that the younger children in the study might outgrow their FHS.

There is no standardized literature regarding a 'positive' challenge outcome. Decisions regarding the challenge outcome were made by a research

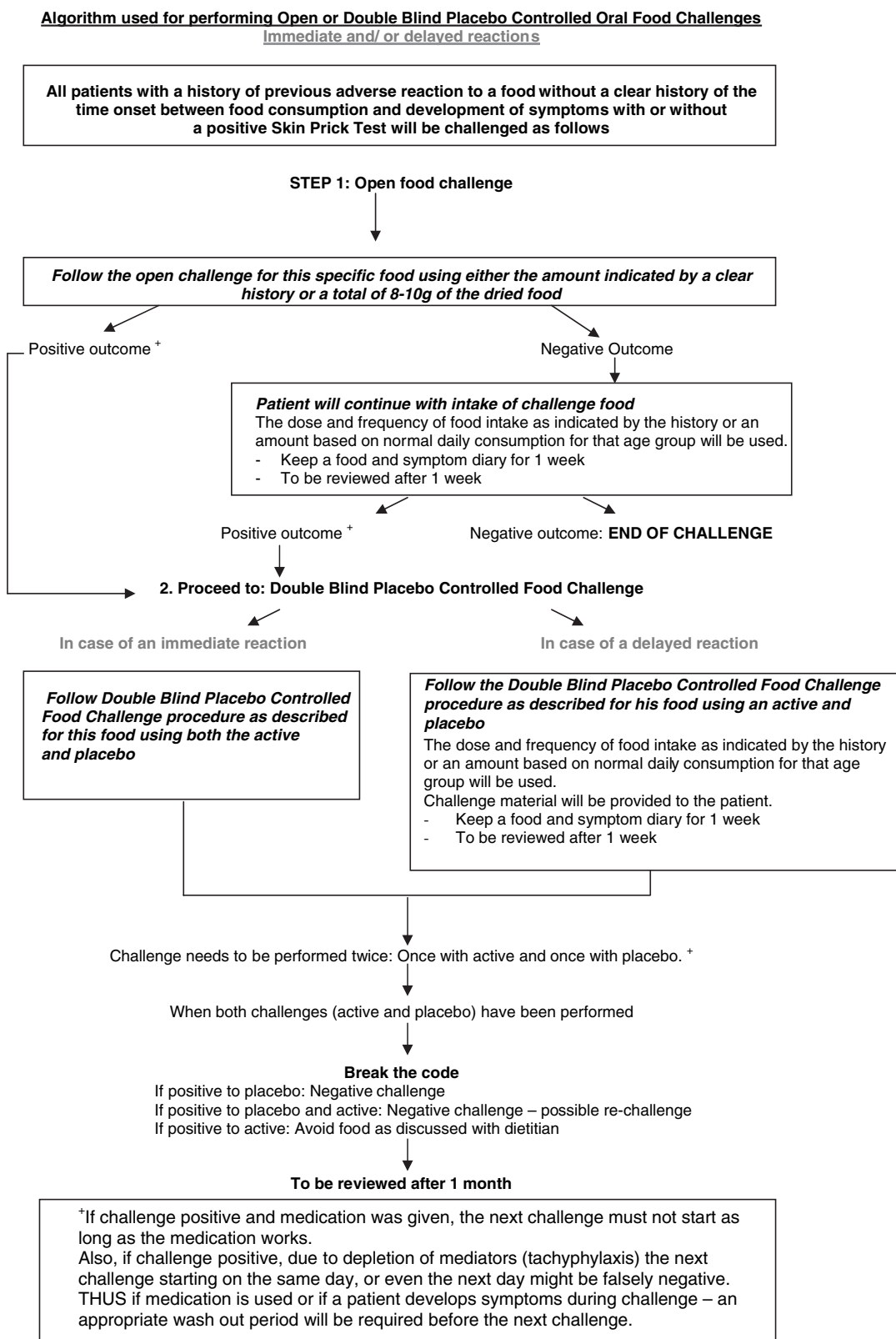


Figure 3 Algorithm used for performing open or double-blind placebo-controlled oral food challenges – immediate and/or delayed reactions.

team with a track record in allergic disease. Underlying diseases such as celiac disease, irritable bowel disease and inflammatory bowel disease were ruled out prior to food challenges.

This study reports on the findings from those who completed both the OFC and DBPCFC.

Parental acceptance of the challenge outcome was determined by checking whether the food was actually avoided or re-introduced into the child's diet based on the challenge outcome.

Parental preference of food challenges (OFC versus DBPCFC) was tested by means of a simple question: Which method of food challenge did you prefer and why?

Data analysis

In view of the small sample size exact *P*-values were computed using either permutation tests or Fisher's exact test, and the Clopper-Pearson method used to estimate confidence intervals for single population proportions. Statistical calculations were performed using StatsDirect™ (Cheshire, England) statistical software.

Results

One-hundred and thirty-seven children underwent a total of 181 OFC between them, of which 80 challenges were positive in 69 children. Of the 101 negative OFCs, sensitization to the food was seen in 27 cases.

The positive challenges ($n = 80$) can be divided into:

- Thirty-seven 1-day challenges (18 amongst 1 year olds, four amongst 2 year olds, three amongst 6 year olds, seven amongst 11 year olds and five amongst 15 year olds).

- Forty-three 1-week challenges (25 amongst 1 year olds, six amongst 2 year olds, seven amongst 6 year olds, two amongst 11 year olds and three amongst 15 year olds).

Pooling the OFC together, it can be noted that 50.4% (69/137) of the children who underwent OFC had a positive challenge outcome.

Of the 69 children with positive OFC, 41 children consented to DBPCFC. Clinical characteristics of these children are shown in Table 1. There were no statistical differences between those who underwent DBPCFC and those who declined these challenges.

Twenty-eight mothers declined the DBPCFC. The reasons for refusing included:

- Seventeen children with severe reactions in the past (either upon OFC or accidental exposure) who did not wish to undergo another challenge.
- Four parents refused the DBPCFC, but agreed to two OFCs.
- Three children had multiple food allergies and other allergic symptoms and the consultant allergist requested no further intervention in these instances.
- One child reacted on skin contact with milk (confirmed in OFC) and consumed milk without any reaction.
- One child lived on the mainland.
- One mother declined a DBPCFC and decided to introduce wheat into the child's diet despite the positive OFC.
- One DBPCFC was not performed due to the difficulties in performing DBPCFC for oral allergy syndrome (OAS).

In total, 46 DBPCFC were carried out in 41 children. Of these, 28 challenges were positive in 22 children.

Table 1 Clinical characteristics of the 41 children participating in the study

Characteristics	No. those that underwent double-blind placebo-controlled food challenge (%)	No. those that declined double-blind placebo-controlled food challenge (%)	<i>P</i> -value (Fisher's exact)
Male	25 (61)	14 (50)	0.46
Age range (years)	1–15	1–15	1.00
Aged ≤ 2 years	26 (63)	17 (61)	
Positive skin prick test to			
Food allergens	13 (32)	11 (39)	0.61
Aeroallergens	6 (15)	6 (21)	0.53
Any allergen	13 (32)	11 (39)	0.61

The positive DBPCFC ($n = 28$) can be divided into:

- Eight 1-day challenges (six amongst 1 year olds and two amongst 15 year olds).
- Twenty 1-week challenges (13 amongst 1 year olds, one amongst 2 year olds, three amongst 6 year olds, one amongst 11 year olds and two amongst 15 year olds).

Pooling the DBPCFC together, it can be noted that 53.7% (22/41) of the children who underwent DBPCFC had a positive challenge outcome.

Therefore, from these challenges, it was possible to compare OFC versus DBPCFC in 41 children who underwent 46 challenges. Based on their clinical history, 11 children underwent 1-day challenges and 30 underwent 1-week challenges. In total, 46 oral challenges were completed. Two children had both 1-day and 1-week challenges. One child had two 1-week challenges to different foods. Another child had one 1-day challenge and two 1-week challenges.

Comparison of open and double-blind 1-day food challenges

Eleven children were challenged to a variety of foods including egg, milk, sesame, prawn and kiwi. Eight of these children were sensitized to these foods. Eight challenges (six sensitized), 73%, [95% confidence interval (CI): 39–94%] were confirmed on double-blind testing (Table 2). Of the three children whose FHS was not confirmed, two presented with subjective symptoms. All the children with a negative DBPCFC following a positive OFC were challenged within the allowed 6 weeks, which should rule out the possibility of the child outgrowing the FHS. Only one child had a reaction during the placebo challenge. He developed a rash during the 1-day food challenge, which was attributed to him playing with a soft toy and possible contact to house dust mite.

Comparison of open and double-blind 1-week food challenges

Thirty children underwent a total of 35 challenges to a variety of foods that included milk, egg, wheat, chocolate and additives and two children

were sensitized to the food (one milk and one wheat). Of these 35, 20 (two sensitized) challenges (57%; 95% CI 39–74%) were confirmed on double-blind testing (Table 3). In all cases where the FHS was not confirmed children presented with subjective symptoms. The time between the challenges varied between 5 and 211 days. Two of the children with a negative DBPCFC following a positive OFC were not challenged within the required 6 weeks. They were challenged after 51 days (a 15 year old) and 57 days (1-year-old child). As the challenges were performed within 3 months, it is unlikely that their negative result was due to them outgrowing their FHS.

Only one child with a positive DBPCFC developed a reaction during the placebo challenge. His mother reported restless nights as a problem. Five children with negative challenges experienced symptoms during the placebo challenge, which were: excessive crying, irritability, diarrhoea, rash, constipation/diarrhoea. It was decided to consider these DBPCFCs negative, as the symptoms were either unrelated to the previous history or symptoms during OFC, or the patients experienced the same symptoms during the active and placebo phase. There was no statistically significant difference between the ages of those with a positive or negative DBPCFC (Mann–Whitney $U = 124$, $P = 0.37$).

A positive 1-day OFC was also not more likely to be confirmed by a positive DBPCFC than a positive 1-week OFC (Fisher's exact test, $P = 0.49$).

Results were also compared of the DBPCFC in younger (≤ 2 years) to older (>2 years) children. Combining both the 1-day and 1-week challenges, 20/31 (65%) challenges in younger children and eight of 15 (53%) challenges in older children confirmed FHS on double-blind testing. The difference in confirmation rates was not statistically significant (Fisher's exact $P = 0.53$). Our findings did not change when the data were analysed separately for 1-day and 1-week food challenges.

Patient-related factors during challenges

Factors such as challenge duration, parental acceptance and parental preference should be considered when deciding on which type of challenge to use.

Table 2 Comparing those 1-day open food challenge that also had a positive double-blind placebo-controlled food challenge

Time between open food challenge and double-blind placebo-controlled food challenge (days)											Open food challenge			Double-blind placebo-controlled food challenge		
Number	Age	Sex	Food item	Skin prick test (mm)	Symptom reported				Reactive dose (g)	Total time to reaction (min)	Symptom	Reactive dose (g)	Total time to reaction (min)	Symptom		
1	1	Male	Egg	7.5	Eczema/rash	106			1	15	Angioedema	0.25	15	Urticaria, rash		
2	1	Male	Egg	5.0	Positive skin prick test but not eaten before	15			0.5	6	Urticaria	0.25	5	Rash, urticaria		
3	1	Male	Egg	2	Eczema, urticaria	18			Labial rub	5	Urticaria	0.5	25	Urticaria		
4	1	Female	Egg	7	Eczema/rash	57			1	5	Urticaria	1.5	25	Urticaria		
5	1	Male	Egg	0	Eczema/rash	57			2.5	2 days	Rash, erythema	1	7	Rash, erythema		
6	1	Male	Egg	3.0	Rash	43			18	30	Urticaria	8	90	Urticaria, erythema		
7	15	Female	Milk	9.5	Vomiting, abdominal pain	232			0.5	15	Nausea, vomiting	100	10	Nausea, vomiting		
8	15	Male	Prawn	8.5	Angioedema	12			Labial rub	20	Urticaria	3	45	Tingling of lips		

Table 3 Comparing those 1-week open food challenge that also had a positive 1-week double-blind placebo-controlled food challenge

Time between open food challenge and double-blind placebo-controlled food challenge (days)							Open food challenge			Double-blind placebo-controlled food challenge		
Number	Age	Sex	Food item	Skin prick test (mm)	Symptoms reported		Reactive dose (g mL ⁻¹)	Total time to reaction (days)	Symptom	Reactive dose (mL)	Total time to reaction (days)	Symptom
1	1	Male	Milk	0	Eczema	49	170	1	Eczema, generally unwell	400	1	Eczema, generally unwell
2	1	Male	Milk	0	Rash	39	15	1	Urticaria, rash	12	30 min*	Urticaria, rash
3	1	Male	Milk	0	Eczema, wheeze	65	230	1	Eczema, vomiting	230	2	Eczema
4	1	Male	Milk	0	Vomiting, eczema	21	230	4	Vomiting, eczema, colic	200	4	Eczema
5	1	Male	Milk	1.25	Vomiting	211	230	2	Diarrhoea, excessive crying	480	2	Diarrhoea, excessive crying
6	1	Female	Milk	0	Previous child allergic to milk, therefore not given milk	70	300	1	Excessive crying, eczema, generally unwell	420	1	Excessive crying, eczema, generally unwell
7	1	Female	Milk	0	Eczema	17	120	1	Eczema	250	2	Eczema
8	1	Female	Milk	0	Eczema/rash	11	420	4	Facial rash	250	3	Facial rash
9	1	Female	Milk	0	Vomiting	33	300	2	Diarrhoea, vomiting	250	3	Diarrhoea, vomiting
10	1	Male	Milk	0	Excessive crying	34	Mother unsure	2	Distended abdomen, diarrhoea, vomiting	250	4	Distended abdomen, diarrhoea, vomiting
11	2	Female	Milk	0	Eczema	180	2 portions i.e. 400 mL	2	Eczema, erythema	500	2	Eczema
12	6	Male	Milk	0	Congested nose	79	2 yoghurts i.e. 160 mL	2	Congested nose	200	2	Congested nose
13	6	Female	Milk	0	Diarrhoea	65	250	2	Diarrhoea, vomiting	200	2	Diarrhoea, vomiting
14	11	Female	Milk	0	Nasal congestion	52	2 portions i.e 400 mL	3	Nasal congestion, abdominal pain	200	1	Nasal congestion, abdominal pain, nausea
15	15	Male	Milk	0	Eczema	36	20 g of margarine/butter	3	Eczema	200	4	Eczema

Table 3 (Continued)

Number	Age	Sex	Food item	Skin prick test (mm)	Symptoms reported	Time between open food challenge and double-blind placebo-controlled food challenge (days)	Open food challenge			Double-blind placebo-controlled food challenge		
							Reactive dose (g mL ⁻¹)	Total time to reaction (days)	Symptom	Reactive dose (mL)	Total time to reaction (days)	Symptom
16	1	Male	Egg	0	Eczema, positive SPT but not eaten before	57	2.5 g	1	Eczema	1 g	7 min*	Eczema
17	1	Male	Egg	2	Positive SPT but not eaten before	47	2.5	1	Urticaria	20 g	10 min*	Urticaria
18	1	Male	Wheat	0	Vomiting, eczema/rash	21	3 portions	2	Rash, vomiting, excessive crying	5 portions	3	Rash, vomiting, excessive crying
19	6	Female	Wheat	0	Eczema	26	1 biscuit	2	Eczema	2 biscuits	2	Eczema
20	15	Male	Wheat	5.25	Distended stomach/bloated, abdominal pain	97	4 portions	2	Stomach ache, distended abdomen	2 cupcakes	2	Stomach ache, distended abdomen

*These cases had a positive OFC at home '1-week challenge', based on their history, but due to the immediate reactions observed, the DBPCFC was performed in hospital.

When the challenge duration for food challenges were compared, the DBPCFC took on average twice as long as the OFC. The 1-day OFC took on average 2 h 13 min and the 1-day DBPCFC 4 h 23 min. The 1-week OFC took on average 4 days, compared to 12 days for the 1-week DBPCFC.

Parental acceptance of the challenge outcomes was high. All 11 parents accepted the outcome for the 1-day challenges (both OFC and DBPCFC). With regards to the 1-week challenges, parents accepted the finding of 94% (33/35) challenges. Reasons for not accepting the outcome included parents thinking that illness or other factors could have influenced the challenge results.

Parental preference for the type of food challenges provided the following data. Parents mentioned preference of the 1-day food challenge for 45% (five of 11) OFC and 18% (two of 11) DBPCFC. Using a Binomial test, the difference was not significant ($P = 0.45$). The remainder had no preference. Those who preferred the OFC stated that they preferred the shorter time duration, whilst those who preferred the DBPCFC, felt this type of challenge was more reliable with a smaller chance of being biased.

With regards to the 1-week food challenges four of 35 (11%) of the parents preferred the OFC, 15/35 (43%) preferred the DBPCFC and the remainder had no preference. Using a Binomial test, the difference was significant ($P = 0.0192$). Those who preferred the OFC stated that they considered the OFC easier to perform, that the children found it more acceptable and that the mothers wanted to know what they were giving their children, whilst those who preferred the DBPCFC felt this type of challenge was more reliable with a smaller chance of being biased.

Parents of all the children with negative food challenges were asked to reintroduce the food into the child's diet and confirmation of this reintroduction and the absence of symptoms within 1 month of the challenge was obtained.

Discussion

It is often claimed that there is a consensus regarding the use of OFC and DBPCFC, with very little evidence to support this. This is the first

study comparing the use of OFC and DBPCFC in the diagnosis of FHS in children, looking specifically at the use of these oral food challenges in younger (≤ 2 years) and older (>2 years) children.

Direct comparison of the results of OFC and DBPCFC was possible in 41 children (11 one-day and 35 one-week challenges). In total, 61% of these challenges (73% 1-day and 57% 1-week challenges) had a positive outcome. It is often suggested that OFC may be suitable to diagnose FHS in children under 3 years (Bahna, 1994; Muraro, 2001; Bindslev-Jensen *et al.*, 2004). However, these data did not find evidence to indicate that the younger children are more likely to have a positive OFC confirmed by a DBPCFC than the older children. DBPCFC are often considered to be more labour intensive than OFC and indeed the data did support this as DBPCFC took on average twice as long as OFC. Acceptance of the findings of both OFC and DBPCFC was very high, indicating that parents will follow either introduction or continued avoidance advice following an OFC or a DBPCFC. In terms of oral food challenge preference, parents were more likely to prefer an open 1-day challenge (not significant), but very interestingly preferred a 1-week DBPCFC to a 1-week OFC (difference significant).

The study data seem to suggest that OFC may be suitable for diagnosing immediate (mostly objective) symptoms, whereas a DBPCFC may be needed for the diagnosis of delayed (mostly subjective) symptoms. Interestingly, 75% (six of eight) of the children with a positive 1-day DBPCFC presented with IgE mediated food allergy and 95% (19/20) positive 1-week DBPCFC presented as non-IgE mediated food allergy. No previous study was found in the published literature addressing this issue. A poster presentation by Shinoda *et al.* (2003) looked at the usefulness of single-blind placebo-controlled food challenge (SBPCFC), OFC or *in vitro* tests compared to DBPCFC. These authors reported similar findings that in the case of immediate reactions, it was possible to diagnose food allergies with OFC in the outpatient clinic because of minimal discrepancies between OFC and DBPCFC. SBPCFC was, however, needed for accurate diagnosis in

the cases where only subjective/delayed symptoms were prevalent.

In terms of parental acceptance of food challenge outcome, only one previous study has addressed this issue. Kaila & Isolauri (1997) compared OFC with DBPCFC in a population of children (2–36 months) with suspected cow's milk allergy (although a within case comparison was not made). One interesting finding in that study was that the parents considered the DBPCFC a more definite test than the open challenge. In children who underwent OFC, 20/85 parents disagreed with the challenge outcome (10 with positive and 10 with negative challenges). In contrast with this, in those children who underwent DBPCFC only four of 71 parents disagreed with the challenge outcome (one with a positive and three with negative challenges). They did not unfortunately divide their food challenges into immediate and delayed symptoms as in this study.

One limitation of this study was that it was not possible to establish specificity and sensitivity of the OFCs. To achieve this, it would have been necessary to perform DBPCFC in children who had negative OFC. This additional burden to the young participants was not justified ethically.

In the absence of standardized procedures for performing food challenges, guidelines set out in previous research studies were followed (Bock, 1987; Baehler *et al.*, 1996; Isolauri & Turjanmaa, 1996; Sicherer *et al.*, 2000; Hill *et al.*, 2001), in addition to procedural manuals (Bock *et al.*, 1988; Metcalfe & Sampson, 1990; Bindslev-Jensen *et al.*, 2004) and guidance papers (Niggemann, 2004). Therefore, it is likely that the foods used in this study were sufficiently blinded as it was tested amongst an independent group of children, parents and staff. They did not, however, comply to the standards set by Vlieg-Boerstra *et al.* (2004).

It is also possible that the failure of 28/69 (41%) children with a positive OFC to have a DBPCFC might have lead to confounding and bias in the patients having DBPCFC. However, although only 41 children were involved in this study, it still represents the largest group comparison between OFC and DBPCFC in the literature. A limitation

of the study was the reliance on a parental report for home challenges when the symptoms could not be objectively assessed by the study clinician, i.e. abdominal pain and nausea. However, these data were collected prospectively with emphasis on the need for accurate reporting with all the parents.

One could argue that in the cases where there was a reaction during the placebo phase of the DBPCFC, the challenges should have been repeated. This was not possible as ethical permission to do so was not obtained and it was felt unlikely they would have consented to another challenge having already undergone both OFC and DBPCFC. Procedures in place included reviewing each case, the particular symptoms reported, and discussing the challenge outcome with the parents. These ensured that the challenges were either positive or negative.

Finally, the study could be biased towards 'milder' FHS because many children with severe clinical reactions upon OFC refused a DBPCFC.

In conclusion, this study investigated the reliability of OFC compared to DBPCFC. The observed positive predictive value for the 1-day OFC was higher than that observed for the 1-week OFC, but neither is reliably estimated. The data suggest that OFC may be suitable for diagnosing immediate (IgE mediated), mainly objective symptoms, whereas a DBPCFC may be needed for the diagnosis of delayed (non-IgE mediated), which were mainly subjective symptoms.

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Appendix A: Food challenge protocol for 1-day challenges

Rub the lower mucosa of the lip with cooked egg

If no reaction, proceed to

1-g egg to be eaten

15-min observation

↓

2-g egg to be eaten

15-min observation

↓

5-g egg to be eaten

15-min observation

↓

10-g egg to be eaten

15-min observation

↓

22-g egg to be eaten

2-h observation

↓

1 egg to be eaten (for children <1 year, 1 medium egg; children >1 year, 1 large egg; children >12 years, 1 extra large egg)

2-h observation

Appendix B: Food challenge protocol for 1-week challenges

For the 7-day challenge, you are expected to provide the following amounts of wheat-containing foods to your child

Age of child

6 months–2 years

2–3 portions

2–3 years

4 portions

6 years

4–5 portions

11 and 15 years

4–6 portions

You could give half portions of a larger variety of wheat containing foods as well, i.e.

To provide 3 portions to a 1-year-old child, you could give $6 \times \frac{1}{2}$ portions

The following foods are all equal to 1-wheat portion

1 slice of bread

3 tablespoons of cereal (not rice cereals or corn cereals)

1 Weetabix or shredded wheat

1 biscuit

1 slice of cake

1 tablespoon pasta

Apart from the foods on the above list, it is important to remain on the wheat free diet as discussed with the dietitian. As your child has been avoiding wheat for the past few weeks or months, we would advise you to trial just 1–2 wheat portions on day 1 if your child has not had an initial challenge at the hospital. Could you please complete the food diary provided to you.