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Suspected food allergy in adults: mapping 208 open food challenges with allergy tests and risk stratification

It is estimated that food allergy affects 5% of adult population.[1] We reported that food-induced anaphylaxis accounts for 21% of all anaphylaxis in British adults in a community setting.[2] Food allergens are important confounders in the diagnostic evaluation of spontaneous anaphylaxis and chronic spontaneous urticaria (CSU) in adults. Best practice guidelines recommend careful interpretation of skin prick tests (SPTs) and serum-specific IgE (SSIgE) in conjunction with clinical history in patients with suspected food allergy.[3] The 'gold standard' for diagnosis of food allergy is double-blind placebo-controlled food challenge but this procedure is onerous, resource dependent and not feasible for most allergy services in the UK due to unmet demand.[3 4] Therefore, adult allergy services in the UK employ a supervised open food challenge (SOFC) to confirm or refute the diagnosis of food allergy when allergy tests (SPTs and/or SSIgE) are inconclusive or discordant with clinical history. However, SOFCs are time consuming and require resources and may not be a preferred option due to safety concerns imposed by COVID-19.

Most published data on food challenges involve paediatric population and there is paucity of information regarding safety and outcomes of SOFC in adults, particularly in a 'real-world' clinical practice. We conducted a retrospective chart review of sequential cases of SOFC at the adult allergy service, University Hospitals Birmingham (UHB) NHS Foundation Trust, one of the largest regional services in the UK. This project (06 August 2006 to 13 July 2018) was registered with the governance unit at UHB as a clinical audit. Data including demographics, comorbidity, clinical presentation, SPTs, SSIgE, serum total IgE and SOFC outcomes were extracted from clinical records and entered on an MS Excel spreadsheet by a single trained specialist clinician with appropriate quality assurance measures in place.

Patients were stratified into four groups (table 1) based on a previous classification from our centre involving penicillin allergy delabelling.[5] Index reaction to the suspected food allergen was carefully mapped to Brown's classification and World Allergy Organization diagnostic criteria for anaphylaxis.[6 7]

Briefly, standard patient pathway involved systematic specialist assessment in clinic including allergy testing as per British Society for Allergy and Clinical Immunology (BSACI) guidelines.[3] As per our standard operating procedure, cases considered for SOFC are further reviewed and ratified by ≥2 other specialists. SOFC is usually pursued in the following clinical scenarios:

a. Allergy tests inconclusive (eg, history suggestive of type-1 hypersensitivity but negative or borderline allergy tests).
b. Clinical history is indeterminate, and SPT and/or SSIgE are positive with a high probability of false positivity.
c. Patient with challenging psychosocial issues restricting diet and/or needing reassurance but history not strongly suggestive of food allergy.
d. Patients with a grossly elevated serum total IgE (eg, atopic eczema) with SSIgE likely to be false positive (negative SPT or when SPT is positive or borderline, clinical suspicion of false positivity is high) with a weak/indeterminate history of food allergy.
e. Armed forces referrals/recruits (positive or negative allergy tests) needing definitive confirmation.

Patients were advised to withdraw antihistamines, 5 days prior to SOFC. Drugs with an antihistamine property and betablockers were also temporarily withdrawn based on their half-life. Written informed consent was obtained. Our SOFC protocol involves supervised administration of an average portion of common and rare food allergens that meets the minimum cumulative dose listed in PRACTALL guidelines[8] (table 2). The procedure was carried out either in multiple sequential dose escalations with 30 min between steps or in an accelerated fashion based on clinical risk stratification. Patients were monitored for signs and symptoms of an allergic reaction and observed for 60 min post SOFC.

Patient characteristics and audit data are summarised in tables 3 and 4. Negative predictive value (NPV) for allergy tests was calculated as follows:

NPV=(Number of true negatives)×100÷(number of false negatives+-number of true negatives).

The overall NPV for combined SPTs and SSIgE was 95%; specifically, 93%, 100%, 100% and 96% for groups 1–4, respectively. Group-1 constituted 50% of cases, and a negative SOFC helped exclude type-1 hypersensitivity to suspected allergen and arrive at an

Table 1 Clinical criteria for group classification*

Group-1 Likely IgE-mediated hypersensitivity reaction	Group-2 Likely non IgE-mediated reaction	Group-3† Food allergy unlikely	Group-4 Indeterminate history
One or more of the following symptoms≤2 hours of ingestion: ► Cutaneous symptoms: rash, urticaria, pruritus, flushing ► Angioedema ► Rhinitis or rhinoconjunctivitis ► Bronchospasm (chest tightness, shortness of breath, wheezing, cough, desaturation, cyanosis) ► Haemodynamic instability (presyncope, syncope, loss of consciousness, arrhythmia, seizures, cardiac arrest)	Isolated gastrointestinal symptoms following ingestion ► Abdominal pain ► Nausea ► Vomiting ► Diarrhoea ► Bloating ► Reflux symptoms	► No temporal association between symptoms and allergen exposure ► Subsequent exposure to the same food without reaction ► Symptoms not suggestive of an immune-mediated reaction (eg, headache, blurred vision)	► The temporal association between food ingestion and onset of symptoms is vague/unknown ► Vague history with no details (eg, childhood label of food allergy)

*Adapted from our previous study on penicillin allergy delabelling; Mohamed *et al*.[5]
†These are usually patients who are anxious and/or request exclusion of food allergy and/or request investigations for reassurance (eg, in the context of chronic spontaneous urticaria).

Table 2 Cumulative dose of allergen used for food challenges*

Allergen	Allergen dose
Tree nuts	12–16 whole nuts
Peanuts	12–16 whole nuts
Seafood	6 whole prawns
Wheat	1 bowl (200 g) plain wheat pasta or 1 slice of bread
Milk	1 glass (200 mL) milk
Egg	1 whole boiled egg
Fruits	1 whole piece of fruit (apple, pear, banana), 4 smaller fruits (eg, strawberries)
Vegetables	1 whole vegetable (eg, potato, carrot), 1 serving smaller vegetables (eg, peas)—approximately 150 g
Seeds	Sesame seed—2 sesame snap bars
Meat	1 serving approximately 150 g
Others (rice, mushroom, coffee, wine)	Rice: 1 small serving approximately 100 g; mushroom—8 whole mushrooms; coffee—1 cup (200 mL) coffee; wine—1 small glass (175 mL) wine

*Since 2016, our service implemented cumulative dose regimen for food allergens as per PRACTALL guidelines (Sampson *et al*).[8]
PRACTALL, Practical Allergy.

alternative clinical diagnoses such as CSU, spontaneous anaphylaxis, pollen–food syndrome, vocal cord dysfunction or an alternative food allergy.

Our patient cohort reflects 'real-world' practice in a UK specialist allergy service. Allergens employed for SOFC included: tree nuts (19%), peanut (17%), seafood (18%), wheat (7%), milk (8%), egg (7%), fruits (7%), vegetables (6%), seeds (5%), meat (2%) and others (4%). Ten out of two hundred and eight SOFCs were deemed positive (table 4); 9/10 were classified as mild as per Brown classification.[7] One patient (army recruit) developed mild–moderate anaphylaxis and required epinephrine and was considered 'high risk' (SSIgE positive to Ara h 1/2; army recruit) prior to SOFC. Objective signs were present in 9 of 10 cases.

This report has limitations. First, it involved retrospective analysis of cases reviewed by multiple specialists within the same service. However, all specialists adhered to a common clinical approach aligned to BSACI guidelines.[3] Furthermore, SOFCs were conducted as per protocol and required prior ratification by ≥2 allergy specialists. Our service operates a quality assurance programme to standardise SPTs between operators and laboratory is accredited and participates in National External Quality Assurance Scheme. Second, SOFC outcome in two patients (table 4) were not 'truly positive'. Third, our sample size was moderate but included common and relatively uncommon food allergens and reflects common clinical scenarios in the UK secondary care specialist practice.

Given the high combined NPV for SPTs and SSIgE and relatively mild allergic response to SOFCs in a very small proportion of cases, a specialist-guided home self-challenge (HSC) procedure may be considered as a means to exclude food allergy and reassure patients during the COVID-19 pandemic. HSC might be possible in majority of cases with no evidence of sensitisation to target allergen. This may prove cost-effective, meet patient

Table 3 Study population characteristics

	Group-1	Group-2	Group-3	Group-4	Whole group
Number of patients	96 (50%)	5 (2.6%)	54 (28.1%)	37 (19.3%)	192
Mean age (±SD) years	34.56 (13.5)	39.8 (15.2)	40.9 (17.6)	29.3 (10.7)	35.5 (14.8)
Males/females; N=(%)	M-26 (27%) F-70 (73%)	M-1 (20%) F-4 (80%)	M-13 (24%) F-41 (76%)	M-10 (27%) F27-(73%)	M-50 (26%) F-142 (74%)
Met WAO criteria for anaphylaxis; N=(%)	39 (37.9%)	0 (0%)	2 (3.4%)	2 (4.87%)	43 (20.67%)
Brown classification					
Mild reactions	63 (61.1%)	0 (0%)	6 (10.16%)	4 (9.7%)	73 (35%)
Moderate reactions	33 (32%)	0 (0%)	2 (3.4%)	4 (9.7%)	39 (18.75%)
Severe reactions	7 (6.9%)	0 (0%)	0 (0%)	0 (0%)	7 (3.36%)
Allergy tests (SPTs or SSIgE positive); N=(%)	16/103 (7.9%)	2/5 (40%)	19/59 (32.2%)	16/41 (39%)	53/208 (25.5%)
SPT positive; N=(%)	8/103 (7.8%)	1/5 (20%)	12/59 (20.3%)	13/41 (31.7%)	34/208 (25.4%)
SSIgE positive; N=(%)	10/103 (9.7%)	1/5 (20%)	11/59 (18.6%)	7/41 (17%)	29/208 (14%)
History of asthma	21 (21.8%)	2 (40%)	19 (35.18%)	15 (40.5%)	57 (29.6%)
History of allergic rhinitis	31 (32.3%)	2 (40%)	18 (33.3%)	14 (37.8%)	65 (33.8%)
History of eczema	12 (12.5%)	0 (0%)	11 (20.4%)	8 (21.6%)	31 (16.14%)
Chronic spontaneous urticaria/angioedema	10 (10.4%)	1 (20%)	6 (11.1%)	4 (10.8%)	21 (10.9%)
Cardiovascular comorbidities	3 (3.1%)	0 (0%)	6 (11.11%)	2 (5.4%)	11 (5.7%)
SOFC* positive N=(%)	6/103 (5.8%)	0 (0%)	0 (0%)	4/41 (9.7%)	10/208 (4.8%)
SOFC* negative N=(%)	96/103 (93.2%)	5/5 (100%)	59/59 (100%)	37/41 (92.5%)	197/208 (94.72%)
SOFC* inconclusive N=(%)	1/103 (0.97%)	0 0%	0 0%	0 0%	1 (0.48%)
NPV for allergy tests (SPT and SSIgE combined); %	93%	100%	100%	96%	95%

*Average number of SOFCs per year during audit period=17.
NPV, negative predictive value; SOFC, supervised oral food challenge; SPT, skin prick test; SSIgE, serum-specific IgE; WAO, World Allergy Organization.

Table 4 Description of positive (and inconclusive) supervised open food challenges

Patient	Age (years)	Sex	Allergen	Asthma (Y/N)	SPT (+/–)	SSIgE (+/–)	Hay fever (Y/N)	Index reaction: anaphylaxis* (Y/N)	Index reaction†	SOFC symptoms/signs	Severity of SOFC reaction†	SOFC outcome (positive/ inconclusive)
1	27	M	Rice	N	(–)	(–)	N	Y	2	Ingested two grains of rice; very itchy within few minutes, redness of face and ears. Test abandoned and patient given chlorphenamine. Vital parameters: no significant change	1	Positive. But later had double-blind challenge. See the footnote below
2	45	F	Wheat	N	Not done	(–)	Y	N	1	After ingestion of half bowl; itching of face, urticaria on the neck which was present throughout the challenge, that did not increase in intensity and also lasted during the 2-hour observation. It was queried if symptoms during challenge were due to idiopathic urticaria. Vital parameters: no significant change	1	Positive. See footnote
3	42	F	Peanut	N	(–)	(–)	N	N	1	Mucosal challenge—patient reported burning sensation of mouth, swelling in throat, tongue and lips and shortness of breath. Vital parameters: no significant change	1	positive
4	28	F	Sesame	N	(–)	(–)	Y	Y	3	Developed urticarial lesions over neck, shoulders, arms and back. Vital parameters: no significant change	1	Positive
5	19	F	Cod	N	(–)	(–)	N	N	1	5 min after lip rub with cod, patient developed tingling of lips followed 5 min later by oedema of her bottom lip. Vital parameters: no significant change	1	Positive
6	19	F	Peanut	Y	(+)	(+)	N	N	Not applicable	Tingling in lip, sensation of throat tightness and a feeling 'like something stuck in the throat' with slight difficulty/pain on swallowing. Vital parameters: no significant change	1	Positive
7	55	F	Cardamom	N	(–)	(–)	N	Y	2	Generalised pruritus, itching in eyes with reddened conjunctivae and scattered urticarial lesions on upper torso and headache. Vital parameters: no significant change	1	Positive
8	61	M	Mustard	N	(–)	(–)	N	Y	2	Soon after consuming the third dose (3/4 teaspoon), raised bumps on both of arms and the right arm was itchy. Vital parameters: no significant change	1	Positive
9	21	M	Tree nuts/ mixed nut peanut, almond, hazelnut and Brazil nut peanut allergy was excluded	N	Positive to hazelnut, almond, walnut negative to Brazil nut	Positive SSIgE to Cor a 1	Y	Y	2	Flushing on chest and urticaria on abdomen/trunk. Vital parameters: no significant change	1	Positive
10	19	M	Peanut	N	(+)	Positive SSIgE to Arah –1, Arah –2 and Arah –8	N	N	Not applicable	Cramping abdominal pain, vomiting, generalised urticaria, sensation of throat swelling, voice change and difficulty in breathing. Tachycardia; blood pressure and SpO_2 remained normal. Treated with intramuscular epinephrine, intravenous chlorphenamine and hydrocortisone and oral cetirizine. (Patient was challenged for confirmation of peanut allergy in the context of army recruitment)	2	Positive
11	17	M	Peanut	Y	(+)	(+)	N	1	2	Within 5 min of lip rub, patient became very anxious and developed a sensation of throat tightness. Symptoms settled in about 30 min. Patient remained very anxious and was reluctant to continue. Vital parameters: no significant change	1	Indeterminate

Patient 1 underwent double-blind placebo-controlled challenge later (rice and corn flour). With both flours developed subjective symptoms intermittently. This included tingling lips, generalised itching, tongue 'feeling funny' and not being able to speak and move tongue. Evidence of facial redness on one occasion, evidence of cholinergic urticaria. Challenge concluded as negative.
Patient 2 continues to include wheat for a period of time, develops an itchy/sore rash on her face and relates to a 'build up phenomenon'. The patient eats wheat-containing foods without much problem. Therefore, this is not in keeping with type-1 hypersensitivity.
Patient 9 carried a childhood label.
Patient 10 given patients aspiration to join the armed forces and atypical clinical childhood history, SOFC was conducted cautiously for confirmation regarding allergy status.
*As per World Allergy Organization criteria.
†As per Brown classification (1: mild allergic reaction; 2: mild–moderate anaphylaxis and 3: severe anaphylaxis).
SOFC, supervised open food challenge; SPT, skin prick test; SSIgE, serum specific IgE.

preference and reduce carbon footprint. HSC should, however, be carried out only after a process of careful risk assessment alongside robust clinical governance framework. HSC may not be suitable for patients with an underlying psychiatric or psychological condition, significant cardiorespiratory comorbidity (eg, uncontrolled or severe asthma) and/or logistic barriers. Feasibility testing and local validation may be needed prior to implementation.

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Handling editor Stephen R A Jolles.

Contributors MTK, KS and OM planned the project. KS collated and analysed data and maintained quality assurance. MTK and KS drafted manuscript and all co-authors critically reviewed and approved final version. All authors were involved in clinical management.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests The department received funds from ALK Abello, Thermo Fisher, MEDA, Allergopharma and other pharmaceutical companies for annual PracticAllergy course. MTK received funds from ALK Abello to attend an international conference. MTK has received research grants from MRC CiC, NIHR, FSA and GCRF; none related to this study. CM reports grants from ALK Abello, grants from Allergy Therapeutics, from null, outside the submitted work. APH reports personal fees from ALK Abello, outside the submitted work.

Patient consent for publication Not required.

Ethics approval Registered as an audit with Governance Unit, University Hospitals Birmingham National Health Service (NHS) Foundation Trust.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Sooriyakumar K, Mohamed O, Osborne T, *et al*. *J Clin Pathol* 2021;**74**:133–136.

Received 28 July 2020
Revised 2 September 2020
Accepted 23 September 2020
Published Online First 20 October 2020

J Clin Pathol 2021;**74**:133–136.
doi:10.1136/jclinpath-2020-206994

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