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ORIGINAL ARTICLE

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Delayed symptoms and orthostatic intolerance following peanut challenge

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Abstract

Background: Clinical reactions to Oral Food Challenge (OFC) in peanut-allergic individuals have been well-characterised, but rates and phenotypes of symptom recurrence beyond the first hour after objective symptoms are less well-characterised.

Objective: To evaluate the rate of new-onset symptoms occurring at least 1 h after stopping OFC in peanut-allergic children and adults undergoing peanut-OFC.

Methods: We prospectively collected data relating to adverse events following positive reactions at double-blind, placebo-controlled food challenges (DBPCFC) to peanut in children and adults evaluated for eligibility to participate in two clinical trials (NCT02149719, NCT02665793). The trials included people aged 8 to 45 with primary, IgE-mediated peanut allergy at DBPCFC. The challenge protocol included consumption of a light meal 1 h after reaction.

Results: A total of 121 participants (64 children, 57 adults) had immediate, objective symptoms at DBPCFC, 25 (17 children, 8 adults) with anaphylaxis. Thirty-three (27%) had progression or recurrence of symptoms ≥ 1 h after objective clinical reaction, of whom 8 developed anaphylaxis. In 23 cases, the onset of new symptoms was associated with consumption of a light meal. In eight cases, symptoms were limited to a symptomatic postural fall in blood pressure noted in preparation for discharge, without any other new features of an allergic reaction.

Conclusions & Clinical Relevance: Progressive or new-onset symptoms ≥1 h following initial allergic reaction at OFC are common and can include orthostatic hypotension. Recurrent symptoms may be temporally associated with food consumption.

KEYWORDS
anaphylaxis, delayed reactions, food allergy, oral food challenge, orthostatic intolerance, peanut, postural hypotension

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1 | INTRODUCTION

Oral Food Challenges (OFC) are important as a means to distinguish between asymptomatic IgE-sensitisation and clinical reactivity.[1] Patient selection has an important impact on the likelihood of reaction at OFC. Previously, OFC were used primarily as a mean to confirm tolerance, and thus associated with a lower rate of positive reactions. However, as allergen immunotherapy increasingly becomes an option for the management of food-allergic patients, more OFC are performed where the outcome is much more like to cause a clinical reaction.

Biphasic reactions are defined as the recurrence of symptoms (after initial resolution) without re-exposure to the trigger.[2] Reported rates of biphasic reaction range from <1% to 20% in the community setting.[3] A recent systematic review and meta-analysis reported a rate of 4.7%, with median time of onset to biphasic symptoms of 11 h.[4] However, lower rates have been reported for OFC conducted under medical supervision.[5-7]

Anecdotally, we observed a number of patients following OFC where further symptoms seemed to occur following discharge, triggered by the consumption of food after OFC. We therefore prospectively evaluated the frequency of recurring clinical symptoms following allergic reactions in patients undergoing OFC, and whether these might be associated with consumption of a light meal prior to discharge as part of our OFC protocol.

2 | METHODS

We prospectively monitored peanut-allergic individuals who underwent double-blind, placebo-controlled food challenge (DBPCFC) as part of screening procedures for two studies: a peanut immunotherapy trial (the BOPI study, Clinical Trials.gov identifier NCT02149719) in young people aged 8–17 years, and in peanut-allergic adults (18–45 years) participating in the TRACE Peanut study at the London site (ClinicalTrials.gov Identifier: NCT02665793). Both studies were approved by the NHS Human Research Authority (reference 15/LO/0287 and 15/LO/0286, respectively).

2.1 | Participants

Participants with a diagnosis of peanut allergy were recruited from local allergy clinics, and nationally (through patient support groups and for the TRACE study, though advertisements in local media). Informed written consent was obtained from participants, or in the case of young people under the age of 16 years, their parent/guardian with written assent from the participant. Exclusion criteria are as previously described.[8,9] Individuals with peanut allergy caused by pollen food allergy syndrome were excluded; individuals with previous anaphylaxis were not excluded unless the reaction required admission to intensive care.

2.2 | Procedures

Skin prick testing (SPT) was performed on commercially available extracts of peanut, soya and birch pollen (ALK-Abello) using single-point lancets, according to national guidelines. Histamine (10 mg/ml) was used as a positive control. Total and allergen-specific IgE was measured with the ImmunoCap system (Thermo Fisher).

DBPCFC were conducted according to international PRACTALL consensus criteria.[1] All subjects underwent peanut DBPCFC challenge over two separate days, at least 14 days apart. Children participating in the BOPI study received, on each day, increasing doses every 30 min of peanut protein (Defatted roasted peanut flour (Golden Peanut Company; 12% fat) at the following doses: 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 1000 mg and 3000 mg until stopping criteria were met (as per PRACTALL consensus). The challenge matrix used was a soya-based spread (Wowbutter; Hilton Whole Grain Millers Ltd,) in a small 3 cm sandwich (Kingsmill 50/50 bread); all participants had undergone an open food challenge to the soya matrix at study screening to confirm tolerance to the matrix.[10] Placebo challenges involved the same matrix without the addition of peanut flour.

Adult participants in the TRACE study underwent a similar challenge at the baseline screening challenge, using the following dosing regimen: 3 μg, 30 μg, 300 μg, 3 mg, 30 mg, 100 mg, 300 mg and 1000 mg, until stopping criteria were met.[9] The challenge matrix used defatted roasted peanut flour (Golden Peanut Company; 12% fat) incurred at the appropriate dose into a water-continuous dessert base matrix, adapted from that developed within the EuroPrevall project for DBPCFC and hydrated prior to use.[11]

For both study groups, the order of active/placebo challenge was determined by computer randomization. Members of the study team were blinded as to the challenge assignment, aside from the technician preparing the challenge material. Anaphylaxis was retrospectively assigned according to the World Allergy Organisation (WAO) 2020 clinical criteria.[12] Participants were monitored for at least 2 h following the challenge, and ate a light meal (e.g. sandwich, salad) after the first 60 min of observation. Participants were contacted on the day after discharge to determine whether any delayed symptoms had occurred which would meet the definition for a biphasic reaction. Symptoms of orthostatic intolerance were defined as the occurrence of skin changes (eg pallor) and light-headedness on standing which resolved with supine positioning. Orthostatic hypotension was defined as a symptomatic decrease in systolic blood pressure of >20 mmHg and/or a decrease in diastolic blood pressure >10 mmHg on standing.[13]

2.3 | Statistical analysis

Non-parametric data are presented as medians. Fisher's exact test was performed to evaluate the associations between binary variables. Statistical analyses were conducted using Graphpad Prism (version 8.4.2). All statistical tests were two-tailed, and a p-value <.05 was considered significant.

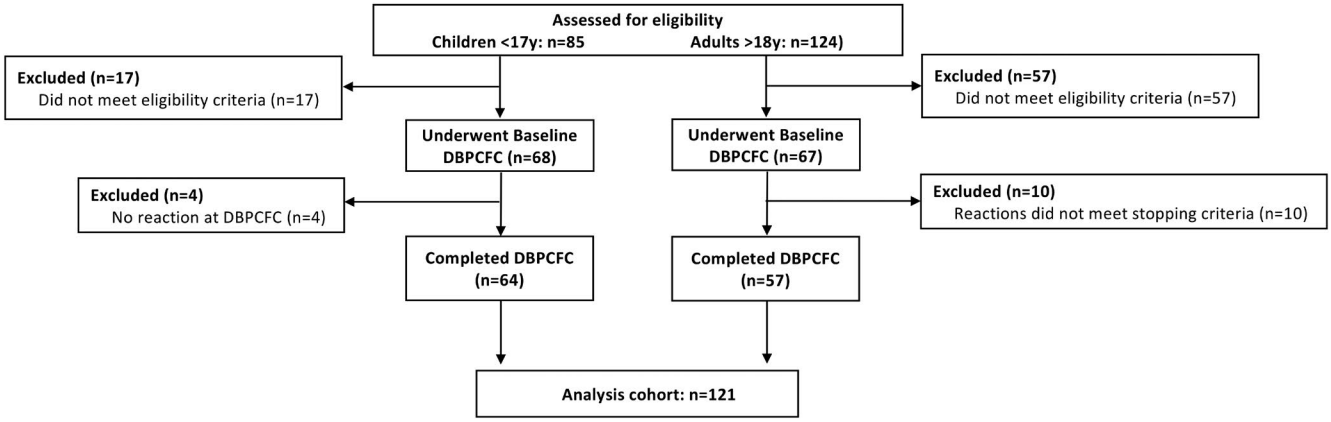


FIGURE 1 CONSORT diagram

3 | RESULTS

One hundred and thirty-five participants (67 adults, 68 children) underwent DBPCFC to peanut (Figure 1), of whom 121 (57 adults, 64 children) met challenge-stopping criteria and thus had confirmed peanut allergy. Baseline characteristics are shown in Table 1.

TABLE 1 Characteristics of the study population

	Children *N* = 64	Adults *N* = 57
Age at enrolment (years)	12 (9, 14)	24 (20, 29)
Sex (Male)	35 (55%)	27 (47%)
Previous anaphylaxis to peanut	28 (44%)	9 (16%)
Asthma	43 (67%)	29 (51%)
Rhinitis	50 (78%)	40 (70%)
Eczema	32 (50%)	27 (47%)
Total IgE kUA/L	504 (287, 1309)	251 (114, 690)
Specific IgE (kUA/L) to		
Peanut	54.1 (5.5, 152)	10.8 (3.6, 26.0)
Ara h 1	6.7 (<0.1, 46.9)	1.7 (<0.1, 11.1)
Ara h 2	24.0 (2.4, 71.4)	5.1 (2.0, 18.0)
Ara h 3	0.7 (<0.1, 14.4)	0.12 (<0.1, 3.0)
Ara h 8	<0.1 (<0.1, 4.0)	0.1 (<0.1, 2.0)
SPT to peanut (mm)	8 (7, 11)	11 (9, 15)
Sensitized to tree nuts	14 (22%)	33 (58%)
Sensitized to non-nut food	24 (38%)	29 (51%)
Cumulative reaction dose (mg peanut protein) at DBPCFC	143 (43,443)	133 (33, 433)
Anaphylaxis as stopping symptom at DBPCFC	17 (27%)	8 (14%)

Note: Data are median (interquartile range).

Thirty-three (27%) participants had progression or recurrence of symptoms beyond an hour following acute objective clinical reaction (due to the presence of symptoms consistent with PRACTALL consensus criteria[1]) (Table 2). Individual patient symptoms are described in the Table S1. The recrudescence of symptoms following reaction was more common in the paediatric cohort (p = .04). In 27 cases, symptoms occurred during or within 30 min of eating a light meal, around 1 h after stopping the challenge. There were 2 biphasic reactions that occurred independent of further consumption of food, one of which met WAO criteria for anaphylaxis. Anaphylaxis as the stopping symptom at challenge was associated with lower risk of symptom recurrence (OR 0.18, 95% CI 0.04 to 0.82, p = .02).

Five participants exhibited symptoms of postural hypotension during the initial reaction, four of whom had a vasovagal episode. A further 8 (6%) had recurrent symptoms consistent with a postural fall in blood pressure when assessed for discharge, without any other allergic symptoms being present. Altogether, 13 (11%) participants had an episode of postural hypotension; in nine cases, objective signs (such as a postural drop in blood pressure or reflex tachycardia at recovery) were present. A representative case history is described in Box 1 and Figure 2. No participant had a medical history of recurrent orthostatic hypotension.

4 | DISCUSSION

In these two cohorts of children and adults with IgE-mediated peanut allergy undergoing DBPCFC, we observed a significant proportion of participants who exhibited symptom progression/recurrence more than 1 h after stopping the challenge. Only 2 subjects experienced a classic biphasic reaction (ie onset of new symptoms following complete resolution of initial phase reaction, without an obvious further trigger), equating to a rate of 1.7%. This is consistent with reported rates in the literature following OFC.[5-7] However, we observed a much larger number of participants who experienced "recurrent symptoms,"—that is, progression or recrudescence of symptoms at least 1 h after stopping the OFC, which was often

TABLE 2 Description of further symptoms experienced following reaction at DBPCFC

	Children	Adults
Number of participants with symptom progression or recurrence more than 1 h after stopping challenge	24/64 (37.5%)	9/57 (16%)
Number with initial anaphylaxis	2	0
Treated with adrenaline	2 of 2	0
Symptom progression following initial improvement	7/64 (11%)	3/57 (5%)
Associated with eating	5 of 7	3
Anaphylaxis	1 of 5	0
Treated with adrenaline	1	n/a
Not associated with eating	2 of 7	0
Anaphylaxis	2 of 2	0
Treated with adrenaline	2	n/a
Symptoms following resolution of reaction	17/64 (27%)	6/57 (11%)
Associated with eating	15 of 17	6 of 6
Anaphylaxis	2 of 15	2
Treated with adrenaline	2	2
"True" biphasic reaction (i.e. symptoms not associated with eating)	2 of 17	0
Anaphylaxis as late-phase reaction	1 of 2	n/a
Treated with adrenaline	1	n/a
Symptoms experienced		
Cutaneous	9/24 (38%)	6/9 (67%)
Gastrointestinal	13/24 (54%)	3/9 (33%)
Lower respiratory (anaphylaxis)	6/24 (25%)	2/9 (22%)
Postural hypotension	7/64 (11%)	6/57 (11%)
Detected at <1 h following stopping of FC	2	3
Anaphylaxis as initial reaction	0	0
Detected at >1 h following stopping of FC	5	3
Anaphylaxis as initial reaction	0	0

temporally-associated with consumption of a light meal. Eight subjects had symptoms of postural hypotension after ≥1 h, without any other evidence of allergic symptoms or haemodynamic compromise (ie blood pressure and heart rate were within normal limits at rest, semi-recumbent positioning). To our knowledge, this is the first report to describe the occurrence of orthostatic intolerance in patients experiencing acute allergic reactions, which do not meet the clinical criteria for anaphylaxis.

Anaphylactic shock occurs as a result of a profound loss of venous tone and fluid extravasation, causing a mix of hypovolemic and distributive shock, which results in a reduced cardiac output.[14,15] There are a number of reports in the literature of fatal outcomes due to anaphylaxis, where the apparent precipitant was a change in posture (for example, from the supine to standing position);[16,17] it was proposed that the change in posture might result in an inability to compensate for reduced venous return to the heart, in the context of peripheral vasodilatation.[16] We recently demonstrated that significant changes in cardiovascular function, including decreased stroke volume, are common and occur during even non-anaphylaxis reactions in adults undergoing peanut-induced allergic reactions.[17] Of note, we observed evidence of cardiovascular compensation—in particular, an increase in heart rate which maintained cardiac output, despite the fall in stroke volume; this mild tachycardic response was evident at rest, with patients supine, indicative of a reduction of circulating blood volume.[18] In contrast, in our participants with features of an orthostatic drop in blood pressure, we did not observe any obvious tachycardia at rest (with patients semi-recumbent), as shown in the exemplar case described in Box 1 and Figure 2. Thus, while the fall in stroke volume previously described during allergic reactions to peanut may be relevant,[18] we have no direct evidence for this and other mechanisms may be relevant. For example, the allergic reaction may have caused a disturbance in normal postural circulatory reflexes, akin to the blunting of postural reflexes which is often observed during anaesthesia.[19] Orthostatic hypotension is associated with a decrease in heart rate variability,[20,21] and previous studies in both children and adults have reported reduced heart rate variability following food-induced allergic reactions, independent of severity.[18,22] Thus, these episodes could potentially represent a more mild form of the postural decompensation

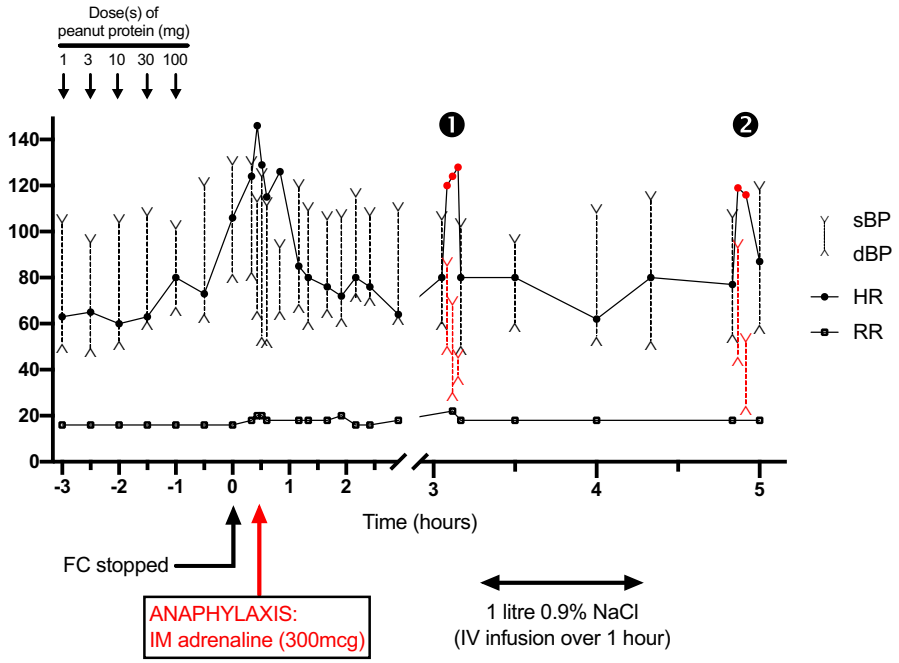


FIGURE 2 Cardiac observations for representative case of orthostatic hypotension following challenge (see Box 1. HR, heart rate (per min); sBP and dBP, systolic and diastolic bloods pressure (mmHg); RR, respiratory rate (per min). Two episodes of significant orthostatic hypotension were noted with no evidence of haemodynamic instability prior. Measurements plotted in red were taken while patient standing rather than supine/semi-recumbent

seen in some cases of fatal anaphylaxis. The mechanism is likely to differ from typical hypotensive anaphylaxis, because of the absence of a clinically relevant tachycardia when supine and in the delayed-onset cases, an absence of other concurrent signs or symptoms of acute allergic reaction. We, therefore, propose that isolated orthostatic intolerance following an acute allergic reaction does not imply anaphylaxis *per se*. In support of this, we did not identify any factors (such as anaphylaxis) associated with the occurrence of orthostatic intolerance, although this observational report was not powered to assess risk factors for this.

Blumchen et al reported that 8% of young people undergoing OFC to peanut exhibited symptom progression from initial objective symptoms (which met stopping criteria for challenge) to more severe ones later,[23] a similar rate to that observed in the two cohorts studied here. However, in our study, reaction progression was usually associated with food consumption. This suggests that some biphasic reactions may in fact be due to further allergen absorption triggered by postprandial gut motility, rather than representing a true "immunologically biphasic" reaction. There is evidence from animal models of food allergy that acute allergic reactions impact upon gastric motility,[24,25] and this is supported by anecdotal data from human anaphylaxis.[26] Thus, our protocol, in which participants consumed a light meal following OFC, may have resulted in an overestimation of the true rate of further symptoms after OFC. The absence of a control group (who did not eat a light meal) is a limitation of this study, but the high rate of temporal association between symptom recrudescence and eating is suggestive of a link in at least a proportion of participants. The challenge matrices used in the children and adult study both incorporated peanut as defatted peanut flour, but were otherwise different formulations—we did not identify any impact of this on the occurrence of symptoms. The impact of other food matrices (or absence of a food matrix, as is common in "open" unblinded food challenges) needs to be assessed.

BOX

A 14-year-old boy underwent double-blind, placebo-controlled challenge to peanut. He tolerated the first four challenge doses without symptoms but then reacted to the 5th dose (100 mg peanut protein) with mild abdominal pain, generalised urticaria and erythema 30 min later. He had a large (500 ml) vomit 20 mins later, with progression of urticaria and the onset of a soft biphasic wheeze. Adrenaline 300 mcg was self-administered using an autoinjector, which resulted in rapid symptom resolution. He subsequently ate lunch an hour later after reaction and then discharged after a total of 2 h observation, completely asymptomatic.

On exiting the hospital, he felt the urgent need to pass a bowel motion. Unfortunately, the toilet was occupied and while waiting, he felt dizzy and fainted. Help was summonsed and on arrival, he was sitting on the toilet, conscious and communicating normally. There was no evidence of haemodynamic compromise. Blood pressure was 106/59 mmHg (semi-recumbent) with a heart rate of 80; however, on standing, he had marked orthostatic hypotension (BP 69/28, HR 120 after 4 min, decreasing further to BP 46/35 after a further minute at which time he was symptomatic (dizzy). On lying supine, symptoms fully resolved with blood pressure normalised (BP 103/48, see Figure 2).

Finally, while the participants in this study may not be completely representative of peanut-allergic consumers in the wider peanut-allergic population, it would seem prudent that patients who have

had a systemic allergic reaction are assessed for symptoms of orthostatic intolerance (including the measurement of standing blood pressure, if indicated) prior to discharge from a medical facility.

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CONFLICT OF INTERESTS

PJT reports grants from JM Charitable Foundation and End Allergies Together, outside the submitted work; personal fees from UK Food Standards Agency, DBV Technologies, Aimmune Therapeutics, Allergenis and ILSI Europe outside the submitted work. MRG is now employed by Laboratorios Leti, this occurred following data lock and completion of study analyses. SRD reports grants from the Immune Tolerance Network, National Institute of Allergy and Infectious Diseases, ALK-Abelló, Regeneron, and Biotech Tools outside the submitted work; personal fees from Anergis, Circassia, Biomay, Merck, Allergy Therapeutics, Med Update GmbH, and Food Standards Agency. RJB reports personal fees from Prota Therapeutics, DBV Technologies, Cochrane Collaboration, John Wiley & Sons on behalf of Clinical and Experimental Allergy, personal fees from giving expert testimony, outside the submitted work. The other authors do not report any conflicts of interest.

DATA AVAILABILITY STATEMENT

Requests for data can be made to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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