

Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: proposal for good practice

P. W. Ewan and A. T. Clark

Department of Allergy, Addenbrookes NHS Trust, University of Cambridge Clinical School, Cambridge, UK

Summary

Background There are few data on the long-term management of children with peanut/nut allergy. Advice is variable and often inadequate; further reactions are common. There is no consensus on the criteria for prescription of rescue medication, particularly adrenaline.

Method A longitudinal prospective and case-control study in a tertiary allergy clinic. Patients/parents/school staff of 747 children with confirmed peanut or tree nut allergy received detailed verbal and written advice on nut avoidance, training in recognition and (self-) treatment of reactions and a written treatment plan. The severity of nut allergy was graded (mild–severe) and emergency medication was allocated according to our criteria: all received oral antihistamines, injected adrenaline (EpiPen) was given to those with reactions with airway narrowing, milder reactions to low-dose exposure or concomitant asthma. At annual follow-up over 25 906 patient-months (median: 39 months) retraining was given and details of further reactions (frequency, severity and treatment) were obtained. Criteria for allocation of EpiPen were evaluated.

Results The worst reaction pre-enrolment was mild in 64% and moderate/severe in 36% (airway narrowing). Of 615 subjects followed up, 21% had a further reaction (eightfold reduction in frequency), mostly mild. There was a 60-fold reduction in the frequency of severe reactions. Of those with a moderate–severe initial reaction, 99.5% had no or a less severe follow-up reaction. No child with a mild or severe index reaction had a severe follow-up reaction. Only 1/615 (0.2%) had a severe follow-up reaction and only 2/615 (0.3%) used adrenaline, both successfully and had it available according to our criteria. Of mild–moderate reactions, 77% required oral antihistamines alone and 15% no treatment. Children who had follow-up reactions had more frequent and severe reactions pre-enrolment.

Conclusion The management plan greatly reduced the frequency and severity of further reactions and was successful for all children. Our criteria for selective prescription of EpiPen in the context of this management plan were appropriate. This is the first study to provide evidence on which to inform practice.

Key words Food, nut, allergy, Management plan, anaphylaxis

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Introduction

Peanut allergy is the most common cause of severe and fatal food-allergic reactions [1–3]. The prevalence of peanut allergy has increased over the past decade, and it now affects 1.5% of children [4–6], approximately half of whom also report allergy to tree nuts [7, 8]. Management of nut allergy is poor, variable and not evidence based; patients are often unable to obtain advice (this applies to most fatal reactions), or adrenaline for self-injection is given to patients with trivial allergy [9]. There is a lack of data on management strategies in nut-allergic

children to prevent or minimize further reactions. Such data are needed to inform general practitioners, paediatricians, respiratory physicians, allergists, school nurses and teachers who encounter such patients frequently. Particular problems in management are which children are at risk of severe reactions, and who should carry pre-loaded adrenaline syringes.

Based on our knowledge of the clinical features of nut allergy [10, 11], we devised a management plan in 1993, consisting of detailed advice on avoidance of nuts and the provision of appropriate rescue medication based on defined criteria to allow early initiation of treatment of reactions by parents or school staff [12, 13]. Reinforcement and retraining were given at annual follow-up. We prospectively evaluated this management plan in nut-allergic children by establishing the frequency of subsequent reactions, their severity and treatment and risk factors for repeated or severe reactions.

Correspondence: Dr Andrew T. Clark, Department of Allergy, Addenbrookes NHS Trust, University of Cambridge Clinical School, Cambridge CB2 2QQ, UK.

E-mail: atclark@doctors.org.uk

Method

Longitudinal study

This was a prospective study of unselected children attending an allergy clinic, mostly referred by their general practitioner. Data were collected at each child's first allergy clinic appointment (enrolment) by experienced allergists, from 747 children with a history of typical features of an acute allergic reaction (Table 1) occurring within an hour of ingestion of a food known to contain a nut, and evidence of nut-specific IgE by positive skin prick test (SPT) (≥ 3 mm). Details were taken of all reactions, and the index reaction (the most severe reaction to date) was graded 1–5 for severity (Table 1). All families were enrolled in our management plan for nut allergy. Where 'nut' is mentioned in this paper, it is taken to mean 'peanut and nut' unless otherwise stated.

Management plan [12, 13]

Avoidance advice Families were counselled in great detail about nut avoidance advice using written and verbal information. This advice focused on principles of understanding labelling, eating in restaurants or on school trips and travelling abroad.

Emergency treatment A written treatment plan was provided with the aim of early recognition and administration of appropriate medication for future reactions. An assessment of the severity of each child's allergy was made, based on the severity of the worst ever reaction to date and the amount of nut that caused it. This assessment enabled us to select emergency medication as follows:

All children were given oral antihistamines. It was our policy to provide an injectable adrenaline device, in addition, for children:

- who had experienced a reaction with any airway involvement, even if minor (grades 4–5),
- who had only ever ingested or been exposed to trace amounts of nut and had a mild reaction. Their sensitivity (and hence future risk) could potentially be greater than that inferred by the nature of the reaction. For example, a child whose only reaction was with urticaria of the head and neck after ingesting a trace of peanut may go on to have a severe reaction if they ingest a large amount of peanut) and
- if there was ongoing asthma (irrespective of the severity of the reaction).

Table 1. Symptoms indicating clinical severity grades of index and follow-up reactions

Grade	Clinical features
Grade 1 (mild)	Localized cutaneous erythema/urticaria/angio-oedema/oral pruritus
Grade 2 (mild)	Generalized erythema/urticaria/angio-oedema
Grade 3 (mild)	At least grade 1 or 2 plus gastrointestinal symptoms or rhino conjunctivitis
Grade 4 (moderate)	Mild laryngeal oedema (voice change, tightening of throat)/mild asthma
Grade 5 (severe)	Pronounced dyspnoea/hypotensive symptoms (light-headedness/collapse/loss of consciousness).

EpiPen was selected (the only licenced product at the start of this study), and it was considered important to use only one device in schools in our region. A written treatment plan was given, describing in lay terms what constitutes mild, moderate and severe reactions and the actions to be taken and medications to be used (IM adrenaline for severe breathlessness and/or light-headedness or collapse). Drugs and doses were individualized for all patients (EpiPen Jr for weight 10 kg, changing to EpiPen when the child's weight was 25–30 kg, which approximates to an age range of 12 months–7 years for EpiPen Jr). A single dose of adrenaline (EpiPen) was provided in each case. Inhaled adrenaline was provided in the early part of the study for mild laryngeal oedema, but was less available after its withdrawal in 1997. A school or nursery visit was made by specially trained paediatric community nurses who explained the prevention, recognition and management of further reactions; thus, this was not restricted to EpiPen training alone [12]. Excellent control of asthma and the accurate diagnosis and effective treatment of other allergies were regarded as important throughout.

Follow-up After an initial early follow-up, annual assessments were arranged, and details of any reaction (known as 'follow-up reactions' graded for severity, Table 1), amount of nut causing it (as previously defined) [13], treatment given and outcome were all recorded prospectively. Skin testing was repeated, as before. Re-education about nut avoidance was provided and the treatment plan was reviewed and rehearsed, including EpiPen retraining. Asthma control was checked and other allergies were treated. Schools were visited annually by the community-based team for retraining.

Case-control study

To identify children at risk of having follow-up reactions, we selected all children from the longitudinal study who had a follow-up reaction (cases), and in a separate analysis, matched them each to a single child who was also followed up, but did not have any further reactions (controls). They were matched for age, sex, age at onset of allergy, age at enrolment and duration of follow-up in the study. Comparisons were made for the frequency and the severity of reactions pre-enrolment, amount and type of nut causing the index reaction and prevalence of other allergies.

Results

Longitudinal study

Participants Six hundred and fifteen children were followed up prospectively. The mean age at presentation was 6.3 years (± 0.3 SEM), range 10 months–15 years. There were 250 (41%) under 5 years, 238 (39%) 5–9 years and 127 (20%) ≥ 10 years. The sex ratio was 1 : 1.4 (M : F). Asthma was present in 338/615 (55%). Of 615 children, 441 (72%) were allergic to peanut, 96 (16%) to Brazil, 67 (11%) to almond, 81 (13%) to hazelnut and 54 (9%) to walnut. One hundred and thirty-two of 747 (18%) children were not followed up. They had similar age at presentation, sex, severity of index reaction and nut type as the group who were followed up (data not shown). The mean SPT weal diameter to the nut type that caused the

index reaction (in 706 children where full information was available) was 8.4 mm (95% confidence interval (CI) 7.8–8.9 mm) for peanut and 7.9 mm (95% CI 7.4–8.5 mm) for tree nuts. For those whose index reaction was to peanut, 61% had peanut SPT diameter of 8 mm or greater.

Index reactions (worst ever before enrolment) The median time between the first ever reaction and time of enrolment was 2 years (25% and 75% quartiles 1.0 and 4.6 years, respectively). During this period, 395/615 (64%) had a mild index reaction, 171 (28%) had a reaction involving airway narrowing and 49 (8%) had a reaction with severe dyspnoea and/or collapse.

Follow-up reactions The median duration of follow-up after enrolment was 3.3 years (total 2030 patient years). One hundred and thirty-one of 615 (21%) had a further reaction during the follow-up period. The sex distribution was 1:1.2 M:F (1.5:1 in those who did not suffer a follow-up reaction). The majority, 97 (74%) had only one reaction, 19 (15%) had two, 15 (11%) had three or more. Children who had a follow-up reaction were older at enrolment (median age 7 vs. 5 years – Fig. 1). In those peanut-allergic children followed up but who did not have a further reaction, 7% had a peanut SPT diameter of 0–2 mm.

Frequency of reactions before and after enrolment The frequency of further reactions for the whole cohort was reduced eightfold from 0.55 reactions/person year (95% CI 0.52–0.58) pre-enrolment to 0.07 reactions/person year (95% CI 0.06–0.08) at follow-up post-enrolment.

Frequency of severe reactions before and after enrolment There was a 60-fold reduction in the frequency of severe (grade 5) reactions after enrolment (3×10^{-2} /patient-year pre-enrolment to 5×10^{-4} /patient year post-enrolment) and a ninefold reduction in the frequency of moderate (grade 4) reactions (9×10^{-2} /patients year to 1×10^{-2} /patient-year post-enrolment).

Severity of follow-up reactions The majority of follow-up reactions were mild (104/131; 79%). Of 395 children with a

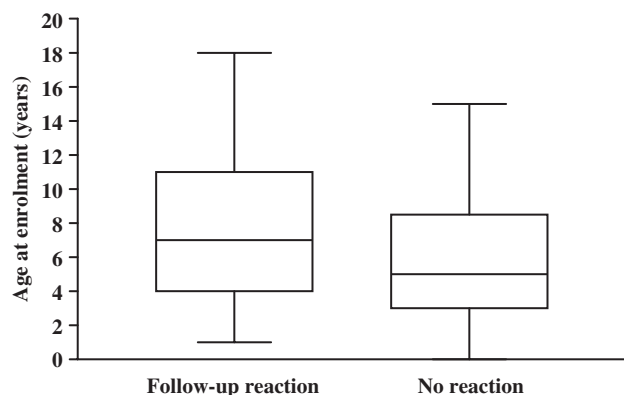


Fig. 1. Age at enrolment in those who later had a follow-up reaction compared with the age of those who did not ($n = 131$; boxes represent 25th–75th percentiles with medians: 7 vs. 5 years; $P = 0.0046$ Mann–Whitney U test; whiskers indicate minimum and maximum values).

mild index reaction (grades 1–3), only 77 had a follow-up reaction, 18% (17/77) of whom were moderately severe (grade 4). Therefore, of the mild index group, 95.7% (381/395) either had no follow-up reaction or a mild follow-up reaction. No child with a mild index reaction went on to have a severe follow-up reaction. Of 220 with a moderate–severe index reaction (i.e. had at least some degree of airway narrowing; grades 4–5), only 54 had a follow-up reaction, of whom 53 (98%) had a less severe follow-up reaction and only one (2%) had a more severe reaction (Fig. 2). Therefore, of the moderate–severe index group, 99.5% had either no follow-up reaction or a less severe one. No one with a severe initial reaction ($n = 49$) had a further severe reaction.

Children who had moderate–severe follow-up reactions were older than those with mild reactions (Fig. 3).

Treatment of follow-up reactions All children had oral chlorpheniramine, and 430/581 (where information was available) (74%) also had injectable adrenaline (EpiPen) available. Of 430 with EpiPen, only 39 (9%) had been prescribed this (usually before enrolment) where it was not indicated by our criteria. Of these, 7/39 had a follow-up reaction, treated successfully with oral antihistamines alone.

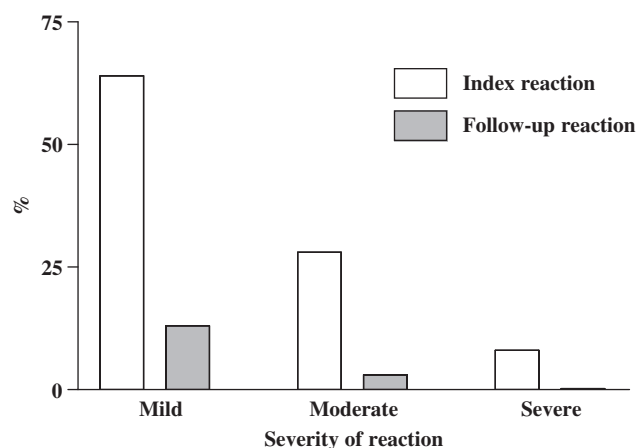


Fig. 2. Relative severity of index and follow-up reactions in 747 children ($\chi^2 = 14.6$, $P < 0.0007$).

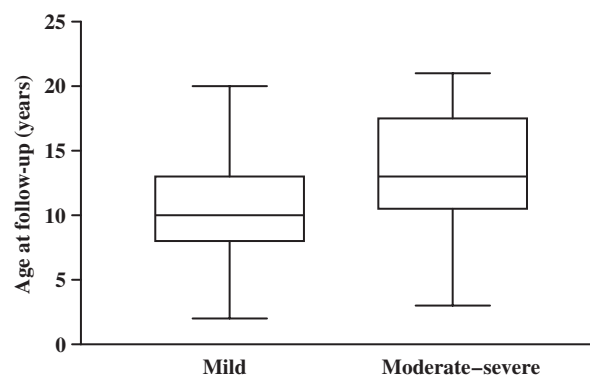


Fig. 3. Age at follow-up in children who had a mild follow-up reaction, compared with those who had a moderate–severe reaction; $n = 131$, mean 10.5 years (95% confidence interval (CI) 9.6–11.2 years) vs. 13.2 years (95% CI 11.4–15 years), $P = 0.0024$ unpaired t -test.

Table 2. Medication administered for treatment of follow-up reactions in 125 children

Treatment	Severity of follow-up reaction (n)		
	Mild	Moderate	Severe
No treatment	17	2	0
Oral chlorpheniramine alone	82	14	0
Inhaled adrenaline*	5	1	0
Epipen*	0	1	1
Hospital IM steroid/antihistamine*	0	2	0
Hospital IM adrenaline*	0	0	0

*Also received oral chlorpheniramine.

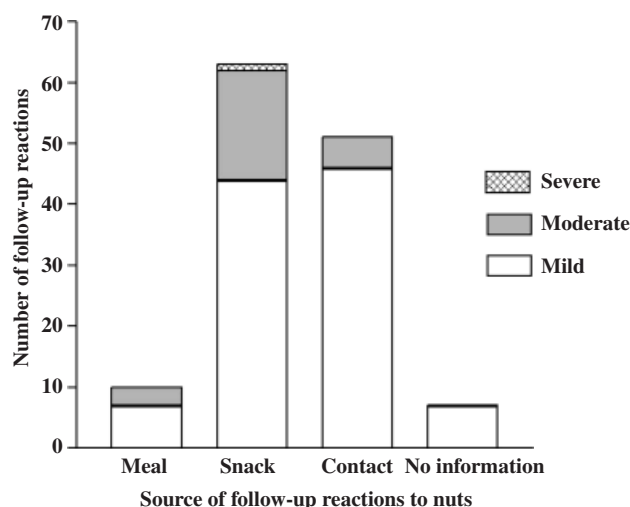
Of mild-moderate reactions (grades 1-4), 77% required oral antihistamines alone and 15% no treatment (Table 2). IM adrenaline was not used for treatment of any mild reactions. All 27 children who had a moderate-severe follow-up reaction (i.e. with symptoms of airway narrowing, grades 4-5) had been prescribed EpiPen. Only 2/615 patients (0.3%) required adrenaline; both had it according to our criteria and it was used appropriately and successfully: once for a moderate reaction in a child with laryngeal oedema and once for a child aged 10 years who had a severe follow-up reaction (grade 5). His index reaction was laryngeal oedema (grade 4) after ingestion of small amounts of hazelnut. During follow-up, he ate a hazelnut chocolate and developed laryngeal oedema, and there was a slight improvement after oral chlorpheniramine but he became drowsy and hypotensive; EpiPen was administered once and he recovered. No child received more than one dose of adrenaline (EpiPen).

Amount and source of nut causing follow-up reactions

Compared with all index reactions, a greater proportion of all follow-up reactions were caused by contact with nut traces (40% vs. 14%), and a smaller proportion were caused by ingestion of large amounts of nut (52% vs. 79%). Seventy-two percent of moderate-severe reactions were caused by ingestion of large amounts of nut. Snacks caused the majority of reactions, including the most severe ones (Fig. 4). Symptoms of airway narrowing were present in 29% (18/63) of reactions to snacks and 30% (3/10) of reactions during meals. Accidental contact caused 39% (51/131) of reactions.

Case-control study

One hundred and twelve subjects who had a follow-up reaction (cases) were compared with 112 subjects followed up who did not have a further reaction (controls) and matched for sex, age at onset, age at enrolment and duration of follow-up. We were unable to find a match for 19 cases (including four with moderate follow-up reactions), who were excluded from further analysis. There was no difference between the groups for asthma, eczema or rhinitis prevalence, the number of nuts sensitized to or the type and amount of nut ingested during the index reaction (Table 3). However, cases had $1.5 \times$ more reactions pre-enrolment than controls: 0.74 reactions/person-year (95% CI 0.70-0.77) vs. 0.49 (95% CI 0.43-0.55). Index reactions of those who had a follow-up reaction later were more likely to involve airway narrowing

**Fig. 4.** Source of nut causing follow-up reaction in 131 children, showing distribution of mild, moderate and severe reactions: a meal (e.g. a curry), a snack (e.g. chocolate bar) or contact (e.g. being kissed by someone who has eaten peanuts).**Table 3.** Clinical characteristics of cases and matched controls pre-enrolment

Characteristic	Cases (n = 112)	Controls (n = 112)
Median age at onset (matched) (years)	2	2
Median age at enrolment (matched) (years)	5	6
Asthma	65 (57)**	55 (40)**
Asthma well controlled (%)	97	94
Eczema	73 (65)	76 (67)
Rhinitis	40 (35)	37 (33)
Sensitized to one nut type only	32 (29)*	43 (39)*
Peanut caused index reaction	76 (67)	81 (72)
Trace amount caused Index reaction	16 (15)	16 (15)

Unless specified otherwise, figures represent numbers of subjects followed by percentages in parentheses.

* P -value > 0.05.

** $P = 0.33$, χ^2 test.

Table 4. Severity of index reaction suffered by cases and controls

Severity of index reaction (Table 1)	Cases (n = 112)	Controls (n = 112)
Mild	66 (59)	81 (72)
Moderate-severe	46 (41)	31 (28)

Figures represent numbers of subjects with percentages in parentheses. $P = 0.03$, χ^2 test.

and life-threatening features than those who did not have a follow-up reaction (Table 4). Asthma control was excellent, showing no difference between groups.

Discussion

There is no consensus on the management of children with nut allergy. Advice given to families is variable and often ill-informed, and further reactions are common. This is the first

study to provide evidence on which to inform practice. There was an eightfold reduction in reaction frequency after enrolment in the management plan, and most reactions were mild (79%) and responded to oral antihistamines. Only 1/615 (0.2%) had a severe reaction, and a single dose of adrenaline was effective. No child with a mild index reaction had a severe follow-up reaction. Of those with more severe index reaction (any airway involvement moderate–severe group; $n = 220$), 99.5% had either no follow-up reaction or a less severe one. By case matching, we identified that children who had follow-up reactions had suffered more frequent and severe reactions pre-referral. Children who had moderate–severe follow-up reactions were older. Snacks and accidental contact were responsible for the majority of reactions. Emergency medication selected on the basis of severity/asthma status criteria that we had developed was appropriate, and all who required adrenaline had an autoinjector available.

A limitation is that we did not use the double-blind placebo-controlled food challenge (DBPCFC) to confirm diagnosis, that causes a small risk of inclusion of non-allergic children, which may cause overestimation of the intervention effect. We reduced the likelihood of this by using (i) a large sample, (ii) those with a clear-cut history of an allergic reaction after definite nut ingestion, (iii) assessed by experts, (iv) after a short interval from last reaction and (v) confirmed by SPT. It would not have been feasible to perform food challenges in 747 children for five nut types each, and these would still have had to be repeated after a follow-up reaction occurred. The mean SPT weal diameter to the index nut type was large (8.4 mm) and above the diagnostic cut-off suggested by Sporik et al., where negative reactions on food challenge or clinical tolerance are rare (> 8 mm) [14, 15]. Follow-up skin test data showed that for peanut, skin tests became negative in 7%, suggesting that they may have outgrown their allergy during the follow-up period, causing an overestimation of the intervention effect.

There is debate as to whether children who have previously had only mild food-allergic reactions (grades 1–3 and no asthma) should have injectable adrenaline available or whether it should be reserved for high-risk groups (grades 4–5 and/or asthma). The disadvantages of the former are that it masks those children at highest risk in schools and nurseries, it creates an extra burden for carers/teachers who require regular training and it allows families/general practitioners to feel that with injectable adrenaline available, they have a 'safety net', which may engender relaxation of avoidance measures/advice. Arguments in favour of universal provision of injectable adrenaline include the fear that children who have had mild reactions may develop more severe reactions over time and that asthma may develop after initial assessment, increasing the chance of a more severe food reaction.

A difficult aspect of the study was devising criteria for provision of injectable adrenaline. It would not have been ethical or acceptable to parents to use random allocation and placebos. Considerations were: after enrolment in a management plan incorporating repeated avoidance advice, children with mild initial reactions do not have severe follow-up reactions [13] and the impression that poor asthma control increases the severity of food-allergic reactions [2, 16, 17]. Our policy, therefore, was not to provide injectable adrenaline for

children who only suffered mild reactions, unless there was ongoing asthma, or if only traces had ever been ingested (and therefore the sensitivity was unknown). All patients, whether carrying EpiPen or not, were asked to carry antihistamines. The observational design used here is the most effective and ethical way to test these criteria. There was only one severe follow-up reaction and this was treated successfully using the allocated emergency medication (EpiPen) without recourse to hospital treatment. By following up children at regular intervals, we were able to detect the development of asthma and change the emergency treatment plan as required.

Anxiety about potential adverse effects of injectable adrenaline is based on reports of fatalities occurring where adrenaline was given at an incorrect dose (10 times too high) by an inappropriate route (intravenous) [16]. Pre-loaded syringes deliver a fixed dose intramuscularly. In the present study, two children received EpiPen injections (appropriately administered—one by a teacher) without any reported adverse effects.

Hence, this study also provides reassurance about the safety and efficacy of IM adrenaline. We believe that antihistamines are an important early treatment and this study supports this; most mild reactions and 67% (14/21) of moderate reactions (involving mild airway narrowing) resolved after treatment with antihistamines alone.

We compared the frequency of reactions before and after enrolment within the cohort. An estimate of reaction frequency can also be obtained from other studies. A large questionnaire study in the UK reported that 50% of adults and children with peanut allergy had a reaction in the previous year and 92% in the past 1–5 years [8]. Subjects were aware of their allergy but the majority had not apparently received a management plan. Another questionnaire study of 122 peanut-allergic children demonstrated that over a median period of 5.4 years from the initial reaction, 55% experienced further reactions, with on average two per patient [7]. They had received advice from an allergy clinic, but details were not stated. A French telephone survey examined the efficacy of personalized care projects (PCP) for 39 children with any food allergy. Over an average of 2 years, 33% of children with a PCP had a further reaction [18]. Interestingly, adrenaline was administered during a reaction in 7%, but antihistamine only in 14.6%. Airway narrowing was common in further reactions, which may account for the increased reaction rate and adrenaline use. We published data from a cohort of nut-allergic adults and children enrolled in a management plan, which showed a follow-up reaction rate of 15% over 21 months and substantially reduced severity [13]. A recent study has shown the follow-up reaction rate for 62 children enrolled by an allergist into a management plan similar to ours to be 38.5% in the first year of review [19]. The present study provides data from a larger group, exclusively children, followed up for a longer time, where 21% had a further reaction over a median of 3.3 years (74% of whom had only one reaction).

To investigate whether there were any risk factors among children who had a follow-up reaction, we performed a case-control study. Children who went on to have follow-up reactions (cases) had more frequent and severe reactions pre-referral than those who did not (controls). No other factors including asthma were identified, but this may be because good control of asthma was part of the management plan. It

is possible that families of cases were less vigilant and/or the children had a higher level of sensitivity that predisposed them to frequent follow-up reactions (this could be assessed by food challenge). While there was no difference in the proportion of index reactions caused by traces of nuts between cases or controls (15%), a greater proportion of cases had moderate-severe index reactions, implying a greater sensitivity. However, there was no significant difference between the two groups for the number of nut types they were sensitized to, prevalence of other allergies or the index nut type.

In the longitudinal study, a greater proportion of follow-up reactions were caused by traces of nuts only, compared with all index reactions (60% vs. 15%), which partly explains why follow-up reactions were less severe than index. It may be that families had successfully avoided obvious nut content in foods following our advice, but were unable to avoid trace contamination. The longitudinal study also identified older age (median of 13 years) as a risk factor for more severe follow-up reactions.

We aimed to provide evidence to inform good practice by developing and then evaluating a management plan that could be universally adopted [12]. Current advice is variable and often ill-informed. Children are seen once with little attention paid to detailed dietary advice or education about food labelling. There is a tendency to prescribe EpiPen irrespective of severity and without the other components of our plan. There is evidence of poor support for these children in schools where such a plan does not exist [9]. We have shown that after enrolment in a comprehensive management plan, led by allergists liaising with community paediatricians [12], the frequency of further reactions reduces eightfold and the majority of children have milder reactions than before.

This protocol takes into account both the clinical features of nut allergy and the individual requirements of each child. We believe that it could be applied as a model of good practice to other common food allergies with a wide spectrum of severity, where the majority of reactions are mild but there is a recognized danger of severe food reactions (e.g. egg and milk allergy). While there are new treatments being developed for nut allergy [20], avoidance is the mainstay of current treatment and should be provided as part of a complete management package.

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