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Anaphylaxis
Investigating and managing an allergic emergency

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Patient education on strategies to reduce the risk of unintentional exposure to triggers and development of an emergency action plan are key components in the long-term management and prevention of anaphylaxis.

Key points

- **The major causes of anaphylaxis are allergy to food, insect stings and medication, most commonly NSAIDs and antibiotics.**
- **The major risk factors for fatal anaphylaxis are the failure to recognise early symptoms, poorly controlled asthma, delayed or absent adrenaline use and the assumption of an upright posture.**
- **The cornerstones of acute management are the patient being in the supine position, intramuscular adrenaline, intravenous saline, airway support and oxygen, and observation for at least four hours after symptom resolution.**
- **Antihistamines have no role in the treatment or prevention of respiratory and cardiovascular symptoms of anaphylaxis.**
- **The mainstays of long-term management are patient education on the recognition of early symptoms and the need to seek early medical attention if required; to carry and be trained in the use of self-injectable adrenaline; and provision of an emergency action plan.**

Anaphylaxis has become an increasing public health burden in developed countries over the last decade, contributing to increased demand for specialty services,[1] significant economic cost of care,[2] and reduced quality of life for patients at risk of anaphylaxis and their families.[3] Effective strategies for primary prevention are lacking, and secondary prevention is limited to strategies to reduce the risk of unintentional exposure. Although specific immunotherapy is available (and recommended) for patients with insect venom allergy, immunotherapy for food allergy remains at the investigational stage.[4]

WHAT IS ANAPHYLAXIS?

Anaphylaxis results from a massive release of mediators from mast cells and basophils by mechanisms that are IgE dependent (most cases) or IgE independent (some cases). Clinically, patients with anaphylaxis resulting from either mechanism present with potentially dangerous respiratory and/or cardiovascular symptoms. It is not possible to distinguish the two, and treatment for both types is identical, although there are implications with regard to allergy testing.

Although flushing or rash is usually present, anaphylaxis should be considered in the differential diagnosis in patients with acute

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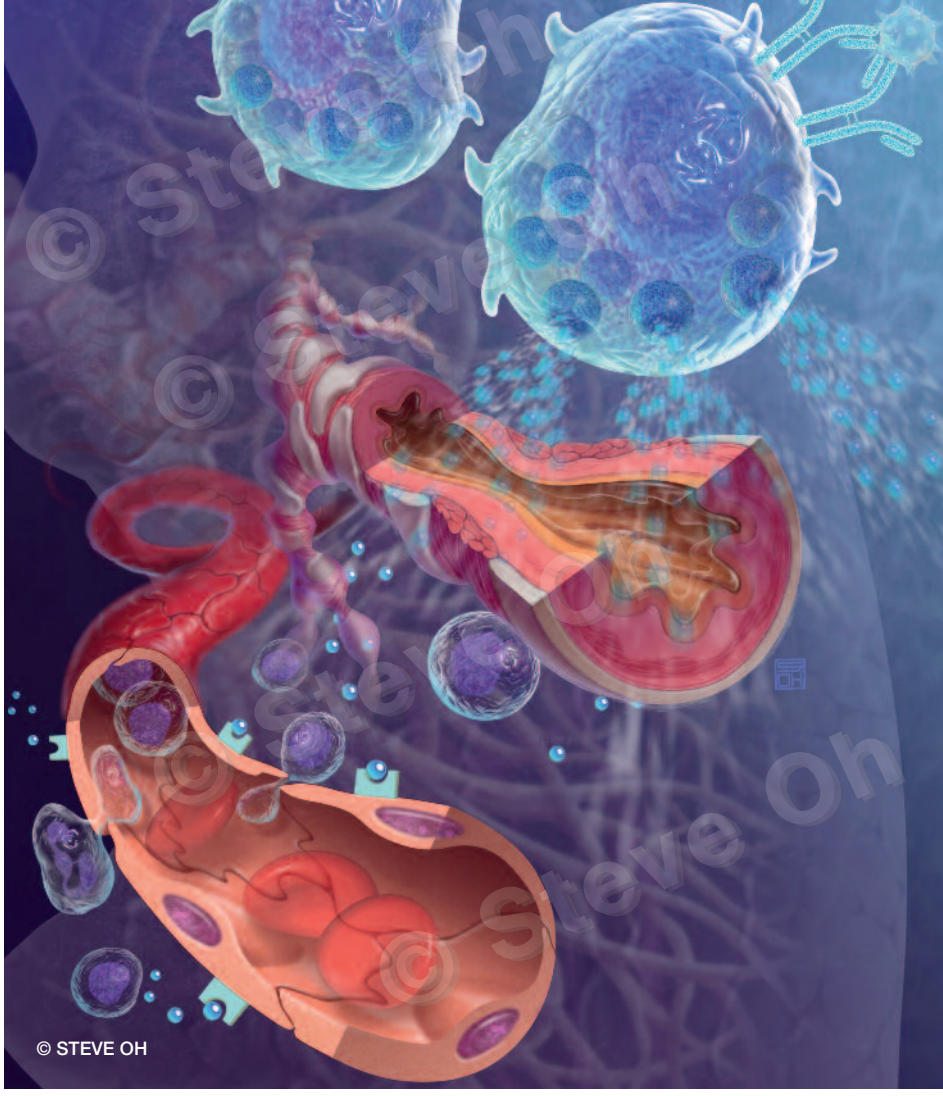

COMMON SIGNS AND SYMPTOMS OF ALLERGIC REACTIONS

Mild to moderate symptoms

- Swelling of lips, face, eyes
- Hives or welts
- Tingling mouth
- Abdominal pain, vomiting (note: these are signs of a severe reaction to insects)

Severe symptoms (anaphylaxis)

- Difficult/noisy breathing
- Swelling of tongue
- Swelling/tightness in throat
- Difficulty talking and/or hoarse voice
- Wheeze or persistent cough
- Persistent dizziness or collapse
- Pale and floppy (infants and young children)

hypotension, bronchospasm or severe upper airway obstruction (see the box on this page and Figure 1). Respiratory symptoms are more common in children, whereas cardiovascular symptoms predominate in adults.[5]

It is important to note that the presence of abdominal pain and vomiting are symptoms of anaphylaxis in patients with insect sting reactions, as their presence correlates with hypotension.

PATHOPHYSIOLOGY

The essential underlying mechanism of anaphylaxis is mast cell and basophil activation with release of various mediators, including histamine, leukotrienes, tumour necrosis factor and various cytokines, with resultant vasodilation, fluid extravasation and smooth muscle contraction. Death may occur from hypoxaemia due to upper airway angioedema, bronchospasm and mucus plugging, and/or shock due to massive vasodilation, fluid shift into the extravascular space and depressed cardiac function. This underscores the importance of physiological antagonism with adrenaline and fluid resuscitation, rather than antagonism of a single mediator such as histamine.[6]

COMMON CAUSES OF ANAPHYLAXIS

Food, insect venom or medication trigger most cases of anaphylaxis, with a variable proportion of patients suffering from idiopathic anaphylaxis, where extensive evaluation fails to identify the underlying cause (see the box on page 18). Paediatric emergency room studies have found that food allergy is responsible for about 80% of anaphylaxis presentations when the cause has been identified,[5] whereas in adults, food is responsible for only 20 to 30% of cases.[7,8] This difference is also reflected in mortality statistics: fatal reactions to foods occur at median ages of 22 to 24 years, whereas fatal reactions to insect venoms and medication occur at median ages of 55 to 67 years.[7]

ANAPHYLAXIS IS INCREASING

New cases of anaphylaxis are estimated to occur at rates of between 8.4 and 49.8 per 100,000 patient-years.[5,7-11] In Australia, one in 170 school-aged children have experienced at least one episode,[12] and, 2 to 3% of adults have experienced anaphylaxis after stings from honey bees or native *Myrmecia* (bulldog) ant

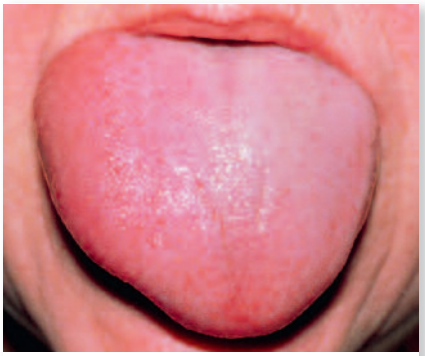

Figure 1. Swollen tongue, a symptom of anaphylaxis.

species (in areas where these are prevalent).[13] There is also evidence that food allergy and anaphylaxis have increased over the past decade in Australia, the UK and the USA, for reasons that currently remain unexplained.[14]

FATAL ANAPHYLAXIS

Deaths from anaphylaxis are likely to be underestimated due to the difficulty of postmortem diagnosis (there are no pathognomonic features), miscoding of anaphylaxis deaths as being due to asthma and under-reporting. Drug and insect allergies are reported as the most common causes of fatal anaphylaxis in Australia.[15] All reported cases of fatal anaphylaxis caused by food have occurred in individuals aged 8 to 35 years.[15]

Major risk factors for fatal anaphylaxis are:

- past severe reactions
- poorly controlled asthma
- delayed (or no) administration of adrenaline
- assumption of the upright posture during an episode
- young adults (fatal food anaphylaxis).[16,17]

COFACTORS

Cofactors are sometimes required before an allergen will provoke a reaction. Intercurrent infection, concomitant medication (particularly alpha blockers, beta blockers, ACE inhibitors or NSAIDs), concomitant intake of alcohol or spicy food, high ambient temperatures and exercise have been associated with increased risk of anaphylaxis. This phenomenon may account for some intermittent episodes of anaphylaxis where a cause has not been established.

Exercise-induced anaphylaxis affects predominantly young adults. Although some of these adults experience symptoms with exercise alone, most are allergic

EXAMPLES OF CAUSES OF ANAPHYLAXIS

Common

- Insect venoms: most commonly honey bees, Australian native ants, wasps
- Foods: most commonly peanuts, tree nuts, cow's milk, egg and sesame in childhood; more commonly peanut, tree nuts and seafood in adults
- Medications: most commonly antibiotics and NSAIDs
- Unidentified (idiopathic)

Uncommon

- Exercise, with or without food
- Biological fluids: transfusions, immunoglobulin, semen
- Latex
- Anaesthetic agents

Rare

- Tick bites, March fly bites
- Hormonal causes: breastfeeding, menstrual cycle
- Cold induced
- Dialysis membranes
- Hydatid cyst rupture
- Aeroallergens: domestic/laboratory animals, pollen
- Food additives: monosodium glutamate, metabisulfite, preservatives, colours
- Iron infusions
- Radiocontrast agents

DIFFERENTIAL DIAGNOSIS FOR ANAPHYLAXIS

Tissue swelling

- Idiopathic urticaria
- Isolated angioedema

Conditions mistaken for upper airway oedema

- Dystonic reactions mimicking the sensation of swollen tongue (e.g. after taking antinausea medication)
- Acute oesophageal reflux (sudden onset of painful throat 'swelling', which can trigger laryngospasm)

Flushing syndromes

- Peptide-secreting tumours (e.g. carcinoid syndrome, VIPomas)
- Alcohol related
- Medullary carcinoma of thyroid
- Red man syndrome (vancomycin-related)

Neurological syndromes

- Epileptic seizures
- Strokes

Other causes of collapse

- Vasovagal episodes
- Systemic capillary leak syndrome
- Shock (septic, cardiogenic, haemorrhagic)

Acute respiratory distress

- Asthma

Panic disorders

- Globus hystericus
- Laryngospasm (more commonly caused by oesophageal reflux)
- Vocal cord dysfunction

Miscellaneous

- Scombroid fish poisoning
- Systemic mastocytosis
- Serum sickness
- Phaeochromocytoma

ACUTE MANAGEMENT OF ANAPHYLAXIS[20]

1. Remove allergen (if still present).
2. Call for assistance.
3. Lay the patient flat. Do not allow patient to stand or walk. If breathing is difficult allow the patient to sit.
4. Give 1:1000 adrenaline intramuscularly into the lateral mid-thigh without delay (0.01 mg/kg – maximum dose 0.5 mg). Repeat doses every five minutes as needed. If multiple doses required or a severe reaction, contact emergency specialist for advice.
5. Call ambulance.
6. Provide supportive management when skills and equipment are available:
   - monitor pulse, blood pressure, respiratory rate, pulse oximetry
   - give high flow oxygen and airway support if needed
   - obtain intravenous access in adults and in hypotensive children
   - if hypotensive, give intravenous normal saline (20 mL/kg rapidly) and consider additional wide bore intravenous access.

Note: Antihistamines have no role in treating or preventing respiratory or cardiovascular symptoms of anaphylaxis. The role of corticosteroids in anaphylaxis is unknown and potential benefits unproven.

Adapted with permission from: Anaphylaxis. Emergency management for health professionals [wallchart]. Australian Prescriber 2011; 34(4). Available online at: http://www.australianprescriber.com/upload/pdf/articles/1210.pdf.[20]

to a food ingested within the previous four hours. Wheat, celery, seafood, nuts, fruits or vegetables are most commonly associated with food-related exercise-induced anaphylaxis.[18] Whether episodes occur may depend on the amount of food ingested, the vigour of exercise and the time between the two.

DIFFERENTIAL DIAGNOSIS

The many causes of hypotension should be considered in shocked patients. Urticaria and angioedema are not always due to anaphylaxis. The box on page 18 lists the differential diagnosis for anaphylaxis.

ACUTE MANAGEMENT OF ANAPHYLAXIS

The cornerstones of acute management are:

- the patient being in the supine position (or left lateral position for patients who are vomiting or pregnant,[19] to reduce the risk of compression of the inferior vena cava by the pregnant uterus and thus impairing venous return to the heart)
- intramuscular injection of adrenaline into the lateral mid-thigh (1:1000 or 1 mg/mL at a dose of 0.01 mg/kg with a maximum dose of 0.5 mg/0.5 mL)
- intravenous fluid resuscitation with saline at 20 mL/kg (repeated up to a total 50 mL/kg over the first half hour)
- support of the airway and ventilation
- supplementary oxygen (see the box on this page).[17,20]

The appropriate dose of an adrenaline autoinjector (if available) can be used instead (see the box on page 21).[21]

Adrenaline acts to reduce airway mucosal oedema, induce bronchodilation, induce vasoconstriction (thus increasing heart rate and blood pressure) and increase the strength of cardiac contraction. Since adrenaline lasts about 15 to 20 minutes, repeated intramuscular doses may be required. Repeat doses can be given after five minutes if the previous dose is ineffective (up to three doses can be given; if the patient is still unresponsive advice from an emergency specialist should be sought).

The supine position helps to maximise venous return in hypotensive patients.

In patients with pre-existing heart failure or in those taking beta blockers, glucagon may be helpful.

Other medications such as antihistamines, H_2-receptor antagonists, corticosteroids and antileukotrienes have no proven impact on the immediate and life- threatening effects of anaphylaxis, although they may ameliorate mild allergic reactions confined to the skin. The only registered antihistamine for parenteral use in Australia (promethazine) can worsen vasodilatation and hypotension and can cause muscle necrosis if injected intramuscularly, and its use is not advised.[22]

A wallchart on the emergency management of anaphylaxis for health professionals is available for download from *Australian Prescriber* and is recommended for reference in medical facilities (http://www.australianprescriber.com/magazine/34/4/artid/1210).[20] A laminated A3 version of the anaphylaxis wallchart is available free of charge for doctors to use in their clinic on request from *Australian Prescriber*.

OBSERVATION AFTER ANAPHYLAXIS

An observation period of four hours after symptom resolution is recommended for all patients, as symptoms may fail to improve or worsen as the effect of adrenaline wears off (protracted anaphylaxis), or return after early resolution (biphasic reactions). More prolonged observation may be required in patients with severe or refractory symptoms, those in whom multiple doses of adrenaline are required and those with asthma, since most fatalities associated with anaphylaxis occur in these groups.

IDENTIFICATION OF THE CAUSE

It is important first to determine whether anaphylaxis occurred, before examining the surrounding circumstances to define

a cause. Although not satisfying the definition of anaphylaxis, rare and short-lived bouts of urticaria and/or angioedema lasting less than 12 hours should prompt suspicion about an allergic cause, whereas patients with ongoing symptoms for days are unlikely to have an allergic origin for their symptoms.

Exposure to potential triggers (e.g. food, medication, insect venom or occupational allergens such as latex), and cofactors in the preceding eight hours should be recorded while the patient's memory of the event is fresh. The Australasian Society of Clinical Immunology and Allergy (ASCIA) has developed an event template for patients to complete, which can be downloaded from its website: http://www.allergy.org.au/health-professionals/anaphylaxis-resources/anaphylaxis-event-record).[23]

Almost all anaphylactic reactions to insect venom occur within one hour. Severe allergic reactions to food and medication can occur rapidly, up to six hours.The presence of known food or drug hypersensitivity should be recorded and the possibility of accidental exposure considered. When insect stings have occurred, the insect appearance and the presence of a stinger left in the skin (which indicates a honey bee sting) may help to identify the cause.

INVESTIGATIONS

Anaphylaxis remains a clinical diagnosis. Mast cell tryptase is an insensitive biomarker for anaphylaxis, although serial determinations (e.g. on arrival to hospital, one hour later and prior to discharge) may improve sensitivity. An elevated tryptase level may help when the diagnosis is uncertain, but a normal result does not exclude anaphylaxis.

Skin-allergy testing to assess sensitisation to food, medications and insect venom carry a small risk of inducing anaphylaxis, so should only be carried out by trained personnel in an environment where anaphylaxis can be treated.

In-vitro testing for allergen-specific IgE is a useful initial test when a trigger is strongly suspected (e.g. in an infant with anaphylaxis after peanut exposure) or in patients in whom skin-allergy testing is best deferred for safety reasons (e.g. pregnancy). Measurement of total IgE, however, provides no useful information and is discouraged. *In-vitro* testing using food mixes often provides misleading or irrelevant results and should not be requested.

Oral food challenges can assist with allergen identification and confirm if the patient has outgrown his or her allergy. However, as there may be a risk of anaphylaxis, the decision to perform an oral challenge should only be made by clinical immunologists or allergy specialists.

There is currently no test to confirm tick-bite allergy, although in one study the presence of specific IgE to alpha-galactose was observed in most patients with tick-bite allergy as well as those allergic to red meat.[24] If the causative insect cannot be identified, testing for all suspected insect allergies is appropriate (honey bee, paper wasp [*Polistes* spp.], European wasp/yellow jacket, fire ant in endemic parts of Queensland). Skin testing for jumper ant allergy is not available outside of research programs in Tasmania, but blood allergy testing is available from Flinders Medical Centre, South Australia. This detects only 80% of cases. Although the subject of ongoing research, no validated test is available to detect allergy to related ant species.

Some drug reactions (e.g. to NSAIDs or radiographic contrast agents) are normally independent of IgE, and there are numerous difficulties in assessing many cases of antibiotic allergy due to lack of suitable reagents for testing (except for the penicillin group of antibiotics). Medically supervised challenges are sometimes required to prove or disprove allergy.

There is no scientific validity for 'alternative testing' (e.g. cytotoxic or Vega testing, hair analysis, kinesiology) and

ASCIA ADRENALINE AUTOINJECTOR DOSE RECOMMENDATIONS[21]

Adrenaline autoinjectors available in Australia and New Zealand are: EpiPen Jr (0.15 mg), EpiPen (0.3 mg), Anapen 150 (0.15 mg) and Anapen 300 (0.3 mg).

- Children weighing less than 10 kg: adrenaline autoinjectors are not usually recommended
- Children weighing 10 to 20 kg: EpiPen Jr (0.15 mg) or Anapen 150 (0.15 mg)
- Patients weighing more than 20 kg: EpiPen (0.3 mg) or Anapen 300 (0.3 mg)

At the time of writing this article, Anapen 500 (0.5 mg) has TGA registration but is not yet launched in Australia and New Zealand. For the current ASCIA prescribing guidelines for all adrenaline autoinjectors, please visit the ASCIA website (http://www.allergy.org.au).

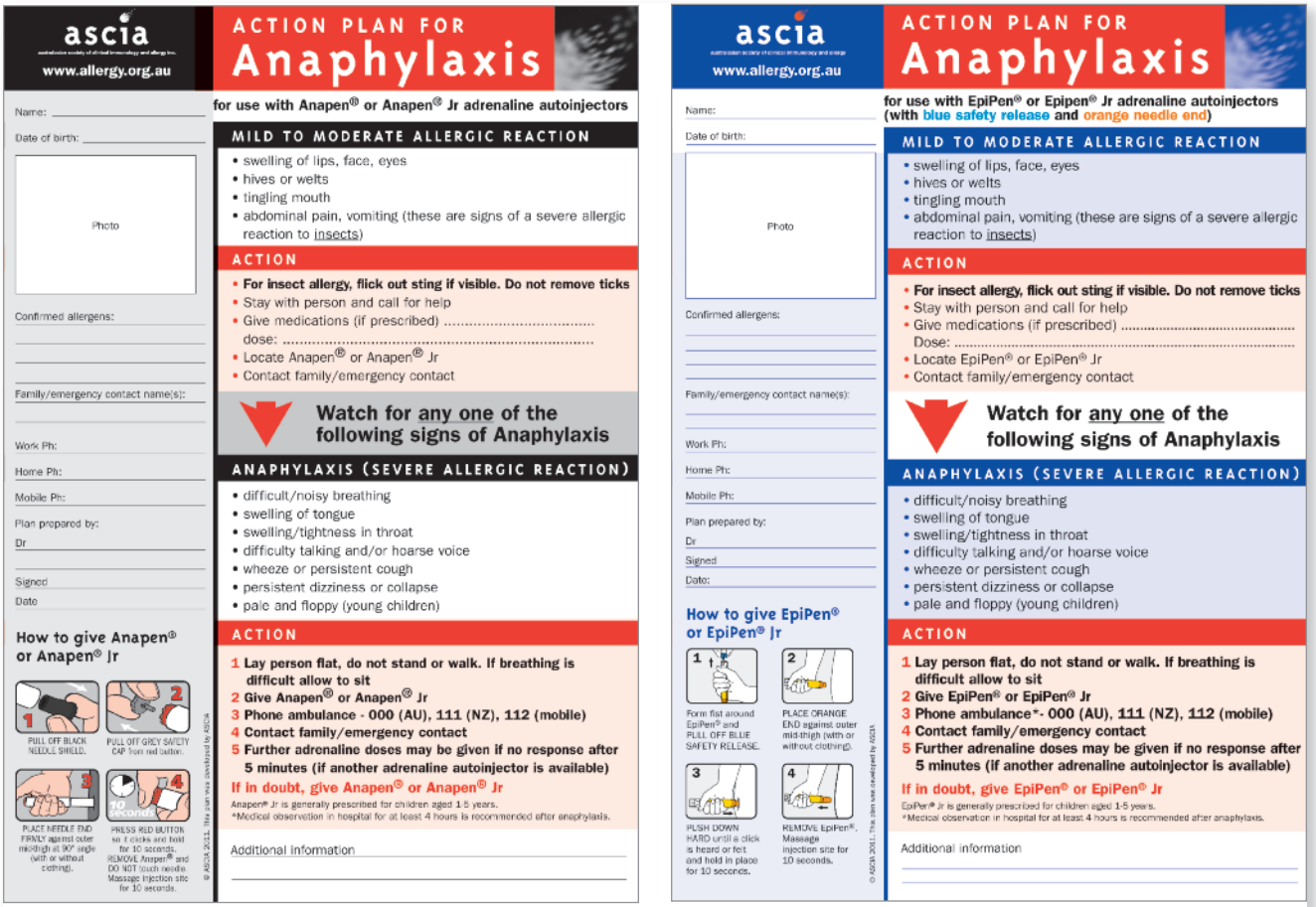

Figure 2. ASCIA Action Plans for Anaphylaxis (personal) for Anapen (left) and EpiPen (right). These plans can be downloaded from the ASCIA website (http://www.allergy.org.au/health-professionals/anaphylaxis-resources/ascia-action-plan-for-anaphylaxis).

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their use should be discouraged. More information on alternative testing is available on the ASCIA website (http://www.allergy.org.au/health-professionals/papers/unorthodox-techniques-for-diagnosis-and-treatment).[25]

WHEN TO REFER

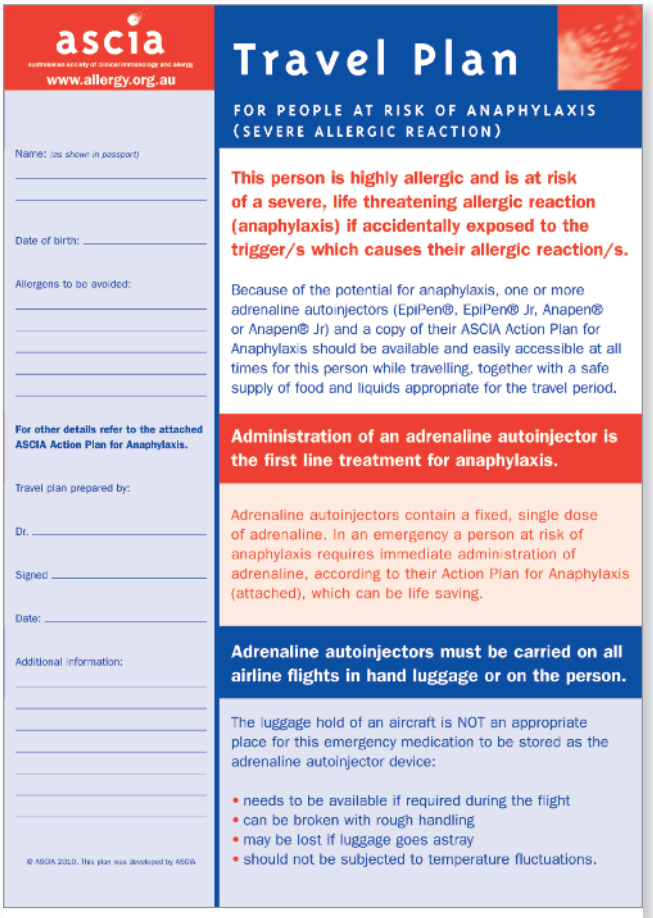
Specialist evaluation of patients is recommended after a diagnosis of possible anaphylaxis to identify or confirm the cause, educate patients on appropriate avoidance strategies, provide an emergency action plan (e.g. using the ASCIA Action Plans shown in Figure 2) and advise them whether immunotherapy is appropriate.

LONG-TERM MANAGEMENT AND PREVENTION

Anaphylaxis to insect stings can be prevented with venom immunotherapy (not available for all stinging insects), which reduces the risk of anaphylaxis from repeated stings, and is associated with an improved quality of life compared with carrying an adrenaline autoinjector alone.[26] Attempts to modify the severity of food allergy using similar techniques have shown early promise but remain in the investigational stage.[4]

The mainstays of long-term management are patient education to reduce the risk of accidental exposure to the trigger, recognise early symptoms, be aware of the need to seek early medical attention if symptoms occur and carry and be trained in the use of self-injectable adrenaline, and the provision of an emergency action plan.

A number of resources, including emergency action plans, a travel plan (see Figure 3) and diet sheets can be downloaded from the ASCIA website (http://www.allergy.org.au/health-professionals/anaphylaxis-resources). A medical bracelet worn by patients at risk of anaphylaxis may provide additional information to attending medical/paramedical personnel regarding known allergies, reduce the risk of administration of allergenic medication and facilitate earlier recognition of anaphylaxis and treatment. An allergy



ascia
www.allergy.org.au

Travel Plan

FOR PEOPLE AT RISK OF ANAPHYLAXIS (SEVERE ALLERGIC REACTION)

Name: *(as shown in passport)*

Date of birth:

Allergens to be avoided:

For other details refer to the attached ASCIA Action Plan for Anaphylaxis.

Travel plan prepared by:

Dr.

Signed

Date:

Additional information:

© ASCIA 2010. This plan was developed by ASCIA

This person is highly allergic and is at risk of a severe, life threatening allergic reaction (anaphylaxis) if accidentally exposed to the trigger/s which causes their allergic reaction/s.

Because of the potential for anaphylaxis, one or more adrenaline autoinjectors (EpiPen®, EpiPen® Jr, Anapen® or Anapen® Jr) and a copy of their ASCIA Action Plan for Anaphylaxis should be available and easily accessible at all times for this person while travelling, together with a safe supply of food and liquids appropriate for the travel period.

Administration of an adrenaline autoinjector is the first line treatment for anaphylaxis.

Adrenaline autoinjectors contain a fixed, single dose of adrenaline. In an emergency a person at risk of anaphylaxis requires immediate administration of adrenaline, according to their Action Plan for Anaphylaxis (attached), which can be life saving.

Adrenaline autoinjectors must be carried on all airline flights in hand luggage or on the person.

The luggage hold of an aircraft is NOT an appropriate place for this emergency medication to be stored as the adrenaline autoinjector device:

- needs to be available if required during the flight
- can be broken with rough handling
- may be lost if luggage goes astray
- should not be subjected to temperature fluctuations.

Figure 3. ASCIA Travel Plan for people at risk of anaphylaxis. This plan can be downloaded from the ASCIA website (http://www.allergy.org.au/health-professionals/anaphylaxis-resources/ascia-travel-plan-anaphylaxis).

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alert should also be entered in medical records.

Regular review by a GP is recommended to:

- re-educate patients on the use of adrenaline autoinjectors
- ensure that the device is renewed at appropriate intervals
- provide updated ASCIA Action Plans
- provide psychological support
- provide specialist referral for review.

ADRENALINE AUTOINJECTORS

Patients diagnosed at risk of anaphylaxis may be prescribed an adrenaline autoinjector (EpiPen or Anapen), which may be obtained over-the-counter at full cost or on PBS authority prescription by patients considered at high risk of severe allergic reactions. Initial PBS prescription must be provided in consultation with an allergy/immunology specialist, paediatrician, emergency specialist or respiratory physician (which can be by telephone in the first instance followed by patient referral to the specialist). The ASCIA guidelines for adrenaline autoinjector prescription and instructions in its use are available from the ASCIA website (www.allergy.org.au).[21]

It is essential that patients and carers are educated in both the recognition and management of allergic reactions. They should be shown how to use the prescribed adrenaline autoinjector using a trainer device and given advice on allergen avoidance measures. They should also be educated about the need to always carry the adrenaline autoinjector and their ASCIA Action Plan for Anaphylaxis.

Where to store adrenaline autoinjectors

Adrenaline autoinjectors should not be exposed to extremes of heat (to protect the adrenaline) and should not be stored in the refrigerator or freezer as this can damage the autoinjector mechanism, causing it to jam. Room temperature is optimal. Regardless of location, everyone who might need to give adrenaline should know where it is located. At school, adrenaline autoinjectors should be stored in an unlocked location that is known and easily accessible to staff.

Dose of adrenaline autoinjectors

The adrenaline autoinjector doses commonly recommended by specialist bodies such as ASCIA (see the box on page 21) are based on consensus of expert opinion and often differ from those stated in the product information leaflet.

TRAVELLING WITH FOOD ALLERGY

Well in advance of travel and before booking and paying for tickets, patients should contact their airline to determine its policies regarding food allergy. All documents, letters and medicines needed should be prepared in advance of travel. An ASCIA Travel Plan can be completed by GPs to authorise patients to carry their adrenaline autoinjector on the plane (Figure 3). Patients should ensure their adrenaline autoinjector is in date. They should also check that their travel insurance covers their allergy. Illustrated travel cards in different languages are commercially available to use when travelling to communicate about food allergy (e.g. http://www.selectwisely.com).

ONLINE RESOURCES

ASCIA maintains regular review of its online resources, and also freely provides online training on food allergy and anaphylaxis for health professionals, which can be completed as part of continuing education programs (http://etraininghp.ascia.org.au).

Allergy and Anaphylaxis Australia (http://www.allergyfacts.org.au) also maintains a number of resources of use to patients and their carers.

CONCLUSION

The first-line treatment of anaphylaxis is to lay the patient flat, administer intramuscular adrenaline into the outer mid-thigh and seek urgent medical attention. Long-term management of anaphylaxis should include patient/carer education in recognising allergic symptoms, specialist referral to assist in identification of potential causes, education in the use of the adrenaline autoinjector and allergen avoidance, and provision of an ASCIA Action Plan for Anaphylaxis. MT

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