

Anaphylaxis: risk factors for recurrence

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Summary

Background There are few studies on the incidence or recurrence of anaphylaxis.

Objective To examine the incidence of anaphylaxis and risk factors for recurrence.

Methods A prospective study of 432 patients referred to a community-based specialist practice in the Australian Capital Territory with anaphylaxis, followed by a survey to obtain information on recurrence.

Results Of 432 patients (48% male, 73% atopic, mean 27.4 years, SD 19.5, median 26) with anaphylaxis, 260 patients were seen after their first episode; 172 experienced 584 previous reactions. fifty-four percent of index episodes were treated in hospital. Aetiology was identified in 91.6% patients: food (61%), stinging insects (20.4%) or medication (8.3%). The minimum occurrence and incidence of new cases of anaphylaxis was estimated at 12.6 and 9.9 episodes/100,000 patient-years, respectively. Follow-up data were obtained from 304 patients (674 patient-years). One hundred and thirty experienced further symptoms (45 serious), 35 required hospitalization and 19 administered adrenaline. Accidental ingestion of peanut/tree nut caused the largest number of relapses, but the highest risk of recurrence was associated with sensitivity to wheat and/or exercise. Rates of overall and serious recurrence were 57 and 10 episodes/100 patient-years, respectively. Of those prescribed adrenaline, 3/4 carried it, 2/3 were in date, and only 1/2 patients faced with serious symptoms administered adrenaline. Five patients each developed new triggers for anaphylaxis, or re-presented with significant psychiatric symptoms.

Conclusion In any 1 year, 1/12 patients who have suffered anaphylaxis will experience recurrence, and 1/50 will require hospital treatment or use adrenaline. Compliance with carrying and using adrenaline is poor. Occasional patients develop new triggers or suffer psychiatric morbidity.

Keywords adrenaline, alginate, anaphylaxis, epidemiology, EpiPen, follow-up, gelatine, Hemacel, psychiatric morbidity, recurrence

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Introduction

Recent studies suggest that new cases of anaphylaxis arise at a rate of 21 per 100 000 patient-years [1]. Community prevalence may be even higher [2], with up to 1/1000 adults and 1/170 school children experiencing at least one episode [3, 4]. There is also preliminary evidence that the incidence of food allergy and anaphylaxis, like that of asthma and allergic rhinitis, may be increasing [5–8].

For many, anaphylaxis is a disorder where the risk of relapse is chronic, but the event unpredictable. Prognosis is based on the natural history of some allergies, the amount of allergen required to trigger reactions, the ability to avoid some triggers/co-factors and the availability of immunotherapy [9–15]. Unfortunately, there are few published studies of the incidence or risk factors for relapse. The current study was designed to examine these issues in a

cohort of 432 patients evaluated in a community-based specialist medical practice in the Australian Capital Territory (ACT).

Methods

Study population

The setting was the ACT, an inland urban city (population ~0.33 million) within rural South-Eastern Australia. Patients were referred for evaluation of possible anaphylaxis to a community-based specialist medical practice between February 1995 and July 2000. Of 432 patients, 259 were resident in the ACT and 173 were resident in surrounding New South Wales (NSW). Occurrence data were derived by examining the subset of ACT residents (defined by their residential postcode), who experienced at least one episode of anaphylaxis during the 5.5-year observation period. The incidence of new cases was calculated by examining those 179 ACT patients whose first-ever episode of anaphylaxis occurred in the 5.5 years between February 1995 and July 2000. The Australian Institute of Health and Welfare (AIHW; a Fed-

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eral government body) provided ACT data pertinent to in-hospital anaphylaxis, derived from the National Hospital Morbidity Database for the years 1993–1998. Hospital cases meeting the criteria of the International Classification of Diseases (Ninth Revision) codes of 995.0 (other anaphylactic shock), 995.4 (shock due to anaesthesia), 995.6 (food) and 999.4 (serum) were included [16]. Data were entered into searchable databases (MediMouse, Practice Innovators, Sydney; Microsoft Access, Microsoft Corporation, Redmond, WA, USA). The term 'index episode' was defined as the most recent episode of anaphylaxis. The study was approved by the Ethics Committee of the John James Memorial Hospital.

Definition of anaphylaxis

Systemic anaphylaxis was defined as the presence of two or more of urticaria/angioedema, bronchospasm, gastrointestinal symptoms or hypotension [17]. Serious symptoms were defined as difficulty in breathing (bronchospasm, upper airway angioedema, severe coughing in a child) or evidence of a drop in blood pressure.

Patient management

All patients were given printed general information about the causes of anaphylaxis, common triggers, co-factors, and the need to avoid β -blockers. Their general practitioners were similarly warned. A written Emergency Action Plan was supplied in all cases. EpiPen autoinjectors were recommended in patients with a body weight greater than 15 kg. A diabetic needle and syringe were recommended for smaller patients. All patients were given verbal and printed instructions on the use of adrenaline. Correct administration was demonstrated in all cases, including practising with an EpiPen trainer where appropriate.

Skin testing

Commercially available glycerinated allergen extracts and histamine 10 mg/mL as a positive control (Dome-Hollister-Stier, Spokane, WA, USA) were purchased from Bayer (Sydney, Australia). Skin prick test (SPT) was performed on the volar aspect of the forearms according to standard guidelines using metal lancets (Dome-Hollister-Stier) [18]. A 10% weight/volume slurry of fresh food in sterile saline was used in the absence of commercial extracts or when initial screening was negative. Positive SPT was defined as a weal diameter 3 mm or larger than the negative control.

Challenge testing

In-hospital challenges (with appropriate resuscitation facilities) were recommended in selected patients where it was important to confirm or exclude triggers when more than one was implicated (e.g. positive SPTs to relevant foods and ingestion of a non-steroidal anti-inflammatory drug (NSAID) around the same time).

Follow-up survey

In August 2000, 432 patients with anaphylaxis were sent a covering letter describing the study and a written questionnaire asking about the timing, frequency and severity of relapse (as rated by the patient), their management, use of adrenaline, current medication and whether another trigger had been identified. If no reply was received, patients were reminded by mail and telephone. Those with serious recurrence were questioned in greater detail by telephone.

Recurrence of anaphylaxis

Recurrence was expressed as (1) the proportion of patients relapsing, and (2) the rate of recurrence/100 patient-years of observation, calculated by dividing the cumulative length of observation by the number of recurrences involving that trigger.

Statistical analysis

Statistical analysis (χ distribution) was performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

Results

Patient characteristics

Patients were generally young (mean age 27.4 years; standard deviation: 19.5; median: 26; range: 1–82; interquartile ranges 1–10, 11–26, 27–39 and 40–82). Twenty-seven percent were of school age (5–18 years). Forty-eight percent were male and 73% were atopic, defined as the presence of inter-current allergic rhinitis (56%), asthma (41%) or atopic dermatitis (26%). Atopy was a significant risk factor for episodes caused by food ($P < 0.01$) but not other triggers. There were no discernible differences in the pattern of symptoms or severity between non-atopic subjects, or between subgroups such as those with asthma, allergic rhinitis or atopic dermatitis (data not shown). Patients with idiopathic anaphylaxis were slightly older (age 37.8 ± 19.4 years, median 37 years), more likely to be female (62%) and less likely to be atopic (59%).

Frequency, seasonality and treatment of anaphylaxis

Of 432 referred patients with anaphylaxis evaluated in 1995–2000, 307 patients (71%) experienced their first episode in that period (Table 1). Of the remaining 125 patients whose first episode occurred before February 1995, 78 patients (18%) were referred after relapse in 1995–2000. An additional 10 patients (2%) relapsed after clinical evaluation but before the end of the survey period (see below).

Two hundred and sixty patients were seen after their first (index) episode of anaphylaxis. The remaining 172 patients (40%) experienced more than 586 previous allergic reactions of variable severity before assessment (median: 1; range: 0–20). Of the 'index' episodes, 54% were treated only in hospital, 10% were managed only by their general practitioner (GP), 5% were seen by their GP and in hospital, and 30% resolved spontaneously without intervention. Two

Table 1. Timing of initial and subsequent anaphylaxis

Date of first anaphylaxis	No.	Anaphylaxis 1995–2000	Questionnaire completed	Relapse	Total anaphylaxis 1995–2000
ACT					
1995–2000	179	179	118	40	179
Before 1995	80	Yes 50 No 30	32 21	19 5	50 5
Total	259	259	171	64	234
NSW					
1995–2000	128	128	102	50	128
Before 1995	45	Yes 28 No 17	19 12	11 5	28 5
Total	173	173	133	66	161

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hundred and eighty-six (67%) patients were seen within 1 month of their index episode, 364 (85%) within 6 months and 378 (88%) within a year (median: 1 month; range: 1 week – 18 years). Comparable data for ACT-resident patients were 183 (73%), 220 (85%) and 229 (88%). Other than stinging insect allergy (more prevalent over summer), anaphylaxis occurred without discernible seasonality. There were no discernable 'time trends' to suggest an increase in occurrence or rate of referral over the study period.

Clinical features

Symptoms included urticaria (61.6%), upper airway angioedema (45.3%), bronchospasm (44.2%), gastrointestinal symptoms (38.8%), dizziness/vascular collapse (33.7%), flushing (6.3%), loss of consciousness (5.1%), rhinitis (3.7%), headache (2.7%), palpitations (2.6%) and fear (2.1%). Seventy percent of patients had serious features. Fifty-eight percent of patients developed symptoms within 15 min of exposure to their trigger, 83% within 1 h and all within 9 h. In six patients with onset beyond 6 h, the cause was food and NSAIDS in three cases each.

Cause of anaphylaxis

Aetiology was defined in 396/432 (91.6%) patients. The most common causes were those of food (60.9%), stinging insects (20.4%) or medication (8.3%) (Table 2). Only 33/48 patients with allergic reactions to fruit/vegetables suffered from oral allergy syndrome (OAS). The remainder suffered recurrent episodes of anaphylaxis if they ingested semi-cooked (e.g. stir-fried) or salad vegetables and then exercised. Food additives/preservatives/MSG were not implicated in any case. Only two cases of anaphylaxis following animal exposure were observed during the study period, perhaps reflecting referral bias and avoidance of an obvious allergen.

SPT with crude extracts of food facilitated the identification of some unusual causes. For example, two cases were triggered by Echinacea, one after the first-ever dose

Table 2. Cause of anaphylaxis

Cause	No. of patients	%	Age range (years)	Age (median)
Food	262	60.9	1–71	20
Peanut/tree nut/seeds	112	26.0	1–65	7
Peanut	62	14.4	1–65	4
Tree nut/seed	49	11.4	1–65	13
Peanut+tree nut/seed	53	12.3	1–65	5
Egg	49	11.4	1–51	3
Fruit/vegetables	48	11.1	5–53	30
Wheat	29	6.7	10–68	31
Crustaceans	27	6.2	1–70	34
Scaly fish	22	5.1	1–68	13
Cow's milk	19	4.4	1–30	3
Soy	8	1.9	6–50	20
Meat	7	1.6	12–71	29
Gelatine	4	0.9	39–71	54
Alginate	1	0.2	40–40	40
Bites and stings	89	20.7	4–79	31
Bee	69	15.8	4–79	28
Jumper ant	13	3.0	7–65	51
Wasp	5	1.1	26–59	36
Tick	2	0.4	52–70	61
Idiopathic	36	8.3	4–82	37
Drugs	36	8.3	7–71	37
Aspirin alone	8	0.2	17–50	30
Paracetamol alone	1	0.2	58	58
Aspirin+paracetamol	1	0.2	32	32
Other NSAIDS	10	2.3	29–70	53
Antibiotics	7	1.1	25–55	33
General anaesthetic	5	1.1	7–71	34
Echinacea	2	0.7	17–38	28.5
Haemaccel	2	0.5	46–73	59.5
Exercise alone	8	0.2	15–38	37
Cold	3	0.7	16–25	21
Latex	2	0.5	43–48	45.5
Animals	2	<0.1	32–68	50

A cause was defined in 396/432 cases (91.6%). Some patients were sensitive to more than one allergen: two patients were allergic to Haemaccel and oral gelatine; one patient was allergic to bee venom and food; one patient was allergic to latex and food; one patient was allergic to antibiotic and food; 262 patients were allergic to 326 foods; 36 patients were allergic to 37 drugs. Only 33 of the 48 patients with allergic reactions to fruit/vegetables suffered from oral allergy syndrome.

[19]. Two suffered intraoperative anaphylaxis attributed to Haemaccel, went on to react to oral gelatine and were found to have positive SPT to both agents. A baker who experienced anaphylaxis to artificial cherries was found to be sensitive to alginate, a seaweed-derived vegetable gum found in a variety of other foods including seaweed crackers, fruit glazes, some dairy products and low-calorie jams [20].

Exercise as a co-factor

Exercise was an important co-factor in 88 patients, either as the sole identifiable trigger (eight subjects), or as a co-factor involved in episodes triggered by NSAIDS (two cases) or food (78 patients). Of these 78 patients, dietary triggers were semi-cooked fruit or vegetables (27), wheat (25), nuts/seeds (9), crustaceans (7), meats (4), soy (3), egg (2) or gelatin (1). Most occurred during exercise and after ingestion of food

(76/78), but two occurred when food was consumed afterwards. Food was ingested within 1 or 6 h in 60% and 99% cases, respectively.

Challenge testing

Seventeen deliberate challenges were performed. Seven challenges were to exclude NSAID sensitivity in patients diagnosed with food allergy (all negative). Challenges were also performed to exclude persistent food allergy in two children whose skin tests had become negative (both negative), and in one adult considered to be sensitive to another food (also negative). Five challenges were positive as expected (three to NSAIDs; two to food and exercise). False-negative challenges were observed in two patients with wheat and exercise anaphylaxis. These patients continued to react to the same triggers until they adopted a wheat and gluten-free diet. One patient who declined to undertake open challenge with aspirin later relapsed following ingestion of another NSAID.

Psychiatric morbidity

Five patients re-presented within 6 months with symptoms of panic attack, with two experiencing unnecessary hospital treatment and administration of adrenaline. Some adult patients (and parents of children with anaphylaxis) described transient fear and sleep disturbance that generally abated within a week.

Estimated occurrence of anaphylaxis in the ACT

Occurrence was estimated by considering the 259 author-derived patients (both hospitalized and non-hospitalized) with an ACT-residential postcode at the time of anaphylaxis, and patients captured by AIHW data for hospitalized patients in the ACT. Of 259 ACT patients, 234 experienced an episode of anaphylaxis during the 5.5-year observation window (179 first-ever episodes, 55 relapsing patients whose first episode occurred before 1995). By considering these patients, a minimum occurrence of 42.5 new referrals/year was calculated, equivalent to 12.9 cases/100 000 patient-years and an overall occurrence of 1/1410 ACT residents over the 5.5-year period. By contrast, AIHW data alone suggested a figure of 5.1/100 000 patient-years and one death every 2.5 years.

New cases of anaphylaxis arising in the ACT

Incidence of new cases of anaphylaxis was estimated by considering the 179 author-derived patients (both hospitalized and non-hospitalized) with an ACT-residential postcode at the time of their first-ever episode of anaphylaxis during the study period (Table 1). This was estimated at 9.9 new cases per 100 000 patient-years, equivalent to 1/1844 ACT residents over the 5.5-year period

Response to questionnaire

In all, 304/432 patients (62% males, 72% females) completed the questionnaire, representing 674 patient-years of follow-up out of a possible 994 years. The maximum duration of

possible follow-up was 5.5 years. Those who completed questionnaires had similar clinical features, atopic status and causation as those who did not (data not shown). While those who responded to the questionnaire were older than those who did not (mean age 29.3 vs. 22.7 years; SD 20.7 vs. 15.4; median 29 vs. 21), these differences were not statistically significant ($P < 0.05$).

Rate and severity of recurrence

In all, 130/304 patients (42.8%) claimed to have experienced a total of 386 episodes of recurrent symptoms (median: 2; range 0–18). Of those suffering claimed relapse, 45 patients experienced one episode, 34 patients had two episodes, 19 patients experienced three episodes and 32 patients stated that they had experienced more than three episodes. Severity was rated as mild (82 patients, 227 episodes), moderate (39 patients, 91 episodes) or serious (45 patients, 68 episodes). Recurrence did not appear to slow down with time. Rates of overall and serious recurrence were 57 and 10 episodes/100 patient-years, respectively. No deaths were recorded. Of 45 patients suffering serious recurrence, 18 administered adrenaline and 26 attended hospital on at least one occasion. Of 85 patients suffering from non-serious recurrence, one administered adrenaline and nine attended hospital on at least one occasion.

Risk factors for relapse

Peanut/tree nuts were numerically the single most common trigger for non-serious and serious recurrence. When expressed in the form of recurrence/100 patient-years of observation, however, patients were more likely to suffer recurrence with idiopathic or exercise-related anaphylaxis (Fig. 1). Atopy was not a risk factor for recurrence; the proportion of atopic patients with recurrent symptoms was identical to the proportion of patients in the original cohort. Fifty percent of patients with serious recurrence had asthma, only slightly higher than the 38.5% of questionnaire responders with asthma ($P > 0.05$). Recurrence was more common in females than in males (48.5% vs. 36.5%; $P < 0.03$). Of the 45 patients experiencing serious recurrence, all but one had experienced serious symptoms in the past. This patient was an egg-and peanut-allergic infant who had experienced urticaria and vomiting with initial presentation, did not have intercurrent asthma at the time of initial evaluation and was not contactable to verify the severity of claimed recurrence.

Idiopathic anaphylaxis

A third of 36 patients with idiopathic anaphylaxis suffered recurrent symptoms and three used injectable adrenaline. No cause was identified with follow-up in any patient.

Relapse in patients undergoing stinging insect immunotherapy

Fifty-eight bee/wasp-allergic patients were contactable. Sixteen of 35 bee-sensitive patients who commenced immunotherapy were re-stung and one (6.25%) had a mild systemic reaction. Of 20 patients who did not undertake bee venom

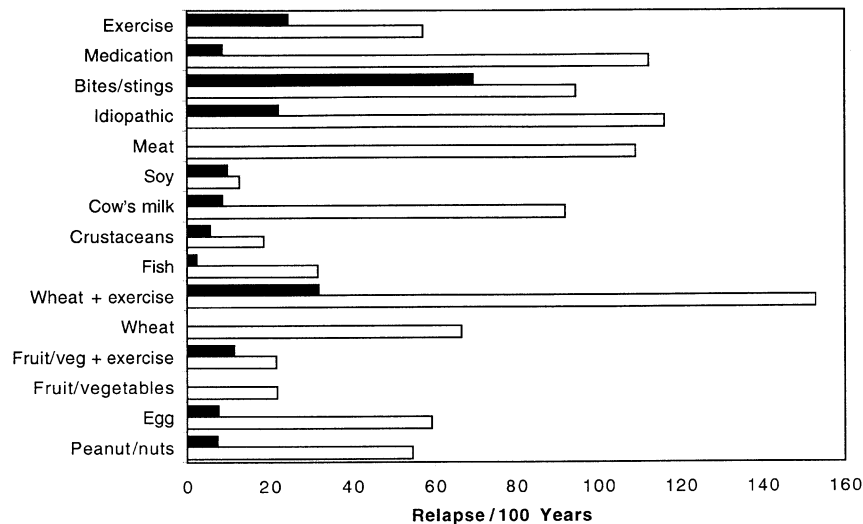


Fig. 1. Recurrence of anaphylaxis. Patients with anaphylaxis were followed up for a mean of 2.2 years (range: 1 month to 5.5 years). The risk of overall recurrence (unshaded bars) and serious recurrence (shaded bars) is expressed as relapse per 100 patient-years.

immunotherapy, 2/4 suffered serious reactions after spontaneous field stings. Of three contactable wasp-allergic patients on regular immunotherapy, one has suffered serious recurrence and needed adrenaline after each of three re-stings.

Use of cardiac medication

Seventeen of 304 patients were using cardiac medication, including β -blockers (3), ACE inhibitors (9), diuretics (5), calcium channel blockers (6) or digoxin (1).

Compliance with adrenaline

Of 229/304 patients advised to carry adrenaline, all recalled being advised to do so, 167 carried it (73%), 148 EpiPens were in date (65%) and 19 patients had used it (8%). Males carried adrenaline more often than females (72% vs. 66%; $P < 0.05$). The likelihood of compliance with carrying adrenaline was inversely proportional to the time since original assessment (compliance rates 1995–2000: 63%, 57%, 63%, 74%, 78% and 78%, respectively).

Development of new or worse sensitivities with time

Thirty claimed to have identified additional triggers. Most were either the same or similar cause (e.g. different nut, another fruit/vegetable). One case in which NSAID and exercise were blamed was re-classified as idiopathic. Five patients were proven to develop new sensitivities with further testing:

- Of two patients with bee venom anaphylaxis, one developed wheat and exercise anaphylaxis and the second developed an allergy to multiple nuts.
- One patient allergic to raw cabbage became allergic to multiple nuts.
- One patient with fruit and vegetable allergy developed sensitivity to multiple nuts.
- One female patient with food- and exercise-induced anaphylaxis due to nectarine presented a year later with

occupational asthma, allergic rhinitis and contact urticaria to latex related to her work as a theatre nurse.

A paediatric patient with a non-anaphylactic urticaria after a bee sting (not included in this study) returned 3 years later with cashew-induced anaphylaxis. Five patients with wheat- and exercise-triggered anaphylaxis started to react to wheat alone (e.g. on an empty stomach or after hot baths or aspirin). Four patients experienced symptoms with sexual activity: two had wheat- and exercise-induced anaphylaxis, two were idiopathic.

Telephone survey of patients with serious relapse

Twenty-two patients with serious recurrence were contactable. Half of all recurrences occurred at home, the remaining episodes occurring at school or child-care (three patients), at the homes of friends or relatives (three cases), work (two cases), or sport oval, restaurant or remote bushland (one case each). Adrenaline was carried by 16 patients and out of date in one. Only 4/11 patients carrying EpiPen were able to describe all five steps required for correct use and another four were able to describe four steps (omitting the need to hold in place for 10 s). One patient each was able to describe one, two or three steps. When recurrent symptoms occurred, three used adrenaline, eight preferred antihistamines, 11 went to hospital, three used bronchodilators and one saw their primary care doctor. When asked why adrenaline was not used or carried, comments included: fear of needles/adrenaline, preference for hospital treatment or the drug being out of date. Of the three patients who used adrenaline, no additional treatment was required, compared to 3/11 who attended hospital.

Discussion

Whereas children with anaphylaxis are estimated to relapse at a rate of 0.98 episodes per patient-year [21], perhaps only a third of adults experienced recurrent symptoms in another study [22]. Unfortunately, few published studies have

examined risk factors for relapse or analysed the incidence or prevalence of recurrent anaphylaxis as a function of time or cause. Advice to patients is therefore based on a knowledge of the natural history of some allergies, the ability to avoid some triggers and co-factors, and the capacity to reduce the risk with specific immunotherapy [9–15]. For example, while sensitivity to cow's milk and egg allergy may improve with time, and exercise-associated anaphylaxis may become less frequent, those with idiopathic anaphylaxis continue to suffer unpredictable episodes [9, 14, 15]. The worst outcome is generally reserved for patients with peanut/tree nut-induced anaphylaxis, who are most likely to suffer recurrent symptoms and fatal outcomes [22–25]. Unfortunately, the literature gives little guidance to the treating physician when patients lie outside these major groups.

In this study, approximately one in 12 patients who had suffered an episode of anaphylaxis complained of recurrent symptoms per year of follow-up, of which a quarter were serious and the remainder less severe than the original episode. While asthma and atopy were common co-morbidities, unlike other studies [22–24], neither condition was identified as a risk factor for serious or non-serious recurrence. Instead, the best predictor of serious recurrence was the presence of serious symptoms on initial presentation. Consistent with previous reports [22–25], allergic reactions to peanut/tree nuts were the most common cause of anaphylaxis and the most common reason for recurrence. Contrary to expectations, however, rates for any given trigger were remarkably similar when expressed as recurrence/100 patient-years and 'low-risk' groups were not identified (Fig. 1). This is not surprising when one considers the difficulty in avoiding major staples. For example, abstinence is normally advised in those allergic to peanut/tree nuts, egg or cow's milk. In contrast, cereal- and fruit/vegetable-sensitive subjects are frequently instructed to eat other members of the same group, or refrain from eating the food within 4–6 h of exercise [26, 27].

Such advice proved inadequate for many patients in this study. Not only were patients sensitive to multiple fruit/vegetables (making it difficult to comply with restrictions), some developed sensitivities to new foods over time. Furthermore, avoidance of food allergen (such as wheat or fruit/vegetables) within 6 h of exercise proved inadequate in preventing recurrence in half the subjects, suggesting that complete abstinence may be required in such cases.

There are potential limitations when interpreting the results of survey-derived patient-reported data. For example, patients without relapse may have ignored the survey, leading to an overestimate of the incidence of relapse. While this seems unlikely given the similarity between those who answered the survey and those who failed to do so (demographics, atopic status and type, trigger), mortality in this group cannot be excluded. In those who did respond to the survey, some may have over-reported mild or intercurrent symptoms (e.g. asthma or urticaria) as representing recurrent anaphylaxis. Even if one interprets reports of non-serious symptoms with caution, it is difficult to ignore the one in six patients with serious symptoms of relapse, requiring adrenaline or hospital treatment.

While 10% of patients claimed to have developed new allergic triggers over the period of follow-up, most were

considered to be of a similar or cross-reactive trigger. Of greater interest is that five patients developed new and not obviously cross-reactive sensitivities and others had more than one trigger for anaphylaxis. While this phenomenon has rarely been described previously [28], it is not surprising given the knowledge of the natural history of other allergic disorders [29, 30]. Taken together with evidence that food allergy can worsen with time [31], this finding provides a rationale for advising patients who have suffered further episodes to document the circumstances and seek review to re-examine diagnostic and management issues.

Double-blind placebo-controlled challenges are sometimes recommended to confirm the diagnosis of food allergy and reduce the need for unnecessary dietary restriction. Routine challenges were not, however, performed in this study, but rather used to confirm or exclude the diagnosis when more than one possibility existed. As in other studies [32], false-negative challenges were observed in at least two patients with wheat and exercise anaphylaxis. These patients continued to react to the same triggers until they adopted a wheat- and gluten-free diet. For this reason, the author considers that while a positive challenge test gives useful information to the treating physician and patient, a negative test does not always exclude the diagnosis. This is another reason to document the circumstances of further episodes and review if the original diagnosis is in doubt. Perhaps the most important information about quality assurance was obtained from the follow-up study, where those who relapsed did so to the same or cross-reactive trigger in almost all cases and the cause was reclassified in only 1/304 patients.

The true incidence of anaphylaxis is difficult to quantify, in part related to disagreement about diagnostic criteria [33], difficulties in distinguishing it from other disorders (e.g. severe urticaria/angioedema) or selection bias based on hospital presentation [7, 34]. In this community-based study, the minimum incidence of new cases was estimated at 9.9 per 100 000 patient-years, much lower than the 21 per 100 000 patient-years reported in Olmsted County [1]. This almost certainly underestimates incidence in the ACT, as it does not take into account patients managed by other medical practitioners or in accident and emergency departments, those in whom the diagnosis was missed, patients who never sought medical attention and those who did or will present later for clinical evaluation. While incidence data from other sources were either incomplete or unavailable, this study was able to demonstrate that 40% of anaphylaxis was treated in the community, a fact to be borne in mind when interpreting hospital-based data [34]. Moreover, when one considers the tendency for relapse, the actual occurrence of episodes of anaphylaxis is likely to be even higher.

Sensitization to pollen has been identified as a potential risk factor for anaphylaxis in epidemiological studies [4]. This may not simply be a marker of atopy (co-sensitization), but rather indicates a role for cross-sensitization via the respiratory route in the pathogenesis of some cases. Thus, an increase in the prevalence of allergic respiratory disease could result in a parallel increase in food allergy as well [35]. This hypothesis is supported by (a) the uniform detection of positive SPT to grass/weed/tree pollens in fruit/vegetable-allergic patients, in the absence of OAS or allergic respiratory disease; (b) the development of OAS/food allergy in pollen-sensitive subjects

[36]; (c) cross-reactivity between pollen- and food-derived profilins and lipid transfer proteins [37]; (d) evidence that sensitization to allergen such as latex may occur via the respiratory route [38]; (e) the ability of 'aeroallergens' to trigger anaphylaxis if ingested [39, 40]; (f) occasional reactions to complementary and alternative medicine upon first known exposure [19, 41–43]; (g) reports of decreased food reactivity in patients undergoing immunotherapy with pollen-derived allergen extracts [44, 45]; and (h) preliminary evidence of an increasing incidence of food allergy/anaphylaxis [6–8].

Exercise was the most important co-factor increasing the risk of food-induced anaphylaxis in this study. Proposed mechanisms include increasing the blood flow and the rate of food absorption, reducing the threshold for mast cell degranulation or altering autonomic activity [46, 47]. The latter may explain why sexual activity was identified as a co-factor as well. A clue to the pathogenesis of these cases may lie in the absolute quantitative signal required to induce mast cell degranulation. For example, only minute amounts of peanut are required to trigger symptoms compared to some other allergens [12], whereas some patients need to ingest more than one food or an NSAID before symptoms develop [32]. Taken together with evidence of immunological cross-reactivity between inhaled and ingested allergen, one could speculate that food and exercise-induced anaphylaxis might be mediated by cross-reactive IgE antibodies with a lower affinity for ingested than inhaled allergen. This hypothesis is consistent with the need for wheat- or fruit/vegetable-sensitive subjects to eat relatively large quantities of food to trigger symptoms, compared to others such as peanut.

Adrenaline is recommended for the initial treatment of anaphylaxis, based on its physiological effects, anecdotal evidence of efficacy, and the mortality associated with absent or delayed administration [22–24]. While the effectiveness and safety of adrenaline has recently been questioned [48], all but one of the 19 patients who used it in this study found it helpful. Perhaps the best published evidence of efficacy is that of Gold and Sainsbury [21] who observed that when adrenaline was given in an outpatient setting, only 2/13 cases needed additional treatment in hospital, compared to 15/32 cases when it was withheld.

Only half of the patients with serious relapse were able to use EpiPen correctly, despite verbal and printed instructions, and practice with an EpiPen trainer. Similar findings have been described in other surveys, where only 22–44% recall how to use the device, 30–78% have it available, 29–79% use it and 0–100% find it effective [21–24, 48–51]. These factors are more important than arguments about whether adrenaline is always effective [48]. Unfortunately, compliance problems were not restricted to carrying and using adrenaline. Some patients were prescribed contraindicated medication, and 40% of serious bee-allergic patients not only failed to commence immunotherapy but also failed to return despite recall letters and further episodes of anaphylaxis [52].

The reasons for these findings are uncertain, but some answers may lie in considering social and psychological aspects of anaphylaxis. Relevant factors include denial, risk taking [53], the diminution of threat with time since recurrence and social factors. Patient education and recall systems are options to improve compliance. Unfortunately, such measures were not always effective in this patient group,

and in theory could actually increase anxiety levels in patients already fearful of further unexpected episodes. Not only has iatrogenic 'pseudoanaphylaxis' been reported [54], but can at times be difficult to distinguish from serious allergic reactions [55]. Despite these findings, social and psychological morbidity has rarely been described or studied [28, 56, 57]. While five patients appeared to have major psychiatric disturbance following anaphylaxis, it is uncertain whether this was a pre-morbid condition or resulted directly from the stress following anaphylaxis.

Anaphylaxis is a disorder where the threat of recurrence is chronic but the event unpredictable. Review after each relapse offers an opportunity to re-educate patients on the use of EpiPen, to ensure that the device is renewed at appropriate intervals, and to provide counselling where appropriate.

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