

RESEARCH LETTER

WILEY

Improved anaphylaxis referral rates to specialized services from an Emergency Department

To the Editor,

The UK has high allergy prevalence rates, with 30%-40% of the population affected by allergy. Hospital admissions for anaphylaxis, its most severe manifestation, have increased sevenfold since 1990.¹ It has long been thought by many that most patients attending hospital as an emergency with anaphylaxis are not referred for specialist evaluation to determine its cause.² This is important in order to identify causative allergens that should be avoided and formulate a plan for managing reactions including training in adrenaline self-administration.^{3,4} Evaluating such patients is a function of a specialized allergy service as delineated in the UK by the Department of Health Specialised Services Definition set No 17.

Cardiff and Vale University Health Board hosts the only Specialised Adult Allergy Service (SAAS) for adults in Wales. We performed an audit in 2007 to determine how many patients attending the Health Board's Accident and Emergency Department (A&E) with anaphylaxis were referred and subsequently seen in the SAAS. We found that 77 patients attended A&E with anaphylaxis in a 6-month period in 2007 but none of these were referred to the SAAS.⁵ In December 2011, the National Institute for Clinical Excellence (NICE) published guidelines advising that after emergency treatment for suspected anaphylaxis all patients should be offered referral to a SAAS and an appropriate adrenaline injector as an interim measure before the specialist appointment.⁶ In 2012 and 2013, both Departments implemented a streamlined referral pathway for these patients and we now report on the effect of these changes.

On arrival at A&E, patients are triaged and treated appropriately and a decision made whether to admit or discharge patients who have had anaphylaxis. In response to the NICE guidelines, the A&E Department introduced in 2013 a comprehensive pro forma document for completion by A&E staff that detailed clinical aspects of patients' presentation with anaphylaxis and its urgent management that incorporated a referral form to the Department of Immunology and Allergy for direct patient referral to the SAAS if indicated.

The Department of Immunology and Allergy wrote a 3-page document (Supplementary information) that defined anaphylaxis, listed its major causes and indicated what long-term changes to patients' treatments should be made immediately, which patients should be referred to the SAAS and which should be followed up in primary care. It was written to distinguish isolated urticaria and angioedema

clearly from anaphylaxis (in order to solicit referral only of patients who had had anaphylaxis) and concisely listed major causes of these conditions and their appropriate management. A request was made for this to be given to the patient to give to their GP (in the case of patients who did not require hospital admission or specialist follow-up, for example when a drug might be stopped or changed if causing drug-induced anaphylaxis) to help inform onward primary care management.

We also established in January 2012 a monthly rapid access outpatient allergy clinic so that all patients referred from A&E with anaphylaxis could be seen within 6 weeks.

The medical records of all patients attending A&E are encoded in an electronic database. In the initial audit, patients attending A&E with anaphylaxis during the 6-month period 1 April to 30 September 2007 were identified by searching the electronic database using the likely keywords: *allergic, allergy, anaphylaxis, anaphylactic, rash, swelling, breathing difficulties, vasovagal episode/attack, convulsion, bite, sting, local infection, insect, bruise, abdominal pain, asthma, reaction or pyrexia*. These identified 200 patients whose full A&E records were retrieved for further scrutiny, among whom 77 patients with anaphylaxis requiring specialist assessment were identified. In the re-audit of patients attending during the same 6-month period from 1 April 2016 to 30 September 2016, the (same) keywords were used, and the keywords *nut and food* were added in order to increase the likelihood of identifying patients. Each full A&E record of patients identified was scrutinized carefully to ascertain exactly which patients should have been referred to the SAAS. The work was approved by the Health Board's Clinical Audit Department.

The SAAS database was searched to ensure that all patients referred to the allergy service during the period of the audit would have been identified, even if they had been wrongly given a routine rather than a rapid access clinic appointment.

In the 2007 audit, 3500 A&E patient records were identified from the keyword search and 77 cases of anaphylaxis identified, none of whom were referred to the SAAS. In the 2016 re-audit, 6590 records were identified and only 41 patients were identified as having had anaphylaxis indicating that they should have been referred to the SAAS. Only 18 of these 41 patients were actually referred. All were given urgent appointments, and 17 attended (Figure 1).

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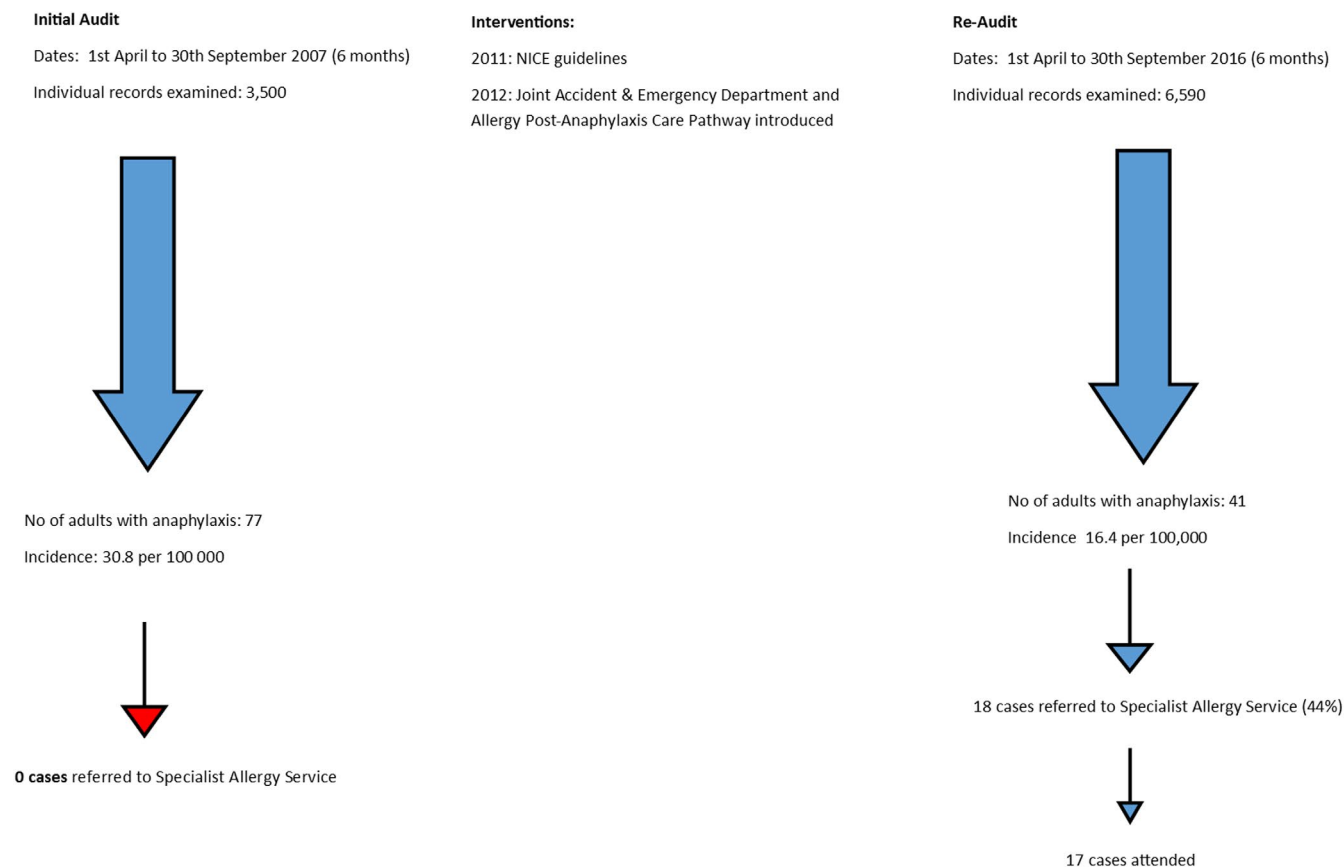


FIGURE 1 Number of A&E records scrutinised, cases identified and referred before (2007) and after (2016) introducing guiding document and patient referral pathway

The 18 patients referred (R) and the 23 patients not referred (NR) were similar in the A&E assessment of the number that had had reactions to food (12R, 10NR), medications (4R, 3NR), insects (0R, 1NR) or plants (0R, 1NR). Suspected precipitants in 10 patients (2R, 8NR) were not documented. Epinephrine for self-administration devices were required for 17 of the 41 patients who required referral and were prescribed by A&E to 14 of those patients (82%), not having been recorded as being prescribed to 3 patients with food allergy (2 to nuts, 1 to egg). Epinephrine was not prescribed to 16 patients (9R, 7NR) at discharge from A&E whose symptoms were due to side effects of NSAIDs, salicylates, other drugs or oral allergy syndrome or who had mild wheezing only, in whom drug therapy was appropriately changed and avoidance of the identified precipitant advised. In the remaining 8 patients not referred to the SAAS, the A&E records were not sufficiently detailed to ascertain if epinephrine device prescription was indicated.

More A&E attendees were identified in 2016 (6590) than in 2007 (3500) indicating the increase in number of patients without anaphylaxis attending A&E. The changes were made in the documentation and patient referral pathway was associated with an improvement in the rate of referral of patients to the SAAS from 0/77 = 0% in 2007 to 18/41 = 44% in 2016. This is a significant improvement in performance, although there is room for further improvement.

World Allergy Organisation anaphylaxis guidelines in 2011 recommended that at the time of discharge from a healthcare setting such patients should be equipped with epinephrine for self-administration and taught why, when and how to administer it, given a written personalized anaphylaxis emergency action plan stating the common symptoms and signs of anaphylaxis, and medical identification.⁷ We wrote our document to guide the onward management of these patients by referral to the SAAS or to their GP to facilitate immediate changes in drug treatment if required, and to aid the management of patients with spontaneous urticaria or angioedema who might be more appropriately managed in primary care.

The incidence of anaphylaxis has been reported in 2008 to vary from 3.2 to 20 per 100 000⁸ or to 49.8 per 100 000 when reliance was not placed upon hospital coding systems.⁹ Despite the reported rising incidence of anaphylaxis,¹ we found a lower incidence in 2016 (41 patients in 6-months = 16.4 per 100 000) than in 2007 (77 patients = 30.8 per 100 000) which we cannot explain. We think it unlikely that patients may have preferentially presented to A&E departments elsewhere outside our Health Board or were misclassified on the A&E coding system, which was unchanged from 2007 to 2016. We think it unlikely that patients may have preferentially seen their GPs first and then been referred by them to hospital Medical Assessment Units (MAU) as patients with acute anaphylaxis are much more likely to attend

TABLE 1 Post-anaphylaxis management

Identifying likely precipitant
Stop suspected drugs (eg ACE inhibitors, A2R antagonists, Amlodipine, NSAIDs, SSRIs, SNRIs, PPIs, Bisphosphonates, Tetracyclines, Statins, Finasteride, and Tamsulosin) even if tolerated for many years, start regular oral antihistamines and arrange GP follow-up
GP follow-up for known nut allergy, and for Oral Allergy Syndrome and specific food allergy if no epinephrine required
Allergy service referral if previously unknown nut allergy, idiopathic anaphylaxis, exercise ± wheat/other food induced anaphylaxis, stinging insect anaphylaxis or if epinephrine required for oral allergy syndrome or reaction to other specific food
Prescribe self-injectable epinephrine for anaphylaxis due to allergy to nuts, other food that is difficult to avoid (eg milk), insect venom, exercise-induced or idiopathic anaphylaxis

A&E immediately than consult their GP first. The post-anaphylaxis management document was sent to all MAUs in Wales in late 2015 and so was available for use at each MAU from that time. Furthermore, a detailed search of the SAAS database failed to identify any patient referred from a MAU during the audit period. It seems unlikely that the lower incidence reflects patients who have previously had anaphylaxis and are treating further episodes at home and not attending A&E afterwards, as it is the minority of patients who experience recurrent anaphylaxis.¹⁰ We think it unlikely that many patients presenting to A&E with anaphylaxis may have been misdiagnosed in 2016 compared with 2007 in view of the increased awareness of anaphylaxis, the publication of the 2011 NICE guidelines and our response to these guidelines.

None of the 41 patients identified as having anaphylaxis at A&E were previously known to the allergy service. Eighteen (44%) were referred to the SAAS, and no statements were made in any of the A&E records of the 23 patients not referred indicated explicitly why they were not referred. Suspected precipitants in 10 patients were not documented, and as only 2 of these were referred and 8 not referred, it is possible that inability to identify a suspected precipitant may predispose to non-referral. All UK A&E departments are extremely busy and it seems most likely that the remaining 56% were not referred because of the pressure under which all A&E staff work. Although all A&E junior doctors receive full and appropriate instruction about anaphylaxis during their induction, the constantly increasing number of patients attending A&E, chronic understaffing, high frequency of junior doctor rotation through A&E (4-6 monthly), the 4-hour waiting time target and IT access limitations may all contribute to some post-emergency management arrangements being incomplete.

Adrenaline for self-administration was prescribed by A&E staff at the time of discharge to 14 of the 17 patients who required this. Adrenaline prescription was not recorded in the remaining 3, two of whom had known food allergy. Adrenaline autoinjectors were in our view justifiably not prescribed by A&E staff to 16 patients who had symptoms from side effects of drugs, oral allergy syndrome or mild wheezing, in whom appropriate changes in drug therapy and

food avoidance was advised. These are reassuring findings and indicate appropriately discriminatory prescribing by A&E staff. Current resources are insufficient for A&E staff to meet all demands in all areas, and redistribution of existing resources within A&E departments is unlikely to improve post-anaphylaxis management. We think that the employment of more advanced nurse practitioners who could review such patients following recovery in a dedicated 24-hour stay facility and more reliably refer them to the SAAS as per written protocol is the most likely way of improving the post-anaphylaxis management of these patients.

In view of the encouraging improvement in referral rates, we have not changed the post-anaphylaxis patient referral pathways suggested. As an initial step, we have however prepared an abbreviated document shown in the Table 1 that may be easier for busy junior doctors to use (full version used shown in Appendix S1). This A&E activity is an area that needs to be more actively targeted by clinical allergy specialists. We hope that other allergy specialists and A&E departments might find this to be a useful document to adapt and customize for their own particular situation.

KEYWORDS

anaphylaxis, audit, emergency, referral pathway

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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

Supplementary information section: Post Anaphylaxis Management

Definition of anaphylaxis

Anaphylaxis is caused by histamine and other mediators released by massive activation of mast cells. They may be activated by IgE-mediated allergy to a protein allergen, or by mechanisms other than allergy – eg by the direct actions of many drugs on mast cells.

Mast cell activation may cause flushing, itchy rash (urticaria) and swelling (angioedema), but can also cause rhinitis, nausea, vomiting, abdominal pain, diarrhoea and anxiety. Anaphylaxis occurs when the activation is so extensive as to cause rapid, physiologically significant, life-threatening disturbances of **Airway, Breathing or Circulation**, sometimes with a feeling of impending doom.

ie **Mast cell activation** $\pm$ **Flushing, Itching, Urticaria, Angioedema, other symptoms**
 Anaphylaxis **= Significant disturbance of A, B or C $\pm$ the above**

Diagnosis

Anaphylaxis is diagnosed clinically from the history and presenting symptoms and signs, after exclusion of other candidate causes of significant disturbances of A,B and C (shock, asthma, respiratory distress etc). The diagnosis may be supported by information in the history such as very recent (<60 minutes) exposure to a known or likely precipitant or consumption of some drugs (see below). It can be confirmed in some instances by a raised serum tryptase concentration.

Immediate Investigations and Treatment

These are directed at the diagnosis and treatment of the physiological disturbances of A,B, C (ie excluding other causes) and **other guidelines cover this** (eg Resuscitation Council UK).

Diagnosis of the cause of anaphylaxis

After the A, B, C disturbances $\pm$ other symptoms have been stabilised, their cause needs to be determined - whether anaphylaxis or simply urticaria/angioedema without anaphylaxis – in order to try and identify any precipitant so that it may be avoided in future. Physical examination doesn't distinguish between different possible causes. A detailed history is required with specific questions seeking to identify evidence of the most likely cause(s). The tables below summarise relevant information about the most likely causes, tests and management actions to take.

Most people get mast cell activation $\pm$ anaphylaxis because of the direct actions of drugs on mast cells, food allergy or reactions to chemicals present in food consumed. Many of the causative drugs (eg ACE inhibitors, SSRIs, statins) can be tolerated normally for some years before symptoms of mast cell activation first occur, thus making the correct diagnosis elusive. Conversely the adverse effects can continue to occur for some months after the causative drugs have been stopped. Blood tests exist for food allergy, penicillin but not to most drug or chemical causes. Blood tests should be requested only for specifically suspected allergens – there is no place for an 'Allergy screen'.

Tryptase is an enzyme expressed inside mast cells whose serum concentration rises after mast cell activation. It then falls with a half-life of a few hours in vivo. If there is clinical doubt about the cause of the ABC symptoms, then a rise and fall in serum tryptase confirms that they were due to anaphylaxis. There is little point measuring serum tryptase in the absence of a significant disturbance of A, B or C. If tryptase assay is required, take 4ml clotted blood when the patient is stable/recovering and another 1-2 hours later. Label the samples and request form with the times of venesection. A baseline value can be measured the next morning or when the patient attends a follow-up clinic, as raised baseline values can occur in the rare clonal disorder mastocytosis.

Cause	Further information	4ml clotted blood test	Follow-up required
Drugs taken regularly	ACE inhibitors, Statins, SSRIs, SNRIs, PPIs, A2R antagonists, Bisphosphonates, NSAIDs, Amlodipine, Tetracyclines, others – look up BNF	Not Available	See table below Stop offending drugs See GP
Drugs given acutely	X-ray contrast drugs containing Iodine Gelofusin, protamine Blood product reactions via Ab-Ag interaction → C3a, C5a.. (complement anaphylotoxin formation) General anaesthetics (neuromuscular blockers)	Tryptase	Discuss with the Dr who gave the material concerned, who should see the patient
Antibiotics or other drugs	Penicillins, 1st & 2nd generation cephalosporins. The service for investigation and management of drug reactions in S Wales is provided by the Dept of Clinical Pharmacology, Llandough Hospital.	Tryptase Penicillin IgE	Drug reaction service
Other antibiotics	Urticaria & angioedema can occur after some other antibiotics	Not Available	GP
Possible nut allergy	If symptoms within a few hours (usually within 1 hour) of eating nuts or food containing nuts, and not known to have nut allergy	IgE against suspected nut	Allergy clinic
Oral Allergy Syndrome	Oral symptoms within 30 min of eating raw fruit or vegetables. Due to IgE anti-pollen antibodies cross-reacting with homologous proteins in the precipitant food	IgE against suspected food + birch pollen	GP usually. Allergy clinic if adrenaline given
Specific other foods	Symptoms within a few hrs of eating the food. Other than nuts the most commonly implicated foods are fish, shellfish egg, milk, wheat	IgE against suspected food	GP usually. Allergy clinic if adrenaline given
Bee / wasp venom	Symptoms within 1 hour of being stung, history obvious. Local reactions normal.	IgE against relevant	GP usually. Allergy clinic if

	Specialist referral only if ABC symptoms	venom	adrenaline given
Exercise ± wheat ingestion	Unusual, but increasing in prevalence. Needs check for IgE against wheat and omega-5-gliadin (sometimes other foods) and specialist referral	IgE to wheat & ω-5-gliadin	Allergy clinic
Idiopathic	No cause identifiable, in particular no drug cause evident after searching all drugs taken in the BNF.	None	GP usually. Allergy clinic if adrenaline given
Idiopathic Angio-edema	NB exclude drug-induced causes first. Recurrent idiopathic angioedema without urticaria needs blood test for HAE (C3, C4) ± referral	C3, C4	GP usually. Refer to Allergy clinic if low C4

Drug taken Regularly	Urticaria Angioedema Itching	Bronchospasm Anaphylaxis	Gut symptoms - abdo pain N, V, D	Rhinitis Sinusitis Pharyngitis
ACE inhibitors	✓	✓	✓	✓ (some)
Statins	✓	-	✓	-
SSRIs /SNRIs	✓	✓	✓	✓
PPIs	✓	✓	✓	✓ (some)
A2R antagonists	✓	-	-	✓ (some)
Bisphosphonates	✓	✓	✓	✓ (some)
NSAIDs	✓	✓	-	-
Amlodipine	✓	-	✓	✓
Tetracyclines (acne)	✓	✓	✓	-
Inhaled β-agonist	✓	✓	-	-
Inhaled steroids	✓	✓	-	-
Finasteride	✓	-	-	-
Tamsulosin	✓	-	✓	✓

Discharge arrangements

After symptoms ± ABC disturbance have been stabilised and it is medically safe to discharge:

- A photocopy of the A&E record should be given to the patient (to inform pt & other doctors)
- Patients should be advised to take antihistamines for mild symptoms
- Every asthmatic patient should be informed of the importance of good asthma control and advised to see their GP if control is or becomes poor
- Patients with known food allergy may wish to buy an alert from www.medicalert.org.uk
- Epipens should be prescribed (and training and written instruction given for their use for ABC symptoms) for:
 - o patients with asthma who have had anaphylaxis due to food or nut allergy
 - o anaphylaxis to food that may be difficult to avoid (eg peanut)
 - o anaphylaxis after exercise
 - o idiopathic anaphylaxis
 - o anaphylaxis to insect venom

- Patients who have had symptoms due to adverse effects of regularly taken drugs do not require Epipens unless they had ABC symptoms that required treatment with Adrenaline
- All patients with ABC symptoms should be given a copy of the British Society for Allergy and Immunology's leaflet on anaphylaxis
- All patients with ABC symptoms should be given a copy of this information sheet to take to their GP to help inform their GP consultation
- Patients who have had **recurrent idiopathic angioedema only** (ie no drug cause identifiable and **without urticaria then or previously**) should have 4ml clotted blood sent for assay of C3 and C4 (to test for Hereditary Angioedema (HAE), prevalence 1 in 50,000). They should be referred to the Regional Immunology/Allergy service if the C4 level is low so that they may arrange to see the patient if necessary.

Follow-up arrangements

The follow-up required depends on symptom severity and their likely underlying cause. All cases of Anaphylaxis should be referred to an allergy service for assessment as per NICE guidance.

- Patients should be **referred to the Specialised Allergy Service** if they have had
 1. symptoms after eating nuts and are not already known to have nut allergy that has been medically assessed already
 2. ABC symptoms after a nut, fruit, vegetable or other food
 3. symptoms after significant exercise
 4. ABC symptoms after bee or wasp stings
 5. Idiopathic anaphylaxis (ie idiopathic ABC symptoms – not just idiopathic urticaria or idiopathic angioedema)
 6. Idiopathic angioedema without urticaria & blood tests showing low C4 concentration
 7. Patients with symptoms due to adverse effects of drugs should be advised to stop those drugs and attend their GP for the necessary changes in drug therapy to be followed up
- All others should be followed up by their GP as indicated above

All patients referred directly to the Allergy Service must have the following details supplied legibly:

- Addressograph label or Name, Address, Postcode, DOB
- Patient telephone (including mobile) no
- Name and address of GP surgery
- The indication for referral (ie 1-6 above)
- A **brief** clinical summary
- A photocopy /printout of the A&E record relating to that attendance
- What blood samples were sent to test for HAE, tryptase, allergy (RAST) tests etc

The name of the referring doctor and the name and telephone no of the Consultant in charge of A&E (to whom all queries will be addressed)