

Allergy

Food allergy in childhood

A T Clark, P W Ewan

Have the dangers been underestimated?

Macdougall *et al* have tried to assess the risks of food allergy in childhood by identifying the incidence of fatal and severe reactions.¹ They conclude that the risk of death is small and play down the importance of severe food reactions. The implication is that epinephrine (adrenaline) autoinjectors are overprescribed. This paper has serious consequences for the management of children with food allergy, so the methodological problems need to be explored to provide a balanced view. The data produced are likely to be misleading by underestimating both severe and fatal reactions.

This is at a time when there is evidence in the UK of a doubling of admissions for anaphylaxis (1991–95),² 385 of whom were children (60 caused by food, but in 240 aetiology was not recorded).³ Food is the commonest cause of anaphylaxis in children,^{3,5} and in an American series nuts were the commonest cause of fatal food allergic reactions.⁶

FATAL REACTIONS

This study will underestimate the incidence of fatal reactions, because the authors incorrectly assume that all such deaths will be correctly registered as allergy (or related terms). Anaphylactic reactions are often mislabelled as asthma deaths, because of a lack of antecedent history or information. This is clear from retrospective analysis of fatal reactions.^{7,8} For example, we know of a teenager who died of almond anaphylaxis, but the cause of death was given as asthma alone. The true cause of death only came to light when the Confidential Inquiry into Asthma Deaths⁹ led by serendipity to case review by an allergist (PWE) who knew of the case. There are four deaths per million per annum in 5–14 year olds¹⁰ apparently caused by asthma, 60-fold more than the deaths identified in the Macdougall *et al* study. Even if only a proportion of these were food induced, this would increase the reported incidence of fatal food allergic reactions greatly. The study assumes that allergy would be previously identified, but food allergy occurs commonly on the first known exposure (for example, in 50% of peanut allergic children).¹¹ In addition, because of the lack of allergists the diagnosis is often not made.

No evidence of allergen ingestion is not evidence of no allergen ingestion, particularly in acute fatal reactions. Three cases were excluded on this basis. Furthermore, as in the case cited above, unless appropriate enquiry is made, the physician is often unaware of prior allergen ingestion. While it is difficult to be certain about such cases, the authors do not acknowledge this or the other many reasons why their study might be an underestimate.

The authors state, as if by way of reassurance, that peanut was the cause of two of eight fatal reactions and there were no deaths from peanut allergy under 13 years. However, they fail to compare this to a much larger and recent American series of food allergy deaths (n = 32) where 80% (8/10) of deaths in under 16 year olds were caused by peanuts or nuts; the youngest patient was 2 years old (4/10 were under 13 years).⁶ Clearly fatalities are more common in older children, but one cannot be totally reassured by the data of Macdougall *et al* in young children.

SEVERE NON-FATAL REACTIONS

The key problem in severe food reactions is respiratory compromise, whereas hypotensive shock, part of the authors' definition, is rare. (In a series of nut allergic patients, of those with a severe reaction, 100% had respiratory symptoms and 14% of these also had hypotension.¹² In none was hypotensive shock the dominant or presenting feature: hypotension always followed severe asphyxia.) Respiratory features vary from wheeze or laryngeal oedema causing mild through to severe dyspnoea, cyanosis, or respiratory arrest. When these patients present acutely it is difficult to establish that this is caused by a food allergic reaction, and the episode is commonly labelled as asthma. Furthermore, early treatment of food induced respiratory symptoms can lead to resolution,^{13,14} but this does not mean the episode was not potentially or actually severe. Provision of an epinephrine autoinjector is therefore essential in patients with a history of even mild respiratory difficulty, and this at-risk group must be identified.

The Macdougall *et al* paper focuses on the tip of the iceberg since their diagnostic threshold for inclusion was too high.

The diagnostic criteria used are undated, unreferenced, and irrelevant to clinical practice. To be included as a severe reaction they required one or more of the following: cardiorespiratory arrest, inotropic support, >20 ml/kg fluid bolus, more than one dose of epinephrine, and more than one dose nebulised bronchodilator. This is ridiculous as the majority of reactions warranting treatment with epinephrine—that is, by accepted definition severe (UK Resuscitation Council¹⁵) will be missed. Furthermore, a single dose of intramuscular epinephrine, if given promptly, is usually effective for the treatment of anaphylaxis^{13,15}—do the authors not consider anaphylaxis severe?

They will therefore have missed the following cases: severe reactions outwith their diagnostic criteria, for example, where epinephrine autoinjector and/or nebulised bronchodilator was used once for severe dyspnoea; reactions treated in the community; and reactions treated in accident and emergency departments (only the minority of patients with anaphylaxis are admitted¹⁶). Furthermore, severe cases were ascertained using only the British Paediatric Surveillance Unit (BPSU). As there is a lack of paediatric allergists and allergy expertise in general paediatrics, many children are referred to allergy centres not run by paediatricians and would therefore not be identified in this study.

For example, taking nut allergy alone, we have 791 children under 15 years, 218 (29%) of whom had reactions with respiratory symptoms, and 58 (8%) with severe dyspnoea and/or collapse. Reactions in 50 children were treated with epinephrine injection: all resolved. The number of children in our centre would be much larger if other foods were included. Thus, the group which paediatricians and allergists need to be aware of has not been identified.

ESTIMATES OF INCIDENCE OF SEVERE FOOD ALLERGY

MacDougall *et al* state that the incidence of severe food allergic reactions is 0.19 per 100 000 children per annum, and for near-fatal (intubated) reactions, 0.02 per 100 000 children per annum.¹ The fact that 1 in 8 were intubated suggests that their criteria for severe reactions were inappropriate.

That these figures are an underestimate is shown by comparison with other data. Sheikh and Alves analysed admissions with anaphylaxis between 1991 and 1995 using the hospital episodes statistics database.² A total of 385 cases were children, which equates to 0.74 per 100 000 children per annum—that is, almost fourfold more (table 1). Furthermore, this will underestimate the true incidence as not all patients would be

Table 1 Estimates of incidence of severe food allergy

Data source	Incidence per 100000 children	Allergy causing anaphylaxis	Comparison to McDougall <i>et al</i> data (no. of times greater)
McDougall <i>et al</i>	0.19	All foods	–
Sheikh	0.74*	All causes	4
Ewan/Clark	7.3†	Nuts	38
Ewan/Clark	11.6‡	Nuts	62

*Food likely to account for >90% of these,⁴ calculated from admitted cases only with discharge coding for anaphylaxis.

†Extrapolated from referrals to a regional allergy clinic to UK population.

‡Extrapolated from referrals to a regional allergy clinic to catchment population (East Anglia), see text.

Table 2 Severity grading of worst reaction before referral

Reaction grade	Clinical features
1. Mild	Localised cutaneous erythema/urticaria/angioedema/oral pruritus
2. Mild	Generalised erythema/urticaria/angioedema
3. Mild	At least 1 or 2 plus gastrointestinal symptoms/rhinoconjunctivitis
4. Moderate	Mild laryngeal oedema (voice change/tightening of throat)/mild asthma
5. Severe	Marked dyspnoea/hypotensive symptoms (collapse/loss of consciousness)

'/' = and/or.

admitted. Food is the commonest cause of anaphylaxis in children and in another series accounted for 94% of cases aged 0–18 years.⁴

Taking nut allergy alone, it is possible to estimate the incidence of severe reactions. The incidence of nut allergy in the UK is 0.7% (ALSPAC, unpublished data). Of 791 children with nut allergy in our care, 8% (58) had severe (grade 5; table 2) reactions. The UK under 16 population is 13 million,¹ so extrapolating from our data we can calculate that there are 7.3 children with severe nut allergy per 100 000 children—that is, 38-fold more than stated by McDougall *et al*, which is for all food allergy. Since we are a regional allergy centre we may see a greater proportion of children with severe nut allergy than in the general population. We therefore calculated the incidence of severe nut allergy in East Anglia, from our catchment population of 2.2 million, containing 0.5 million children. We have identified 58/791 children with severe nut allergy, giving an incidence of 11.6 per 100 000 children—that is, 62-fold more than McDougall *et al* estimated for food allergy. While we recognise that these are estimates, we care for 58 children with severe (grade 5) reactions so that this figure must be the *minimum* incidence, and this is for food allergy alone. The estimates of McDougall *et al* are therefore *at least* 62-fold too low.

The discrepancy in incidence between our data and that of Sheikh and Alves is mainly because not all patients with severe (grade 5) reactions are admitted;

also data from admissions depend on accurate discharge coding, and the term anaphylaxis is under used.

ASSESSMENT OF SEVERITY

Severity varies from trivial (facial urticaria) to life threatening. We have proposed a method of assessing severity in peanut and nut allergy⁸ which could be applied to food allergy. Reactions were graded 1–5 (table 2).¹³ It is important also to consider the amount of allergen causing the reaction as this is one of the factors determining severity. Thus, a patient with a mild or moderate reaction to trace exposure such as inhalation or contact with a food containing nuts, might have a severe reaction on ingesting a small amount of nut. This grading system emphasises the importance of respiratory symptoms which are known to be the main severe feature of food allergy. Applying this to an unselected series of 539 patients with nut allergy (table 3), half the patients have mild, predominantly cutaneous reactions (grade 1–3), 35% have mild airway involvement (grade 4), and 13% have severe (grade 5) reactions.

WHO NEEDS EPIPEN?

This is the most difficult issue and there is debate. Many of those claiming Epipen is overprescribed fail to understand that Epipen should be seen as part of a complete management package.^{17,18} We do not claim to know the answer, and this will require extensive data on natural history and may differ in different allergies. Egg and milk allergies in young

Table 3 Severity of worst reaction before referral in 539 patients with nut allergy

Severity grade*	Number	%
1	130	24.1
2	56	10.4
3	91	16.9
1–3	277	51.4
4	191	35.4
5	71	13.2
4–5	262	48.6

*See table 2.

children mostly resolve, whereas peanut and nut allergy are perceived to be more severe and persistent. However, we have devised a system in food allergy to decide whether Epipen is required and have used this over several years; those with grade 4–5 reactions receive Epipen and those with only grade 1–3 reactions do not, but receive oral antihistamines. There are variations:

- (1) If the patient has ongoing asthma of other cause, Epipen is prescribed
- (2) If a trace exposure had caused a grade 1–3 reaction, Epipen is prescribed.

The reason asthma is taken seriously is that patients with fatal or near-fatal reactions mostly have asthma, as found in American series (100%)¹⁴ and McDougall *et al* (83%),¹ and asthma is often poorly controlled.

Our criteria for Epipen provision have been evaluated within an overall management plan for nut allergy.¹³ Patients are reviewed annually when details of further reactions are collected and they are retrained in all aspects of the management plan. The severity of the worst reaction to date is graded (table 2) and the amount of allergen causing this reaction noted. It is important to emphasise that Epipen prescription was part of a complete management package, in which there are many other elements, and should not be seen in isolation. Those given Epipen also received oral antihistamines.

OUTCOME DATA ON EPIPEN PRESCRIPTION

In this study of 567 patients (70% <16 years old) with nut allergy followed over 13 610 patient-months, there were 88 (15%) further reactions, most of which were mild (n = 62) and required no treatment or oral antihistamines.¹³ Intramuscular epinephrine was used in 3/3 severe reactions and 6/23 moderate reactions; all patients improved (a single

patient received two doses). There were no unwanted effects. Intramuscular epinephrine was therefore safe and effective in this large series.

A total of 172 patients were not given an Epipen. Only 1/567 (0.002%) had a severe follow up reaction requiring epinephrine when this had not been prescribed. This patient's worst reaction before referral was mild. Hospital treatment with epinephrine was effective. Our emergency treatment plan was inadequate in 0.002% of patients, but no patient came to harm as a result of our criteria for Epipen prescription.

SAFETY OF INTRAMUSCULAR EPINEPHRINE

There is a misconception that epinephrine is dangerous. However, the dangers of epinephrine are when this is given by the intravenous route without appropriate care.¹⁵ Epinephrine by intramuscular injection is very safe and there are no reports of deaths in children related to Epipen. A fatal reaction often quoted as caused by appropriate use of epinephrine was a result of medical error and overdose of intravenous epinephrine: 35-fold more than the normal dose was given using the intramuscular solution (1 mg/ml) instead of the dilute (1 mg/10 ml) intravenous solution.⁷ The child had simple urticaria and not anaphylaxis.

WHY NOT GIVE EPIPEN TO ALL CHILDREN WITH FOOD ALLERGY?

The prescription of Epipen should highlight a child at risk. Widespread provision of Epipen to all food allergic children means those at risk are less easily identified and care diluted. If the allergy is mild, Epipen can create anxiety, make socialising difficult, and create work for community paediatric teams and school staff. If Epipen is given to all children with food allergy, a child with localised facial urticaria caused by egg would receive one. This is inappropriate. Unfortunately, because nut allergy is known to be potentially life threatening, anxiety is generated in parents and doctors and it is assumed that all children

with nut allergy require Epipen. This problem highlights the need for good data on the clinical features and natural history of nut allergy in children.

CONCLUSIONS

The McDougall *et al* paper¹ has identified only the extreme end of the severe spectrum of food allergic reactions and this should not be used as the only end point to inform management. The inferences drawn are of little relevance to clinical practice and are not helpful in deciding which children require an epinephrine autoinjector. While we would agree that there are not likely to be many deaths as a result of food allergy in the under 15 age group, these data should not be used to minimise the problem or reduce appropriate care. We present estimates suggesting the incidence of severe food allergy must be much higher than McDougall *et al* propose: in nut allergy alone this was approximately 11 per 100 000 children (62-fold higher). There is evidence that an integrated management plan can significantly reduce further reactions in number and severity.¹³ Management requires accurate diagnosis and assessment of severity. Patients/parents should be given detailed advice on avoidance, emergency medication (it should be emphasised that each child is different and may require different medication), a written treatment plan, training in the use of medication, and education of school staff.¹³ Criteria for Epipen prescription are proposed. Control of asthma and other allergies is important and retraining essential. Provision of epinephrine autoinjectors is only one part of this and should not be viewed in isolation. Most deaths are in the late teens and twenties, when continued vigilance and appropriate care is necessary.^{6, 7, 14}

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Authors' affiliations

A T Clark, P W Ewan, Addenbrooke's Hospital, Cambridge, UK

Correspondence to: Dr A T Clark, Box 40, Addenbrooke's NHS Trust, Cambridge CB2 2QQ, UK; pwe123@hotmail.com

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