

The use of adrenaline autoinjectors by children and teenagers

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Summary

Background Although adrenaline is recommended as first line treatment for anaphylaxis, it is often not utilized. There has been a debate about when adrenaline autoinjectors should be prescribed and how many should be dispensed.

Objectives To see how many adrenaline autoinjectors were used during anaphylactic reactions and to determine why they were not used in situations where they were clinically indicated.

Methods Patients were recruited prospectively at 14 paediatric allergy clinics throughout UK. Participants completed a questionnaire covering demographic data, atopic status and details of allergic reactions in the previous year and reasons for using more than one device.

Results A total of 969 patients were recruited of whom 466 (48.1%, 95% CI: 37.9–58.2) had had at least one reaction in the previous year; 245 (25.3%, 95% CI: 16.2–34.4) of these reactions were anaphylaxis. An adrenaline autoinjector was used by 41 (16.7%, 95% CI: 11.7–21.3) participants experiencing anaphylaxis. Thirteen participants received more than one dose of adrenaline, for nine of these a health professional gave at least one. The commonest reasons for using more than one were severe breathing difficulties (40%), lack of improvement with first dose (20%) and miss-firing (13.3%). The commonest reasons for not using adrenaline in anaphylaxis were 'thought adrenaline unnecessary' (54.4%) and 'unsure adrenaline necessary' (19.1%). Many with wheeze did not use their autoinjector.

Conclusions and Clinical Relevance Adrenaline is used by only a minority of patients experiencing anaphylaxis in the community. Thirteen of the 41 patients with anaphylaxis who used their autoinjector needed another dose of adrenaline. Further research is needed to consider how to best encourage the usage of adrenaline when clinically indicated in anaphylaxis.

Keywords adherence, adrenaline autoinjector, anaphylaxis, paediatrics

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Introduction

Anaphylaxis is an important paediatric emergency [1–3]. Food allergy is the commonest trigger of anaphylaxis in children with important allergens being peanuts, tree nuts, milk, egg, fish and sesame [4]. The mainstay

of management is the avoidance of potential triggers. Despite educating patients and their families, accidental exposures continue to occur [5, 6] and families must therefore be ready and able to manage anaphylactic reactions. Intramuscular adrenaline is recommended as first line treatment for anaphylaxis [2].

The appropriate patient selection for prescribing adrenaline autoinjectors depends on the accurate prediction of the risk of anaphylaxis. Most paediatric allergists would agree that previous anaphylaxis is an indication for an autoinjector [2]. There is much less agreement about the other indications [5, 7]. It has been suggested [2] that co-existent asthma [8–10] and adolescence are other indications [11, 12]. There is increasing evidence that co-factors, such as exercise and viral respiratory tract infections are important [13].

Given this debate, there is a need to obtain accurate data regarding the rate of subsequent allergic reactions and the utilization of adrenaline autoinjectors by those for whom adrenaline autoinjectors are prescribed. Previous studies examining the rate of reactions and the number of devices used have generally been surveys of patient support organizations [14, 15], emergency departments [16, 17], primary care patients [18] or tertiary paediatric allergy clinics [19, 20]. They are unlikely to be truly representative of patients attending a general paediatric allergy clinic. They are also mainly studies on North American patients and can therefore not be directly extrapolated to the UK population. The primary aim of this study was to assess a sufficiently large number of patients who have been prescribed adrenaline to provide a precise estimate of the rate that autoinjectors are used and the number of devices used for each reaction. Secondary aims were to document the triggers for these reactions and understand why autoinjectors are not used in all episodes of anaphylaxis.

Methods

Design

A prospective, multi-centre, questionnaire-based study located in the United Kingdom. Participants attending secondary and specialist tertiary level general paediatric allergy clinics were asked about any allergic reactions that they had experienced in the previous year.

Participants

Participants were children and teenagers aged up to 18 years who had been prescribed an adrenaline autoinjector for at least a year. Indications for adrenaline prescription included previous anaphylaxis, reaction to trace amount, food allergy with asthma and nut allergy. Patients prescribed adrenaline were verbally informed and given written information by an allergy doctor and/or nurse based on as well as an allergy management plan for indications when adrenaline should be administered. They were trained in administration with an appropriate trainer device. Management plans were developed by each unit although advice

given was uniform with training provided in line with European guidance by both doctors and nurses [1]. They were attending clinics at Cardiff University Hospital, Hillingdon Hospital, Newcastle General Hospital, Northwick Park Hospital, Poole Hospital, Royal Free Hospital (London), Royal Manchester Children's Hospital, Scunthorpe General Hospital, Singleton Hospital (Swansea), St Mary's Hospital (Isle of Wight), St Mary's Hospital (London), St Peter's Hospital (Chertsey) or St Thomas' Hospital (London). Sites were selected on a geographical basis to attempt to reflect current practice from across the UK, only sites which collected data were listed here. There were no specific exclusion criteria. Informed consent was obtained from the parents and, where appropriate, participants by allergy clinic staff at their appointment. The study was approved by the Royal Free Hospital Research Ethics Committee (08/H0720/152).

Questionnaire assessment

Participants completed a single page questionnaire, developed by a team of paediatric allergists and piloted with 368 patients. The questionnaire was sent out to the Paediatric Allergy Group e-forum for comment and modified according to the comments received. It was unlinked and anonymous. Participants were asked to list their allergies, any co-existing asthma or eczema and how many allergic reactions they had had in the previous year. For reactions they were asked for the perceived cause, symptoms (prompting for clinical features of anaphylaxis including difficulty in breathing, itchy throat or throat tightness, changing voice, vomiting, diarrhoea, difficulty swallowing, wheezing, dizziness and loss of consciousness) [21] and any treatment received. Where adrenaline was used, they were asked who gave it and where. If more than one was used, they were asked why. Where an autoinjector was not used, they were again asked why with no restriction on the number of options selected.

Sample size collection and analysis

It was estimated that 10% of participants would have used their epinephrine autoinjector in the previous year and that a fifth of these would have used at least two devices. Assuming this, and that a thousand subjects were recruited into the study, it would be possible to estimate the rate of multiple autoinjector use as 20% [95% confidence interval (CI): 12.7–29.2].

Stata version 9.2 (STATA Corps, College Station, TX, USA) was used for analysis. Where a participant had experienced more than one reaction in the previous year, only the most severe one was included. Anaphylaxis was defined as any reported loss of consciousness,

difficulty in breathing, difficulty in swallowing, feeling of impending doom, wheeze, throat tightness, change in voice or dizziness acutely after allergen exposure [21]. Data are presented as means (standard deviations) or frequencies (percentages) as appropriate. The analysis was undertaken using the STATA svy command STATA (V11, College Station, TX, USA) to take into account any effect of clustering by centre. Comparisons between groups are undertaken with a two-sample *T*-test, Chi-squared test or Fisher exact test as appropriate. Associations between symptoms and the use of an autoinjector or between potential risk factors and anaphylaxis are assessed using logistic regression analysis.

A *P*-value of less than 0.05 was taken to indicate statistical significance.

Results

Participants

A total of 1304 patients were screened, 969 (74.3%) satisfied the inclusion criteria. No patients screened refused to participate. The demographic and clinical details of the participants are described in Table 1. Their mean age was 8 years, there was a slight predominance of males and the majority were of a white

Table 1. Demographic and clinical details of the participants

	Participants				Comparison, <i>P</i> -value	
	All (<i>n</i> = 969)	No reactions (<i>n</i> = 503)	Allergic reaction, not anaphylaxis (<i>n</i> = 221)	Anaphylaxis (<i>n</i> = 245)	Anaphylaxis vs. non-anaphylaxis reaction	Anaphylaxis vs. all others participants
Age (years)	8.6 (4.1)	9.4 (3.9)	7.2 (3.9)	8.1 (4.3)	0.02	0.05
Gender						
Male	569 (58.7)	309 (61.4)	115 (52.0)	145 (65.6)		
Female	371 (38.3)	183 (36.4)	96 (43.4)	92 (41.6)	0.15	0.81
Unknown	29 (3.0)	11 (2.2)	10 (4.5)	8 (3.6)		
Ethnicity						
White	615 (63.5)	349 (69.4)	137 (62.0)	129 (58.4)		
Asian/Asian British	146 (15.1)	61 (12.1)	39 (17.6)	46 (20.8)		
Black/Black British	63 (6.5)	28 (5.6)	13 (5.9)	22 (10.0)		
Mixed race	34 (3.5)	16 (3.1)	7 (3.2)	11 (5.0)	0.04	<0.01
Other	45 (4.6)	18 (3.6)	16 (7.2)	11 (5.0)		
Unknown	66 (6.8)	31 (6.2)	9 (4.1)	26 (11.8)		
Asthma	545 (56.2)	277 (55.2)	114 (51.6)	154 (62.9)	0.02	0.02
Prescribed inhaled corticosteroids	479 (87.2)	238 (88.9)	97 (85.8)	138 (90.8)	0.21	0.34
Eczema	717 (74.0)	346 (68.8)	172 (77.8)	199 (81.2)	0.36	<0.01
Prescribed topical corticosteroid	528 (73.6)	249 (73.7)	127 (74.7)	151 (77.0)	0.60	0.42
Allergens reported by participants						
Food allergens						
Peanut	690 (71.2)	383 (76.1)	149 (67.4)	158 (64.5)	0.51	<0.01
Tree nut	579 (59.8)	293 (58.3)	128 (57.9)	158 (64.5)	0.15	0.08
Egg	257 (26.5)	107 (21.3)	75 (33.9)	75 (30.6)	0.44	0.09
Cow's milk	144 (14.9)	61 (12.1)	28 (12.7)	55 (22.5)	0.01	<0.01
Shellfish/seafood	106 (10.9)	47 (9.3)	28 (12.7)	31 (12.7)	1.00	0.32
Fruit	88 (9.1)	34 (6.8)	28 (12.7)	26 (10.6)	0.49	0.34
Seeds	74 (7.6)	32 (6.4)	28 (12.7)	14 (5.7)	0.01	0.19
Other legumes	57 (5.9)	16 (3.2)	20 (9.1)	21 (8.6)	0.86	0.04
Wheat	19 (2.0)	10 (2.0)	4 (1.8)	5 (2.0)	0.86	0.92
Soya	28 (2.9)	11 (2.2)	5 (2.3)	12 (4.9)	0.13	0.03
Other foods	27 (3.0)	6 (1.3)	8 (3.9)	13 (5.7)	0.31	0.02
Drugs	18 (1.9)	8 (1.6)	5 (2.3)	5 (2.0)	0.87	0.81
Venom	7 (0.7)	5 (1.0)	1 (0.5)	1 (0.4)	0.94	0.50
Idiopathic	22 (2.3)	2 (0.4)	5 (2.3)	15 (6.1)	0.04	<0.01
Prescribed adrenaline autoinjector	969 (100.0)	503 (100.0)	221 (100.0)	245 (100.0)	–	–

Only participants fulfilling the inclusion criteria included. Data presented as number of individuals (%) except age which is the mean (SD). *P*-values represent two-sample *t*-test, a Chi-squared test or Fisher exact test. Other foods represent other vegetables, buckwheat, herbs, mustard and meat. Anaphylaxis defined as loss of consciousness, difficulty swallowing, feeling of impending doom, wheeze, throat tightness, change in voice, difficulty breathing or dizziness. The italicized values are subgroups.

demographic. About half had co-existent asthma and most had co-existent eczema. The most prevalent food allergens were peanuts and tree nuts and all, but two had been prescribed Epipens.

Rate of allergic reactions

A total of 466 participants had experienced an allergic reaction in the previous year, a rate of 48.1% (95% CI: 37.9–58.2). A total of 97 (10.1%), 41 (4.3%), 28 (2.9%) and 59 (6.2%) had experienced two, three, four or more than four reactions, respectively, in the previous year. The more common triggers were peanuts, tree nuts, egg, milk, shellfish, seafood or fruits. For 20%, there was no identifiable trigger. No particular triggers were associated with anaphylaxis as opposed to a more minor reaction (Table 2). The most frequent symptoms seen with allergic reactions were urticaria (26.6%), redness of the skin (25.5%), swelling (19.9%), itchy throat (18.4%), wheezing (15.5%), difficulty breathing (12.9%), vomiting (12.5%) or throat tightness (10.2%) (Table 3). A total of 245 (52.6%, 95% CI: 43.1–62.1) reactions met the study definition of anaphylaxis. Excluding the symptoms used

Table 2. Allergens triggering an allergic reaction in the previous year

	Participants			P-value
	All (n = 466)	Allergic reaction, not anaphylaxis (n = 221)	Anaphylaxis (n = 245)	
Food allergens				
Peanut	141 (30.3)	70 (31.7)	71 (29.0)	0.527
Tree nut	142 (30.5)	58 (26.2)	84 (34.3)	0.060
Egg	53 (11.4)	30 (13.6)	23 (9.4)	0.155
Cow's milk	35 (7.5)	14 (6.3)	21 (8.6)	0.360
Shellfish/seafood	25 (5.4)	14 (6.3)	11 (4.5)	0.377
Fruit	26 (5.6)	18 (8.1)	8 (3.3)	0.022
Seeds	8 (1.7)	3 (1.4)	5 (2.0)	0.571
Other legumes	9 (1.9)	7 (3.2)	2 (0.8)	0.066
Wheat	7 (1.6)	1 (0.5)	6 (2.5)	0.077
Soya	4 (0.9)	2 (0.9)	2 (0.8)	0.917
Other foods	7 (1.6)	5 (2.3)	2 (0.8)	0.200
Animal dander	6 (1.2)	2 (0.9)	4 (1.6)	0.487
Drug	2 (0.4)	0 (0.0)	2 (0.8)	0.178
Venom	1 (0.2)	0 (0.0)	1 (0.4)	0.342
Idiopathic	94 (20.2)	38 (17.2)	56 (22.9)	0.128

Data presented as number of participants (%). Participants may have reported reactions to more than one allergen. Others foods included wheat, honey, parsnip, popcorn, quinoa and tomatoes. Anaphylaxis was defined as loss of consciousness, difficulty swallowing, feeling of impending doom, wheeze, throat tightness, change in voice, difficulty breathing or dizziness. *P*-value represents the statistical difference between participants experiencing an allergic reaction in the previous year that was and was not anaphylaxis (Chi-squared or Fisher exact test).

Table 3. Symptoms reported by participants experiencing a reaction in the previous year

Symptom	Participants			P-value
	Any allergic reaction (n = 466)	Allergic reaction, not anaphylaxis (n = 221)	Anaphylaxis (n = 245)	
Urticaria	258 (26.6)	128 (57.9)	130 (53.1)	0.292
Skin redness	247 (25.5)	112 (50.7)	135 (55.1)	0.339
Swelling	193 (19.9)	65 (29.4)	128 (52.2)	<0.001
Itchy throat	178 (18.4)	59 (26.7)	119 (48.6)	<0.001
Wheezing*	150 (15.5)	0 (0.0)	150 (61.2)	–
Difficulty breathing*	125 (12.9)	0 (0.0)	125 (58.7)	–
Vomiting	121 (12.5)	44 (19.9)	77 (31.4)	0.005
Throat tightness*	99 (10.2)	0 (0.0)	99 (40.4)	–
Abdominal pain	82 (8.5)	27 (12.2)	55 (22.5)	0.004
Difficulty swallowing*	59 (6.1)	0 (0.0)	59 (24.1)	–
Diarrhoea	34 (3.5)	10 (4.5)	24 (9.8)	0.029
Dizziness*	31 (3.2)	0 (0.0)	31 (12.7)	–
Change in voice*	24 (2.5)	0 (0.0)	24 (9.8)	–
Feeling of impending doom*	20 (2.1)	0 (0.0)	20 (8.2)	–
Loss of consciousness*	12 (1.2)	0 (0.0)	12 (4.9)	–

Data presented as number (%) of subjects reporting symptom. Where a participant had more than one reaction, only data from the most serious is reported. Participants may have reported more than one symptom. Anaphylaxis defined as loss of consciousness, difficulty swallowing, feeling of impending doom, wheeze, throat tightness, change in voice, difficulty breathing or dizziness (all marked with an asterisk). *P*-value represents the statistical difference between participants experiencing an allergic reaction that was and was not anaphylaxis (Chi-squared test); symptoms used to define anaphylaxis were excluded from this analysis.

to define anaphylaxis in this study, the presence of swelling, and itchy throat or abdominal pain were statistically associated with anaphylaxis (Table 3).

Risk factors for anaphylaxis

Within a univariate model, the most important risk factors for anaphylaxis were previous reactions to an unidentified allergen (odds ratio: 6.68, 95% CI: 2.69–16.58), cows' milk allergy (odds ratio: 2.07, 95% CI: 1.42–3.00) and non-white ethnicity (odds ratio: 1.85, 95% CI: 1.37–2.47) (Table 4). Within a multivariate analysis, the risk factors for anaphylaxis were previous reactions to unidentified allergens (adjusted odds ratio: 6.76, 95% CI: 2.59–17.62), cows' milk allergy (adjusted

Table 4. Risk factors for anaphylaxis

	Univariate		Multivariate	
	OR	95% Confidence interval	Adj. OR	95% Confidence interval
Age (years)	0.96	0.93–1.00		
Non-white ethnicity	1.85	1.37–2.47	1.59	1.17–2.17
Asthma	1.44	1.07–1.93	1.37	1.00–1.87
Allergens causing previous reactions				
Food allergens				
Peanut	0.66	0.48–0.89	0.61	0.43–0.86
Tree nut	1.31	0.97–1.77	1.55	1.10–2.18
Egg	1.31	0.95–1.81		
Cow's milk	2.07	1.42–3.00	2.00	1.37–2.95
Shellfish/seafood	1.25	0.80–1.96		
Fruit	1.27	0.78–2.05		
Seeds	0.67	0.37–1.22		
Other legumes	1.79	1.02–3.13		
Wheat	1.06	0.38–2.96		
Soya	2.28	1.06–4.89		
Animal dander	1.15	0.75–1.76		
Drugs	1.14	0.40–3.23		
Venom	0.49	0.06–4.09		
Idiopathic	6.68	2.69–16.58	6.76	2.59–17.62

The odds ratios (OR) and their 95% confidence intervals are presented for the relationship between each of the factors and a history of anaphylaxis. All factors with $P < 0.1$ were entered into a backward multiple logistic regression analysis to generate adjusted (Adj.) ORs.

odds ratio: 2.00, 95% CI: 1.37–2.95), tree nut allergy (adjusted odds ratio: 1.55, 95% CI: 1.10–2.18), non-white ethnicity (adjusted odds ratio: 1.59, 95% CI: 1.17–2.17) and asthma (adjusted odds ratio: 1.37, 95% CI: 1.00–1.87). A previous reaction to peanuts was a protective factor in this cohort (0.61, 95% CI: 0.43–0.86).

Management of allergic reactions

Most allergic reactions were treated with oral antihistamines alone (83.3% for anaphylactic reactions, 86.4% for others; $P = 0.3$). Of the 245 participants experiencing an episode of anaphylaxis, only 41 (16.7%, 95% CI: 11.7–21.3) received adrenaline. Of the participants who had reactions that did not fulfil the study definition of anaphylaxis, six (2.7%, $P < 0.001$) used their adrenaline. These six participants had different presentations, but all included angio-oedema. Within a multivariate model, loss of consciousness, difficulty in swallowing, feeling of impending doom, difficulty in breathing and swelling were all found to be independent predictors for using an autoinjector (Table 5). Notably, relatively small numbers of participants with wheeze utilized their autoinjector (Table 5). Adrenaline was administered by parents (26, 55%), health professionals (18, 38%) or the patient (2, 4%). Autoinjectors were usually administered

at home (25, 53%) with other participants receiving them in hospital (12, 26%), in an ambulance (5, 11%) or in other locations, such as a play centre or outside (5, 11%).

Use of multiple doses of adrenaline

Of the 41 participants who had an episode of anaphylaxis and used their autoinjector, 13 (32%, 95% CI: 10.2–55.0%) received more than one dose of adrenaline. Twelve received two doses and one had three (Table 6). Only five (38%) of these 12 participants had co-existing asthma. They had reactions to a variety of foods. Ten (77%) had symptoms of difficulty in breathing, wheeze or loss of consciousness in association with swelling. More than one dose of adrenaline was given because of severe difficulty in breathing (6, 40%), lack of improvement after the first dose (3, 20%) misfiring of the first pen (2, 13%), a continuing rash (1, 7%) or loss of consciousness (1, 7%). The participant who received three doses of adrenaline was an adolescent who had been prescribed two junior Epipens, he used both before paramedics gave a 0.3 mg dose. For 75%, a health professional gave at least one of the doses.

Why were adrenaline autoinjectors not used?

Although 245 participants had described a reaction in the previous year that met the study's criteria for anaphylaxis, 204 (83%) did not use their adrenaline autoinjector. This was despite them experiencing symptoms, such as loss of consciousness, difficulty swallowing, difficulty breathing, throat tightness and wheeze (Table 5). The usual reason given for not using an autoinjector was that they either thought it was unnecessary (54.4%) or were unsure whether or not it was necessary (19.1%). Other reasons were had called an ambulance (7.8%), device was not available (5.4%), were too scared to use it (2.5%), not trained (2.5%), attended an emergency department (1.5%) or the device was out of date (1.0%).

Discussion

This study represents a unique cohort of patients asked to recall their experience of allergic reactions over the previous 12 months using direct interview. Of the 969 children and teenagers reviewed, half experienced at least one allergic reaction in the previous year and a quarter had symptoms of anaphylaxis. Anaphylaxis was defined as having had cardio-respiratory symptoms following ingestion of an allergen [21]. Only 17% of participants experiencing an episode of anaphylaxis used their adrenaline autoinjector despite many of them experiencing potentially life threatening symptoms such

Table 5. Symptoms associated with the use of an adrenaline autoinjector

Symptoms	Number using autoinjector (%)	Univariate		Multivariate	
		OR	95% confidence interval	Adj. OR	95% confidence interval
Loss of consciousness*	6 (50.0)	10.07	2.94–30.85	5.51	1.31–22.51
Difficulty swallowing*	19 (32.2)	6.43	3.09–11.65	3.07	1.36–6.33
Feeling of impending doom*	8 (40.0)	6.96	2.73–18.89	3.52	1.18–11.40
Difficulty breathing*	29 (23.2)	5.42	2.65–9.18	2.59	1.15–4.82
Swelling*	35 (18.1)	4.82	2.50–9.83	3.44	1.74–7.63
Throat tightness*	24 (24.2)	4.79	2.38–8.19	–	–
Dizzy*	9 (29.0)	4.27	2.12–10.99	–	–
Change in voice*	5 (20.8)	2.51	0.84–6.66	–	–
Wheeze*	23 (15.3)	2.20	1.10–3.70	–	–
Itchy throat	25 (14.0)	2.00	1.04–3.46	–	–
Vomiting	17 (14.1)	1.72	0.87–3.08	–	–
Skin redness	28 (11.3)	1.35	0.68–2.28	–	–
Abdominal pain	9 (11.0)	1.12	0.59–2.61	–	–
Diarrhoea	3 (8.8)	0.85	0.40–3.52	–	–
Urticaria	24 (9.3)	0.82	0.47–1.55	–	–

*Symptoms used to define anaphylaxis. Participants may have reported more than one symptom. Data presented as number of subjects (%) reporting each symptom who used an adrenaline autoinjector. The odds ratios (OR) is presented for the relationship between each of the symptoms and the use of an autoinjector. All symptoms with $P < 0.1$ were entered into a backward multivariate logistic regression analysis to generate adjusted (Adj.) ORs.

as loss of consciousness, difficulty in breathing, throat tightness and wheeze. This is less than, but in line with other centres where adrenaline was not utilized in a majority of cases despite a systemic reaction [9, 20, 22]. It has been suggested that some resolve spontaneously due to the endogenous production of vasoconstrictors [23]. Of those who chose not to use their autoinjector, they mostly thought it was not necessary or were unsure whether it was necessary. Administration of an adrenaline device when given was by a parent in 55% of cases similar to other studies [20]. Thirteen of the 41 patients with anaphylaxis who used their autoinjector needed another dose of adrenaline meaning that 1% of participants had used more than one dose of adrenaline in the previous year, in these patients adrenaline was initially administered by a parent in 69% of cases supporting good recognition of a reaction and prompt treatment in this sub-group.

Within this group there were a much higher rate of allergic reactions than in other retrospective [20] or prospective studies [15] although these studies enrolled children with both mild and severe cases. The risk factors for anaphylaxis were a reaction to a previously unidentified allergen, cows' milk allergy, tree nut allergy, co-existent asthma and non-white ethnicity. Reactions to unidentified allergens has not been highlighted before as a risk factor for anaphylaxis, but this is clinically plausible given that the patient will not know what to avoid. Co-existent asthma has been identified as a risk factor for anaphylaxis in a number of studies [14–16]. We did not collect data on socioeconomic status and so

could not exclude the possibility that non-white ethnicity is acting as a marker of relative economic deprivation rather than differences in allergen exposure. Lastly, it is intriguing that peanut allergy was associated with a lower rate of anaphylaxis in this study. This probably reflects the tendency to prescribe an autoinjector for all children with peanut allergy, regardless of whether they are at low or high risk for anaphylaxis in the UK whereas for other foods, only children at high risk of anaphylaxis are usually prescribed.

Only 17% of participants experiencing an episode of anaphylaxis used their adrenaline autoinjector despite many of them experiencing potentially life threatening symptoms, such as loss of consciousness, difficulty in breathing, throat tightness and wheeze. This is even lower than other studies which have recorded rates of autoinjector use of about a third [15, 16]. Mostly they thought using autoinjectors wasn't necessary or were unsure whether they were necessary. Being unsure has been identified by previous questionnaire studies of patients experiencing anaphylaxis [14]. All our families had been educated to recognize and manage severe allergic reactions. Although education has been shown to improve knowledge, there is still sub-optimal understanding of how to manage an allergic reaction 3 months after training [6]. It has been suggested that the delayed use of adrenaline is associated with both increased morbidity [19] and mortality [8, 9]. We need to ensure that our patients understand the risks of anaphylaxis and exactly when they should make use of their autoinjector by providing written material,

Table 6. Summary of participants receiving more than one dose of intramuscular adrenaline

Allergen	Asthma	Presenting symptoms	Number of doses given	Who gave each dose			Why additional doses were given
				First	Second	Third	
Cashew	Yes	Difficulty in breathing and swallowing, change in voice, wheeze, dizziness, itchy tight throat, swelling, urticaria, vomiting	3	Parent	Parent	Paramedic	No improvement with first dose (junior Epipen, adolescent participant)
Unknown	Yes	Difficult breathing, rash	2	Parent	Paramedic	–	No Improvement with first dose
Seafood	No	Swelling, diarrhoea, skin redness, vomiting	2	Unknown	Unknown	–	No improvement with first dose, continued rash
Unknown	No	Loss of consciousness, swelling	2	Hospital	Parent	–	Severe breathing difficulties, loss of consciousness,
Plum	Yes	Difficulty in breathing, wheeze, itchy, tight throat.	2	Paramedic	Hospital	–	Severe breathing difficulties
Peanut	No	Wheeze, itchy tight throat, abdominal pain, vomiting	2	Parent	Parent	–	Severe breathing difficulties
Sesame	No	Difficulty in breathing and swallowing, wheeze, swelling itchy tight throat	2	Mother	Hospital	–	Severe breathing difficulties
Poppy seeds	No	Difficulty in breathing and swallowing, wheeze, swelling, itchy tight throat	2	Mother	Hospital	–	Severe breathing difficulties
Nuts	No	Difficulty in breathing and swallowing, wheeze, swelling, itchy tight throat	2	Mother	Hospital	–	Severe breathing difficulties
Brazil nut	No	Difficulty in breathing and swallowing, wheeze, swelling, itchy tight throat, skin redness, urticaria, vomiting, abdominal pain	2	Hospital	Parent	–	First device miss-fired
Cow's milk	Yes	Difficulty in breathing and swallowing, wheeze, swelling, throat tightness, urticaria, vomiting	2	Parent	Paramedic	–	First device miss-fired
Nuts	Yes	Difficulty in breathing, wheeze, swelling, throat tightness, vomiting	2	Parent	Parent	–	Unknown
Unknown	No	Difficulty in breathing, dizziness, rash	2	Parent	Parent	–	Unknown

perhaps with example case histories also ensuring staff providing training to families are well trained themselves [24].

In this study, we found that 13 (32%, 95% CI: 18–48) of the 41 participants using an autoinjector for anaphylaxis received more than one dose of adrenaline. This is very similar to two studies that surveyed patients support groups [14, 15], but twice the rate estimated from the review of community [18] or emergency departments' medical records [16]. It is also much higher than a retrospective's questionnaire study based in a tertiary paediatric allergy centre where all participants' reactions were recorded [20]. It is important to ascertain whether multiple doses of adrenaline were given appropriately. Our data suggests that 1.3% (95% CI: 0.7–2.3)

of children and teenagers at risk of anaphylaxis will need at least two doses of adrenaline to treat an allergic reaction over the period of a year. This supports the need for immediate availability of a second dose of adrenaline for children at risk. This could be made available with the rapid attendance of paramedics, the availability of a second generic autoinjector at a central location in a school or by ensuring the parents or teenagers carry two devices. Lastly, we know that autoinjectors are often not carried by patients [22, 25], teenagers feel awkward about carrying them around with them often because they don't have anywhere obvious to carry them [12, 22, 26].

In this study, we set out to maximize the inclusion of families and the reliability of their responses by

utilizing only a short questionnaire which was anonymized. Although this approach allowed us to recruit a large number of children and teenagers prescribed an adrenaline autoinjector, it limited our ability to extensively describe the population. For example, it would have been useful to know the severity of each of the presenting symptoms. The anonymous nature of the data also prevented the reassessment of participants using more than one dose of adrenaline in more detail.

Adrenaline is still under-used by patients with many not using their autoinjector despite experiencing potentially life-threatening symptoms. We need to consider how patient training and support can be improved, possibly by the use of real-time simulation. A total of 13 of the 41 (32%) patients using their autoinjector to treat anaphylaxis over a 1-year period needed another dose of adrenaline. This emphasizes the need for patients at risk of anaphylaxis to have access to a second adrenaline autoinjectors. The National Institute of Allergy and Infectious Diseases in the United States has recently recommended that such patients are prescribed two autoinjectors [23]; alternatively a second one could be made available from a central first aid kit or a paramedic responder. We are in need of novel biomarkers to predict the severity of future allergic reactions to allow us to more rationally prescribe adrenaline autoinjectors in this patient group; an improved evidence base to our guidelines might improve their adoption by health professionals [27]. Lastly, we need better educational interventions to improve compliance of patients with the use of their autoinjectors when they experience an anaphylactic reaction.

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