

ORAL FOOD CHALLENGES

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ABSTRACT

Food challenges remain the gold standard investigation for the diagnosis of immediate and delayed food-induced allergic reactions and are essential to the practice of allergology. Oral food challenges (OFCs) are generally a safe procedure with the proviso that they should be performed by experienced health care workers and with caution. Severe allergic reactions are extremely rare but should be anticipated.

It has long been accepted that oral food challenge (OFC) tests represent the gold standard investigation for the diagnosis of both immediate and delayed food-induced allergic reactions.^{1,2} It is frustrating therefore that centres which perform OFCs remain oversubscribed and underprovided – a situation which is true in both the UK³ and Southern Africa.

RATIONALE

Food challenges are generally performed to achieve an end goal of dietary expansion through establishing tolerance. Challenges may also be performed to confirm a diagnosis of food allergy. Food challenges may occasionally be performed to test non-typical food allergens or other environmental agents suspected of causing allergic reactions, e.g. toothpaste.

MAKING A DIAGNOSIS OF FOOD ALLERGY

The need for food challenges can be significantly reduced when use is made of well-established diagnostic modalities such as: clinical history, physical examination and allergy testing. In unusual circumstances, a challenge may have the express purpose of causing a reaction in a child. If children have had anaphylaxis to a food but they were too young to remember it, the challenge provides them with an opportunity to better recognise future reactions. In parts of Europe, challenges are performed in known allergic children, in an attempt to establish a 'threshold of reactivity'. The intention is to be better able to advise the child as to whether a strict policy of allergen avoidance is required or not. This approach may prove risky as the threshold of reactivity may fall over time, e.g. if airway inflammation worsens.

When making a diagnosis of food allergy, a rigorous **clinical history** is essential: allergy testing should never be performed in the absence of a clinical history. In young children it is important to realise that food

allergy may masquerade as a food aversion. For example, babies with egg allergy may refuse rather than react to egg, so asking the parents, 'Does your child have egg allergy?' may be misleading, even if the parents answer 'No'. The history should aim to establish if the child can eat an appropriate quantity of the food allergen for their age. For instance, a non-allergic 5-year-old child should be able to tolerate a peanut butter sandwich, a whole egg, a whole slice of bread, or a full glass of milk. Only if these criteria are fulfilled can it be said that the child is tolerant to that food.

The **physical examination** is helpful to determine if the patient appears 'atopic'. The physical examination should assess the anthropometrical status of the patient and exclude signs suggestive of nutritional failure such as iron deficiency and rickets. The respiratory and dermatological examination should also seek to document the presence or absence of concomitant allergic conditions such as asthma and/or eczema. Allergy testing is performed to ensure that the history has correctly identified the cause of the index food reaction. Testing should also establish if the patient is co- or cross-allergic to other food allergens, particularly if the patient has yet to eat these foods or if the foods were previously tasted but 'disliked'. Testing should also seek to identify allergens which may influence the control of co-morbid allergic disorders; for example, pet dander allergy may exacerbate asthma which in itself is a risk factor for more severe food-induced allergic reactions.

There are only two scientifically **validated allergy tests** for the investigation of IgE-mediated food allergy; the skin-prick test (SPT) and specific-IgE testing. The candidate food allergen/s to be tested should be identified on history; if this is not possible, then a 'screening allergen panel' is required. Screening panels should not be open-ended and should include allergens which are relevant to the patient's age, allergic condition and geographical location. In practice, testing for peanut, tree nuts, egg white and cow's milk will account for the majority of childhood food allergies. In older children and adults, fin-fish, shellfish, kiwi and sesame should also be added to the panels (unless an unequivocal history of tolerance to these foods is obtained). Allergy test results may fall within positive or negative predictive ranges. Positive predictive values have been established for the diagnosis of egg, cow's milk, peanuts, and fish allergy (Table I).^{4,5} The use of allergy test predictive values significantly reduces the need for diagnostic dietary investigations. Allergy tests are able to predict the likelihood of future allergic reactions if accidental exposure were to occur; however, this testing cannot predict the severity of these reactions.

Food challenges: There are many variations to the way in which food challenges may be performed. The most appropriate challenge is selected according to clinical history, age of patient and associated factors at the time of the index reaction. Challenge variations include: open, blinded, double-blinded and triple-blinded challenges. While the double-blind placebo-controlled food challenge (DBPCFC) remains the gold standard for the diagnosis of food allergy, it is both time-consuming and labour-intensive and usually only carried out in research studies or when the suspected

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Table I. Positive predictive values for food-specific IgE and skin-prick tests

≥ 95% Specific IgE levels (kU/l) positive predictive values	
Egg	7
Infants ≤ 2yrs	2
Milk	15
Infants ≤ 2yrs	5
Peanut	15
Tree Nuts	15
Fish	20
≥ 95% Skin-prick tests (wheal diameter in mm) positive predictive values	
Milk	8
Infants ≤ 2 yrs	6
Egg	7
Infants ≤ 2yrs	5
Peanut	8
Infants ≤ 2yrs	4
NB Negative allergy tests (specific IgE levels (<0.3 kU/l) and/or skin-prick tests) may still be associated with clinical reactions. Allergy tests should therefore never be interpreted in the absence of a thorough allergy history.	

food has only caused subjective symptoms. For most cases of immediate food allergy, where symptoms can be objectively observed, open food challenges are usually all that is required for the determination of tolerance, which is the most frequent indication for performing oral challenge tests. All negative DBPCFCs should be followed by an open food challenge in order to openly 'prove tolerance' to the patient. A food challenge should not be performed if the individual is unwilling to continue eating the food in the event of a negative result; this is not only a waste of a precious resource but food allergy has been shown to recur in patients who returned a negative oral challenge result but then continued to avoid the allergen.

Methods

There are a multitude of variables involved in food challenges, including: choice of food allergen, vehicle, placebo, route of exposure, total time allowed for challenge, incremental doses and cumulative doses.^{6,7} In essence a supervised food challenge entails no more than exposing the patient to incremental doses of one or more food allergens and then continuing to eat the food on sequential days. The top challenge dose achieved should approximate that of an age-appropriate portion of food; in younger children it may only be possible to achieve a cumulative dose which approximates an age appropriate portion of the food as excessive incremental feeds may upset the child or induce non-specific gastrointestinal symptoms which may prove difficult to interpret. Despite the many websites and texts which detail common recipes and placebos there is no replacement for an experienced on-site paediatric dietician to deal with the many novel scenarios which arise when performing OFCs.⁸ Table II includes examples of milk, egg and peanut challenge protocol from our department.

Consent, and if appropriate assent, should always be obtained prior to the commencement of a food challenge. Patients should always be thoroughly examined prior to the commencement of the challenge to assess general well-being and, in particular, the presence of

rashes and/or wheezing. Failure to do so may result in difficulty in interpreting equivocal symptoms and signs during the challenge: it is not uncommon for children who are closely observed for 6-12 hours to develop non-specific 'blotches'. It should be checked that the patient has stopped all medication, such as antihistamines, which may mask allergic reactions when they occur.

Food challenges are by definition a potentially risky procedure.⁹ As medical professionals are placing the patient at risk, there is a clear responsibility to ensure that this risk is minimised. Safety should therefore be the major priority when performing an OFC. Procedures should be in place to deal with allergic reactions and staff should be well trained in their recognition and emergency management. Age- and weight-appropriate emergency medications that may be required should be scripted prior to commencing the challenge.^{10,11} Careful assessment of patients prior to performing the challenge, including assessment of lung function, helps ensure that if reactions do occur, they are not in the context of pre-existing airway inflammation, which is a major risk factor for severe anaphylaxis. There is current interest in the role of exhaled nitric oxide, in quantifying this risk. Patients who are at higher risk of experiencing a severe reaction should ideally be cannulated prior to commencement of the challenge. High-risk scenarios may include: food-dependent exercise-induced anaphylaxis (FDEIA), exercise-induced anaphylaxis and chubby babies (as access may be difficult if hypovolaemia were to set in), brittle asthmatics and patients with a history of severe anaphylaxis at the time of their index reaction or to other foods. Such high-risk challenges should take place in environments where paediatric intensive care facilities are close at hand. If patients are carefully assessed by experienced staff in a safe environment, then although many allergic reactions occur as a result of challenge, severe reactions are a rare complication.⁹

Determination of OFC outcome

Although supervised OFCs usually result in an unequivocal outcome, indeterminate scenarios are not uncommon, particularly in children. As with all medical conditions – the easiest diagnoses are made at the extremes of clinical presentation, i.e. the child who happily and knowingly eats an age-appropriate portion of a food allergen is tolerant; likewise, the child who eats any amount of a food allergen in a blinded-challenge and who then develops immediate-onset severe symptoms of anaphylaxis is allergic. The more difficult diagnostic scenarios arise when open challenges are performed and when symptoms and signs produced are mild or atypical. Further complicating this scenario is the fact that early-onset symptoms which appear to be of an allergic nature are generally treated early on and therefore do not progress to more obvious findings.

Despite the use of rigorous criteria a great emphasis should always be placed on the experience of nurses and dieticians who frequently perform OFCs. Their gut feelings, particularly when added to the parents' opinion, are often best at detecting early symptoms or those symptoms which are non-specific, e.g. emotional and behavioural changes; whereas older children may report a 'feeling of impending doom', younger children may become 'suddenly quiet' or 'clingy' – a more subtle variation of this is the 'TV sign', where young children who had been entranced by electronic entertainment of some sort suddenly show no interest. More rigorous criteria are required for research scenarios such as the LEAP study (www.leapstudy.co.uk) for which the investigators devised a diagnostic regimen which is currently being validated (Table III). A positive

Table II. Examples of milk, egg and peanut challenge protocols from Allergy Department at Evelina Children's Hospital, London

Allergen	Cow's milk (or soya milk)	Egg	Peanut
Vehicle	Milk can be added to child's normal milk to disguise flavour	Boiled egg	Peanut butter or roasted peanuts
Age	From 6 months	From 3 years	From 5 years
Observations at baseline	TPR/Sats/PEFR	TPR/Sats/PEFR	TPR/Sats/PEFR
Lip/cutaneous challenge	Rub drop of milk on lower lip	Rub egg on lower lip	Rub pinch of ground peanut onto lip
Observations at 20 minutes	TPR/Sats/PEFR	TPR/Sats/PEFR	TPR/Sats/PEFR
Dose 1	5 ml	0.5 g	0.25 g
Observations at 20 minutes	TPR/Sats/PEFR	TPR/Sats/PEFR	TPR/Sats/PEFR
Dose 2	10 ml	2 g	0.5 g
Observations at 20 minutes	TPR/Sats/PEFR	TPR/Sats/PEFR	TPR/Sats/PEFR
Dose 3	20 ml	5 g	2 g
Observations at 20 minutes	TPR/Sats/PEFR	TPR/Sats/PEFR	TPR/Sats/PEFR
Dose 4	40 ml	10 g	4 g
Observations at 20 minutes	TPR/Sats/PEFR	TPR/Sats/PEFR	TPR/Sats/PEFR
Dose 5	100 ml	30 g	10 g
Observations at 20 minutes	TPR/Sats/PEFR	TPR/Sats/PEFR	TPR/Sats/PEFR
Dose 6	200 ml	See below re raw egg	15 g
Observations at 20 minutes	TPR/Sats/PEFR	TPR/Sats/PEFR	TPR/Sats/PEFR
Period of observation. Length depends on whether challenge was positive or negative			
Positive challenge	Avoid all cow's milk (soya) products	Avoid all egg products	Avoid all peanut products
Negative challenge	Introduce cow's milk (soya) into diet	Introduce cooked egg into diet. Allergy to raw egg may still be present and child should avoid scrambled egg, meringue, quiche, fresh mayonnaise as well as cooking lessons involving egg until a raw egg challenge has been completed.	Introduce peanut into diet. Failure to have regular peanut in diet after negative challenge has been associated with apparent resensitisation ²
TPR – temperature, pulse, respirations, Sats – saturations, PEFR – peak expiratory flow rate			

as 'failed' or 'passed' is too emotive for children. The most common reason for an indeterminate challenge result is being unable to get the child to consume adequate quantities of food to demonstrate tolerance. It is perhaps surprising that this does not happen more often given that children are asked to eat a food they have been continuously told to avoid, sometimes for many years. This situation may be avoided in a number of ways. Firstly, children should only be challenged when they are old enough for there to be a realistic expectation that they can eat enough of the allergen. In our department egg challenges are only performed after 2.5 years of age and nut challenges at 5 years. Furthermore, 'creative dietetics' may be required to make the food palatable, especially when the child has become averse to the food as a result of previous bad experiences. For example, egg may be disguised in French toast and nuts in mince pies. It is also worthwhile asking mothers to omit giving the child breakfast, thus encouraging appetite during the challenge.

Scoring of intermediate and delayed-food induced allergic reactions

Food challenges may also be performed to assess for intermediate

food challenge should be done for children who experience one or more major criteria OR two or more minor criteria, an indeterminate result is made if only one minor criterion is present, and a negative food challenge is made in the absence of any criteria. Importantly, all symptoms should be of new onset and not due to ongoing disease. Symptoms must occur no later than 2 hours after the last dose.

OFC outcomes should be described as positive, negative or indeterminate – describing challenge outcomes

and delayed-food-induced allergic reactions such as the induction or exacerbation of underlying eczema. The same is true if oral challenges are performed in the investigation of: colic, reflux or non-IgE-mediated gastrointestinal disorders such as food protein-induced enterocolitis syndrome (FPIES). Delayed food-induced allergic reactions will not be diagnosed using the approach in Table I. It is important therefore that all food challenge patients be followed up for the scoring of delayed symptoms; this is best done by examination but a telephonic follow-up may suffice.

Table III. Scoring of immediate-onset reactions (LEAP Study)

Major criteria

- Confluent erythematous pruritic rash
- Respiratory signs (at least one of the following)
 - wheezing
 - inability to speak
 - stridor
 - dysphonia
 - aphonia
- ≥ 3 urticarial lesions
- ≥ 1 site of angio-oedema
- Hypotension for age not associated with vasovagal episode
- Evidence of severe abdominal pain (such as abnormal stillness or doubling over) that persists for ≥ 3 minutes

Minor criteria

- Vomiting
- Diarrhoea
- Persistent rubbing of nose or eyes that lasts for ≥ 3 minutes
- Persistent rhinorrhoea that lasts for ≥ 7 minutes
- Persistent scratching that lasts for ≥ 3 minutes

Food exercise challenges

Modified exercise-dietary tests such as open food-exercise challenges (OFEC) and double-blind placebo-controlled food-exercise challenge (DBPCFEC) are required for the diagnosis of FDEIA. Persistent rhinorrhoea that lasts for ≥ 3 minutes. During modified food-exercise challenges, patients are asked to eat an age-

appropriate portion of the suspected food allergen prior to exercise. Confounding factors unique to the patient's presentation may be required to reproduce FDEIA, e.g. particular forms of exercise or extreme environments. Therefore, although logistically difficult, a more ideal food-exercise challenge is for the patient to repeat the exercise under similar environmental conditions as that which induced the index reaction.

Declaration of conflict of interest

The authors declare no conflict of interest.

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