Management of anaphylaxis

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Anaphylaxis is the most serious allergic event, and even though Portier and Ritchet[1] first described anaphylaxis in the scientific literature about 100 years ago, it is a disease of modern times.

During the early decades of the twentieth century anaphylaxis occurred mainly in health care settings and the main trigger was iatrogenic, the injection of biologic agents (vaccines). Over the last 10 years there has been an 'epidemic' of food anaphylaxis. One in 170 Australian school-aged children have suffered an episode of anaphylaxis.[2]

Traditionally *anaphylaxis* was used to describe the IgE-mediated immune allergic reactions and *anaphylactoid reaction* was the term used to describe non-IgE, non-immune reactions, e.g. reactions to non-steroidal anti-inflammatory drugs, radiocontrast dye and exercise. Although the aetiological distinction is important, as the clinical manifestation and the immediate management are identical, the label anaphylaxis is now commonly used to describe both of these clinical syndromes.

Causes of anaphylaxis

(A retrospective survey of anaphylaxis outside hospital and treated at Mayo Clinic Emergency Dept)[3]

- Foods 33%
- Idiopathic 19%
- Hymenoptera (venom) 14%
- Medication 13%
- Exercise 7%
- Other 4%
- False diagnosis 10%

Idiopathic anaphylaxis

Idiopathic anaphylaxis accounts for approximately one-third of cases in several retrospective studies.[3] However, the prevalence varies widely, from 40% in Memphis, down to 10% in Canberra, Australia.[4] This might have to do with it being a diagnosis of exclusion. Detailed serial histories and diagnostic tests for foods, spices, fruit and vegetables have occasionally identified the cause in patients previously presumed to have idiopathic anaphylaxis. For example, it is known that the commercial extracts for doing skin prick tests to fruits and vegetables often give false negative results, so testing with the fresh fruit, doing a 'prick-prick' test is the only reliable way to diagnose fruit allergy.

Fatality from idiopathic anaphylaxis is extremely rare with only one case reported in the literature.[5] Being a diagnosis of exclusion, some of these cases might not be 'true anaphylaxis', but masqueraders such as globus hystericus and panic attacks.

Food-induced anaphylaxis

In most countries of the world food is now the most common cause of anaphylaxis. Food-induced anaphylaxis accounts for one-third to one-half of anaphylaxis cases treated in emergency departments in North America, Europe, and Australia.[3] Anaphylaxis to peanut and tree nuts is responsible for most of the anaphylactic deaths due to food. In most cases (approximately 80%) this allergy is life-long. Investigators have also noted that more than half (52%) of the children with peanut allergy experience life-threatening symptoms with subsequent reactions even when atopic dermatitis has been the only previous adverse clinical manifestation.[4]

Another disturbing fact is that peanut allergy most commonly begins in the second year of life[5] and the majority of reactions (81%) occur with the first known ingestion, implying prior occult sensitisation.[6]

In evaluating food-induced anaphylaxis, it is important to consider associated co-factors, such as exercise after food ingestion (food-related, exercise-induced anaphylaxis). From my own experience the most common food involved in this type of response is wheat.

Risk factors for fatal food-induced anaphylaxis

- Peanut and tree nut allergy
- Asthma
- Prior anaphylaxis
- Failure to treat promptly with adrenaline
- Adolescence/young adults

Exercise-induced anaphylaxis (EIA)

EIA is a unique, fairly recently recognised form of physical allergy, which is being recognised with in-

creased frequency as society becomes more health conscious. It was first described in 1980. It is usually seen in fit young adults (male:female = 2:1) with the usual presentation being generalised pruritus with or without urticaria, upper airway obstruction and/or vascular collapse. The inconsistent development of EIA after apparently similar degrees of exertion suggests the possibility of co-factors such as foods (food-related EIA), alcohol, drugs (e.g. aspirin) and caffeine. In one patient exercise in the rain caused prolonged collapse on two occasions.

Management of EIA

- Avoid exercise for four to six hours after eating;
- Avoid co-factors (specific foods, alcohol) before exercise;
- Avoid aspirin and non-steroidal anti-inflammatory drugs before exercise;
- Discontinue exercise at earliest premonitory symptom
- Always exercise with a buddy;
- Exercise with auto-injectable adrenaline available;
- Wear Medic Alert identification;
- Prophylactic antihistamines are not useful in preventing EIA.

Hymenoptera venom anaphylaxis

- Up to 75% of patients with a history of anaphylactic sting reactions develop systemic reactions when restung.
- The risk of reaction falls to <5% in two to three months on venom immunotherapy.
- Venom immunotherapy should be offered to all adults and children with a history of severe systemic reactions, including respiratory or cardiovascular involvement, with documented sensitisation to the respective insect with either skin tests or specific serum IgE (RAST-type) tests.
- Venom immunotherapy is not indicated for local reactions in adults or children.

Anaphylaxis to drugs

- Penicillin is still the most common cause of drug-induced anaphylaxis.
- Penicillin skin tests are negative in 90% of patients with a history of penicillin allergy.
- Penicillium mould allergy or atopy is not a risk factor for penicillin allergy.
- The negative predictive value of penicillin skin testing is between 97% and 99% (depending on the reagents used), and the positive predictive value is about 50%.
- Four per cent of patients proven to have penicillin allergy by means of penicillin skin testing react to cephalosporin challenges.
- Aspirin and non-steroidal drugs are the second most common cause of drug-induced anaphylaxis.

Box 1

Is it anaphylaxis?

In my practice it is not uncommon to see patients who either have been mislabelled as having anaphylaxis or have possibly had one anaphylactic reaction followed by several panic attacks. These are usually patients whose diagnoses have not been confirmed by an expert but they have been given an EpiPen. The number of foods they start reacting to gradually increases to the point where they are terrified to eat and each time they are injected with adrenaline their anxiety/phobia increases further. When the history is taken in more depth or, even better, when one of these reactions is witnessed following skin prick test for the alleged allergen, it is confirmed that the response is a panic attacks or globus hystericus. It is usually very difficult to convince these patients that they are safe to eat whatever they want and that they don't need to carry adrenaline. I find it useful to give these patients a letter stating that 'this patient's diagnosis of anaphylaxis is being questioned and he/she needs to be monitored for objective signs of anaphylaxis before adrenaline is given'. When the patient has an attack, instead of using their EpiPen they should be taken into an emergency department or to their doctor to be monitored for signs of anaphylaxis, before they are injected with adrenaline.

Other conditions that should be considered in the differential diagnosis of anaphylaxis include the following:

- Vasovagal syncope
- Psychiatric disorders (usually associated with benign acute urticaria) that mimic anaphylaxis
- Scombroid Fish Poisoning caused by histamine produced by bacteria in spoiled fish. The symptoms can be identical to fish-induced anaphylaxis.
- Systemic Mastocytosis
- Isolated Angioedema (hereditary and drug-induced)
- Severe asthmatic attack
- Other causes of flushing e.g. Carcinoid Syndrome

- Over-the-counter preparations such as bee pollen, propolis, echinacea and other herbal preparations should always be considered in 'idiopathic' anaphylaxis.

Causes of anaphylaxis during general anaesthesia (intra- and post-operative)

The incidence of anaphylaxis during anaesthesia has been reported to range from one in 4000 to one in 25 000. Anaphylaxis during anaesthesia can present as cardiovascular collapse, airway obstruction, flushing, and/or angioedema.

- Neuromuscular blocking agents such as suxamethonium are the most common cause.
- Latex has been clearly documented especially in atopic patients who have had multiple surgical procedures or many health care workers.
- Thiopentone allergy has been documented with skin tests.
- Opioid analgesics cause direct mast cell-mediator release.
- Antibiotics administered perioperatively.
- Blood transfusions can elicit both IgE-mediated and non-immune reactions.

Causes of fatal anaphylactic reactions in the UK[10]

- Venom 25%
- Anaesthetics 19%
- Nuts 18%
- Antibiotics 12%
- Other foods 10%
- Iatrogenic 10%
- Radiocontrast 6%

In this study approximately half of the 20 fatal reactions recorded each year in the UK were iatrogenic and a quarter each due to food or insect venom. All fatal reactions thought to have been due to food involved difficulty in breathing that in 86% led to respiratory arrest; shock was more common in iatrogenic and venom reactions. The median time to respiratory or cardiac arrest was 30 minutes for foods, 15 minutes for venom and five minutes for iatrogenic reactions. Twenty-eight per cent of fatal cases were resuscitated but died three hours to 30 days later, mostly from hypoxic brain damage. Adrenaline was used in the treatment of 62% of fatal reactions but in only 14% before arrest.

Treatment of anaphylaxis in emergency settings often inadequate

Anaphylaxis is preventable and treatable but international studies (and observation in New Zealand) show that many emergency physicians and primary care providers do not follow the recommended treatment for allergic reactions.

In a recent study of emergency department treatment of food allergies, Carmago and colleagues[11] reviewed the medical chart of 678 patients from 21 hospitals who went to an emergency department with allergic reactions to various foods. The recommended treatment for severe (anaphylactic) reaction to food is adrenaline, yet only 16% of the entire cohort received this drug but 72% were given antihistamines and 485 were given steroids. Only 40% of the patients were advised to avoid the causative allergen, only 16% were prescribed self-injectable adrenaline and only 12% were referred to an allergist. My impression, after seeing patients following treatment of food allergic reactions in Emergency Departments is that the situation is much the same in New Zealand.

Probably the main reason for the inadequate management of anaphylaxis worldwide is that until very recently there was no universally accepted definition of anaphylaxis. There is no doubt that the child who has just eaten a cookie and immediately starts wheezing, is covered in hives and then collapses, is having an anaphylactic reaction. However, if the child has only hives after eating the cookie, is this anaphylaxis? Also, anaphylaxis may be misdiagnosed when a satisfactory history is unavailable, for example when a person is found unconscious at the side of the road following a bee sting. This person may not have the common manifestations of anaphylaxis such as urticaria and angioedema that are usually present in more than 90% of patients who have anaphylaxis.[12]

Definition of anaphylaxis

Because any guideline for the management of anaphylaxis is useless without a clear understanding of what constitutes anaphylaxis, I will spend some time on the definition of anaphylaxis.

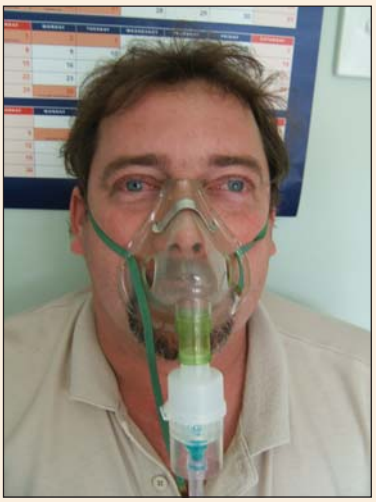


Figure 1. This asthmatic man was seen on several occasions (and once admitted) with acute abdominal pain and treated as gastritis following NSAID use. During an aspirin challenge he developed severe abdominal pain 10 minutes after taking 75mg of aspirin. Forty-five minutes later he developed rhinoconjunctivitis, severe asthma, generalised urticaria, diarrhoea and hypotension. He required a total of 0.75mg adrenaline IM to be stable enough to be transported to hospital.

In retrospect, it is apparent that he was getting angioedema of the bowel from NSAID hypersensitivity.

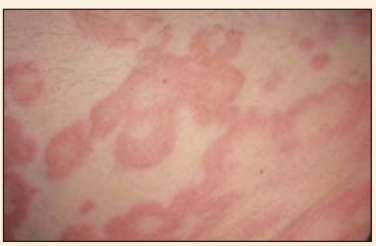


Figure 2. Close up of rash, which persisted even after adrenaline was given.

There are numerous definitions of anaphylaxis in the literature. One that I have found useful is that of Lockey in *Anaphylaxis: Synopsis*, on the World Allergy Organization website: *'Anaphylaxis is an acute, potentially life-threatening hypersensitivity reaction, involving the release of mediators from mast cells, basophils and recruited inflammatory cells. Anaphylaxis is defined by a number*

of signs and symptoms, alone or in combination, which occurs within minutes, or up to several hours, after exposure to a provoking agent. It can be mild, moderate or severe. Most cases are mild, but any anaphylaxis has the potential to become life-threatening.'

Symposium on the definition and management of anaphylaxis

As there is no universal agreement on the definition of anaphylaxis or the criteria to diagnose it, the National Institute of Allergy and Infectious Diseases (NIAD) and the Food Anaphylaxis Network (FAAN) co-sponsored a multidisciplinary symposium in April 2004 on the Definition and Management of Anaphylaxis.[14] A second symposium[15] was held in July 2005, and participants agreed on a brief, broad definition of anaphylaxis that would be most useful to the medical and lay community: *'Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.'*

There has been confusion in trying to identify individuals experiencing such a reaction, so the clinical criteria for diagnosing anaphylaxis were revised (see Box 2).

The definition of anaphylaxis, on which the New Zealand Anaphylaxis Action Plan is based, is that of the Australasian Society of Clinical Immunology and Allergy (ASCIA), in which a distinction is made between *Anaphylaxis* and *Generalised Allergic Reaction*:

***Anaphylaxis** is a rapidly evolving generalized multisystem allergic reaction characterized by one or more symptoms or signs of respiratory and/or cardiovascular involvement and involvement of other systems such as the skin and/or the gastrointestinal tract. Symptoms/signs of respiratory/cardiovascular involvement are:*

Respiratory

- *Difficulty/ noisy breathing*
- *Swelling of the tongue*
- *Swelling/tightness of the throat*
- *Difficulty talking and/or hoarse voice*
- *Wheezing or persistent cough*

Cardiovascular

- *Loss of consciousness*
- *Collapse*
- *Pale and floppy (in young children)*
- *Hypotension*

***Generalised Allergic Reaction** is characterized by one or more symptoms or signs of skin and/or gastrointestinal tract involvement without respiratory and/or cardiovascular involvement.*

Skin

- *Generalised pruritus*
- *Urticaria/Angioedema*
- *Erythema*

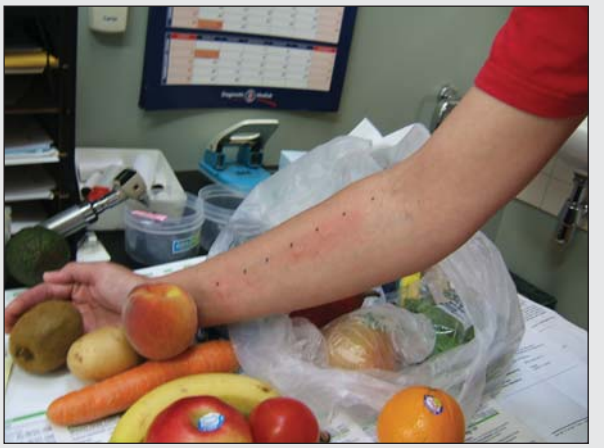
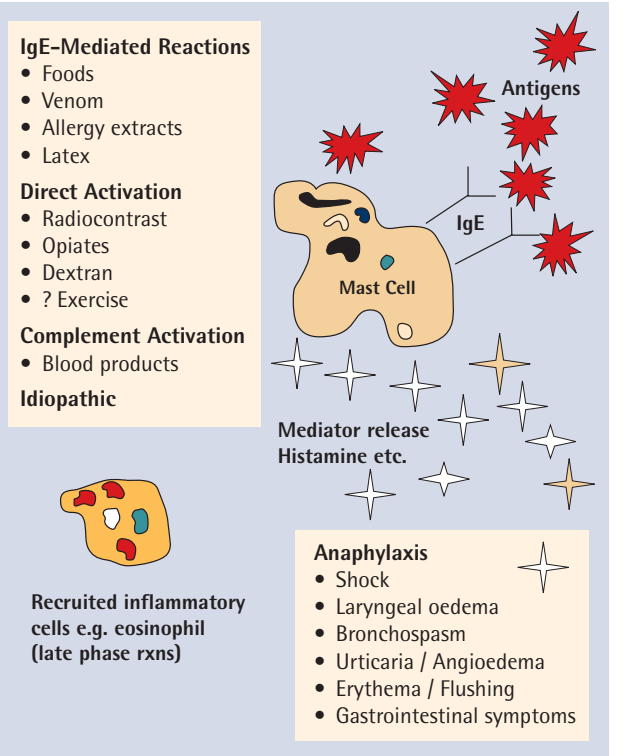


Figure 3. This woman develops rhinoconjunctivitis from peeling potatoes and has had anaphylaxis from contact with apples and nectarines. She developed flushing and light-headedness 15 minutes after this prick-prick test to nectarine and raw potato. She required 0.3mg adrenaline to settle.

Figure 4. Mechanisms of mediator release in anaphylaxis



Gastrointestinal

- *Abdominal pain*
- *Vomiting*
- *Loose stools*

Patients often report a 'sense of doom' as an early feature of anaphylaxis.

Grading of anaphylaxis

There are several grading scales for anaphylaxis in the literature. The simplest and probably most practical is one by Ringer and Messmer:[16]

- *Grade 1:* Skin reaction only
- *Grade 2:* Systemic, non-life-threatening reaction
- *Grade 3:* Life-threatening reaction
- *Grade 4:* Cardiopulmonary arrest

Investigations in anaphylaxis

An in-depth history is the most important tool to establish the cause of anaphylaxis. This should take precedence over all diagnostic tests.

Mast Cell Tryptase is the only useful test at the time of the reaction. Tryptase is released from mast cells in both IgE-mediated (immune) and non-IgE mediated reactions. The half-life of histamine is too short for its measurement to be clinically useful.

Serum tryptase peaks 60–90 minutes after the onset of anaphylaxis and persists for six hours. Ideally, the measurement should be obtained between one and two hours after the onset of symptoms.

In bee sting and drug-induced anaphylaxis, serum tryptase has been shown to rise over the first hour and may remain elevated for up to 12 hours. However, it is not elevated in most cases of food anaphylaxis.[17] The reason for this is not clear but basophils or monocytes might be more important than mast cells in the pathogenesis of food-induced anaphylaxis.

Postmortem serum tryptase may be useful to establish anaphylaxis as a cause of death, but is not diagnostic of an anaphylactic death.

Skin prick tests and serum allergen-specific IgE tests (RAST)

- Skin testing or RAST can be performed to detect allergen-specific IgE to foods, venom, latex, insulin and penicillin.
- Since skin testing carries a small risk of anaphylaxis it must be carried out where anaphylaxis can be appropriately treated.
- If the allergen-specific IgE (skin tests or RAST) are negative it might be necessary to repeat them four to six weeks after the anaphylactic event, as there may be false negative results for up to six weeks due to temporary anergy, especially after venom anaphylaxis.
- Skin prick testing for fruits and vegetables is very unreliable when commercial extracts are used, as the shelf life is too short. Much better results are obtained using fresh fruits and vegetables. This should be done in a setting where resuscitation is possible, as anaphylaxis may occur.
- Occasionally it is necessary to repeat testing with the actual food prepared as eaten.

Box 2

Anaphylaxis is very likely when any ONE of the following three criteria are fulfilled:

1. Acute onset of illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalised hives, pruritus or flushing, swollen lips/tongue/uvula) AND AT LEAST ONE OF THE FOLLOWING:
   (a) Respiratory compromise (e.g. dyspnoea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
   (b) Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia, syncope, incontinence)
2. Two or more of the following, occurring rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   (a) Involvement of the skin or mucosal tissue (e.g. generalised hives, itch/flush, swollen lips/tongue/uvula)
   (b) Respiratory compromise (e.g. dyspnoea, wheeze bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced BP or associated symptoms (e.g. hypotonia, syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
   (a) *Infants and children:* low systolic BP* (age specific) or greater than 30% decrease in systolic BP
   (b) *Adults:* systolic BP of less than 90mm Hg or greater than 30% decrease from the person's baseline

PEF = Peak Expiratory Flow

BP = Blood Pressure

* Low systolic blood pressure for children is defined as less than 70mm Hg from one month to one year, less than 70mm Hg + [2 x age] from one to 10 years, and less than 90mm Hg from 11 to 17 years.

(Adapted from NAID/FAAN Second Symposium JACI, Feb 2006)

- In a search for the cause in patients with possible food anaphylaxis, leftover food or vomit can be a useful source of antigen for testing.
- Overall, RAST is considered less sensitive and specific than the skin prick test. But in high quality labs a 3+ to 4+ RAST probably has a positive predictive accuracy similar to a skin prick test that is 3mm greater than the negative control.
- Recent studies with the newer test for serum allergen-specific IgE, the CAP-RAST have shown a better positive predictive accuracy than the RAST. For example, a level of greater than 15kU/L of specific IgE to peanut has greater than 95% positive predictive accuracy for predicting a positive challenge.

Supervised oral challenges

Sometimes it might be appropriate to do a supervised food or drug challenge in an allergist's office or hospital. Food challenges are contraindicated in patients with unequivocal history of anaphylaxis following the isolated ingestion of a food to which they have significant IgE antibodies. If several foods were ingested and the patient has several positive skin tests to several foods, the CAP-RAST may clarify which foods need to be challenged.

First aid management of anaphylaxis

I. Immediate intervention / First line therapy

- Recognising the symptoms and signs of anaphylaxis. Is it anaphylaxis? Beware of the masqueraders (especially vasovagal reactions, glolobus hystericus, and panic attacks).
- Seek emergency assistance (Call 111).
- Follow standard resuscitation measures, assess airway, breathing and circulation (ABC).
- Give intramuscular adrenaline 1:1000 dilution, 0.2-0.5ml (0.01mg/kg in children, max 0.3mg dosage into the arm or thigh (preferably) every five minutes, as necessary to controls symptoms and blood pressure. Alternatively, an adrenaline autoinjector (e.g. EpiPen® [0.3mg] or EpiPen® Jr. [0.15mg] may be administered intramuscularly through clothing into the lateral thigh. Repeat every five minutes as necessary, avoiding toxicity. Adrenaline should be the first drug given once anaphylaxis is suspected.
  There is no absolute contraindication to adrenaline injection in anaphylaxis.

II. Subsequent measures that may be necessary depending on response to adrenaline

- Lie flat with legs elevated unless respiratory distress (asthma) makes sitting up more comfortable
- Establish and maintain airway. Nebulised beta agonist may be required for bronchospasm. (A)
- Administer oxygen at 6–8 litres / min. (B)
- Establish venous access (C)
- Normal saline IV for fluid replacement. May require large volumes of fluid. 1–2 L of normal saline can be given to adults in the first five minutes. Children can receive up to 30ml/kg in first hour. If hypotension persists rapid infusion of volume expanders (colloid-containing solutions) may be required.

III. Second line drug therapy

- IV antihistamine (e.g. phenergan) in combination with IV ranitidine or cimetidine are slower in onset of action than adrenaline. They have very little effect on blood pressure and should be considered second-line treatment for anaphylaxis. They may provide dramatic symptomatic relief for skin symptoms (urticaria, flushing and angioedema).
- IV hydrocortisone 5mg per kg, or approximately 250mg IV (or prednisone 20mg orally in mild cases). The rationale is to reduce the risk of biphasic or protracted reactions. The benefit is not realised for six to 12 hours after administration.
- Glucagon may be given in refractory cases not responding to adrenaline when a beta-blocker has been taken.

Observation after first-aid treatment of anaphylaxis

All individuals receiving emergency adrenaline should immediately be transported to a hospital, even if symptoms appear to have resolved. In the majority, one injection of adrenaline will be effective. However, because some patients will have a biphasic response, observation in a hospital setting for at least four hours after symptoms subside is necessary. For severe reactions or reactions requiring more than a single dose of adrenaline, a longer period of observation (12–24 hours) or admission may be necessary.

Adrenaline

Adrenaline is the recommended first line treatment in anaphylaxis and all the studies on anaphylaxis fatality suggest that fatality increases with delay in initiating adrenaline therapy. In an animal model it has been confirmed that adrenaline given at the nadir of shock fails to produce haemodynamic recovery despite an elevation in plasma adrenaline concentration. [26]

Pharmacology of adrenaline

- $\alpha 1$: Increases vasoconstriction and vascular resistance, decreases mucosal oedema
- $\alpha 2$: Decreases insulin release, decreases noradrenaline release
- $\beta 1$: Increases ionotrophy and chronotrophy
- $\beta 2$: Increases bronchodilation, vasodilation and glycogenesis
- $\beta 2$: Decreases release of mediators from mast cells and basophils

Dose of adrenaline

There is some disagreement about the recommended dose of adrenaline for adults. Almost all the literature agrees on 0.01mg/kg in infants and children.

North American guidelines suggest a dose in adults of 0.3–0.5ml of adrenaline 1:1000 (0.3–0.5mg), whereas European literature suggests 0.5–1mg. No comparative trials have been conducted. Repeat doses may be given at five minute intervals until symptoms improve.

Due to the unpredictable nature of anaphylaxis, there are no prospec-

Box 3

Key to successful management of acute anaphylaxis includes:

- Prompt recognition of anaphylaxis and exclusion of common masqueraders.
- Early administration of IM adrenaline
- Early replacement with IV fluid for hypotension.
- Knowledge and access to second-line therapy.

tive, randomised placebo-controlled studies regarding the use of adrenaline in humans. However there have been animal studies and a long history of observational studies regarding the use of adrenaline in human anaphylaxis. Simons has done several studies on the use of adrenaline in anaphylaxis and some of her conclusions include:

- 0.95% of the population in Manitoba, Canada had adrenaline dispensed.[18]
- Adrenaline in an 'anaphylactic' dose may not reverse established shock.[19]
- In a DBPC landmark trial, intramuscular absorption of adrenaline was significantly shorter (approximately five minutes) compared with subcutaneous absorption (approximately 20 minutes). Therefore the recommendation is to administer adrenaline IM for the management of anaphylaxis.[20]
- EpiPens are spring-actuated adrenaline self-injectors designed for patients. The expiration date is clearly marked on the device and unfortunately is only about 18 months shelf-life. Simons study showed that the effectiveness of EpiPen® correlates with the number of months past the expiration date.[21]
- One quandary that confronts the clinician is the fact that EpiPen® comes in only two strengths: 0.15mg (EpiPen® Jr) and 0.3mg (EpiPen®). The usual dose for treating anaphylaxis is from 0.1mg/kg to 0.3mg–0.5mg given IM. What should be done if the child's weight falls between the 0.15mg and 0.30mg dose? Should you 'overdose' or 'under-dose'? Simons suggests using the adult dose (0.3mg) if one or more of the following condition(s) apply:
  – Patient has a concurrent diagnosis of asthma.
  – The trigger for anaphylaxis is tree nut, peanut, milk, eggs, or fish.
  – There is poor access to medical services.
  – There is a dysfunctional family situation.
  – No reliable transportation is available.
  – The patient has a history of previous life-threatening reactions.

Box 4

ASCIA Guidelines for EpiPen® Prescription in Australia

1. RECOMMENDED

History of anaphylaxis (if the patient is considered to be at continuing risk).

2. MAY BE RECOMMENDED

History of generalised allergic reaction with one or more of the following factors:

- **Asthma – concurrent or past history**
- **Age**
  (i) Adolescents and young adults who have a greater risk of fatal food anaphylaxis. The majority of recorded reactions to foods (~90%) occur in children over the age of five years.
  (ii) Adults who have a greater risk of fatal stinging insect anaphylaxis than children.
- **Specific allergic triggers**
  Nut allergy – Most deaths from food anaphylaxis occur from nuts. Generalised allergic reactions can be triggered by exposure to trace or small amounts of nuts, which can be difficult to avoid. Subsequent allergic reaction to nuts may be unpredictable.
  Stinging insect allergy (bees, wasps, jumper ants) in adults.
- **Co-morbid conditions** – Ischaemic heart disease.
- **Limited access to emergency medical care** – In remote locations early administration of adrenaline may not be possible unless an EpiPen® is available.

These factors should be considered when deciding whether an EpiPen® is prescribed, as they are known risk factors for more severe or fatal reactions.

3. NOT NORMALLY RECOMMENDED

- **Asthma** – In patients with asthma without anaphylaxis or generalised allergic reactions.
- **Elevated specific IgE only (positive RAST and/or skin test)** without a history of clinical reactions. Positive reactions alone do not necessarily mean there is allergic disease. The patients may be referred to an allergy specialist for assessment of their risk of allergy and anaphylaxis. This may include further investigations such as challenge testing.
- **Family (rather than personal) history of anaphylaxis or allergy**
- **Local reactions to insect stings in children and adults**
  Whilst the risk of allergy is inherited, anaphylaxis is not inherited.
- **Generalised skin rash (only) to bee or wasp stings in children**

Other recent studies on adrenaline in anaphylaxis

- EpiPen® is used in only 29% of reactions[22]
- Repeat adrenaline injections are needed in 35% (retrospective chart review)[23]

Reasons for lack of response to adrenaline

- Rapidly progressive anaphylaxis
- Failure to administer adrenaline promptly
- Failure to use an adequate dose
- Administration by suboptimal route e.g. SC vs IM
- Patient taking a beta-blocker
- Patient allergic to sodium metabisulfite
- Outdated adrenaline

Box 5

Management points on prevention and treatment of future episodes of anaphylaxis

- **The most important component of anaphylaxis management is prevention.**
- **An anaphylaxis action plan** is probably the most important way of ensuring the proper management of future anaphylaxis.
- **Provide adrenaline auto-injectors EpiPen® with an action plan.**
- **In-depth education** of patient, family and caregivers on allergen avoidance and the use of an EpiPen®.
- Advise patients to wear or carry a medical alert identification to warn medical personnel of anaphylaxis risk.
- **Avoid prescribing beta-blockers**, angiotensin-converting enzyme inhibitors (ACE-inhibitors), tricyclic antidepressants and monoamine oxidase inhibitors to anaphylactic patients.
- Avoid administering **cross-reacting agents.**
- **Refer to an allergist** to identify trigger and **risk assessment for future life-threatening reactions.**
- If re-exposure to an offending medicine is necessary administer the medication **orally** and observe the patient for 30 minutes.
- **Consider pre-treatment** with steroids and antihistamine for radiocontrast allergy.
- **Consider desensitisation** for aspirin, penicillin and a number of other antibiotics.
- **Immunotherapy** is more than 95% successful in preventing venom anaphylaxis.
- Consider alternate day **prednisone and antihistamines** for frequent episodes of idiopathic anaphylaxis.
- Inform patients of **Allergy New Zealand**, which is a non-profit support organisation with important information and educational material on anaphylaxis (www.allergy.org.nz).

Intravenous adrenaline in anaphylaxis

Intravenous adrenaline has been associated with fatal cardiac arrhythmias and myocardial infarction. Major adverse events usually occur when adrenaline is given too rapidly, inadequately diluted or in excessive dose. IV adrenaline should be reserved for those with unresponsive anaphylaxis, who deteriorate despite receiving IM adrenaline. It should only be given in a resuscitation area with ECG monitoring by medical staff who are trained in its use.[25]

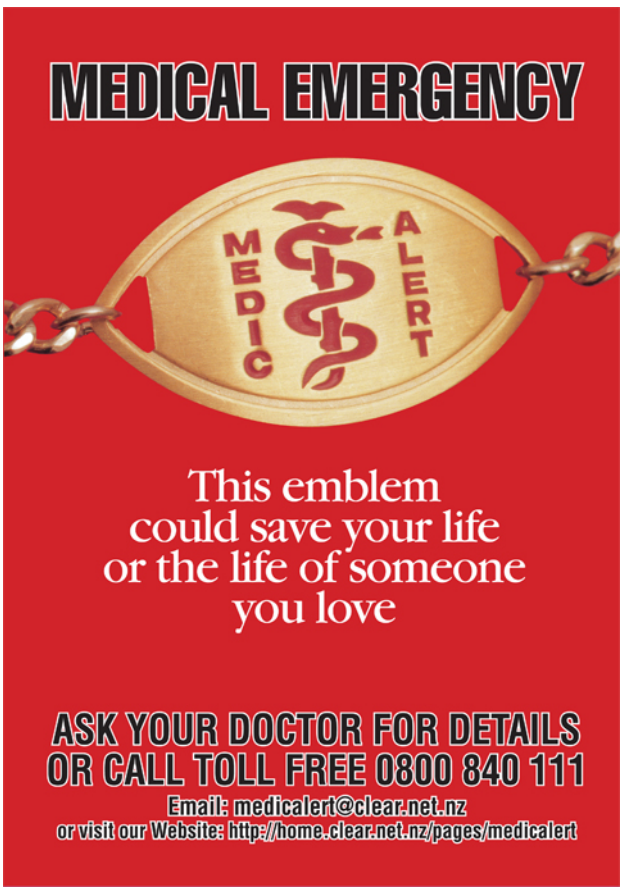
Drugs interfering with the action of adrenaline

- Beta-blockers worsen anaphylaxis, as they interfere with the effectiveness of adrenaline. Paradoxically the dose of adrenaline should be halved owing to the increased risks associated with unopposed stimulation of α-receptors; reflex bradycardia, hypertension, coronary artery constriction and bronchoconstriction
- Tricyclic antidepressants and monoamine oxidase inhibitors potentiate adrenaline and increase the risk of arrhythmias. The dose of adrenaline should be halved.
- Cocaine sensitises the heart to adrenaline and is therefore relatively contraindicated.

Biphasic anaphylactic reaction

1. Biphasic anaphylaxis occurs when the typical initial explosive episode is followed by an apparent resolution, only to be followed by return of symptoms, usually four to eight hours later, but recurrence has been described up to two to three days later.
2. Biphasic reactions to foods may occur in one-third of patients experiencing fatal or near-fatal, food-induced anaphylactic reactions.[25]
3. The incidence of biphasic anaphylactic reactions has been reported in other studies and shown to range between 2% to 20% of cases.
4. Factors associated with biphasic reactions include:
   - A delay in the administration of adrenaline;
   - Failure to give adrenaline;
   - Inadequate dose of adrenaline;
   - Very severe early phase with hypotension;
   - An inadequate dose of corticosteroids in the first phase (this point is controversial).

Figure 6. Medic Alert identification



Competing interests

None declared.

References

1. Poreter P, Ritchet C. De l'action anaphylactique de quelques venins. Comptes Rendus de Societe Biologique 1902; 54: 170-172.
2. Boros CA, Kay D, Gold MS. Parent reported allergy and anaphylaxis in 4173 Australian children. J Paediatr Child Health 2000; 36:36-40.
3. Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a 3-year survey. Mayo Clin Proc 1994; 69:16-23.
4. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: a population-based study. J Allergy Clin Immunol.1999; 104: 452–456.
5. Lieberman P. Unique clinical presentations of anaphylaxis. Immunol Clin N Am 2001; 21:813-25.
6. Kransick J, Patterson R, et al. A fatality from idiopathic anaphylaxis. Ann Allergy Asthma Immunol 1996; 76:376-378.
7. Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. J Paediatr 2000; 137:749-55.
8. Hourihane JO, Kilburn SA, Dean P, Warner JO. Clinical characteristics of peanut allergy. Clin Exp All 1997: 27:634-639.
9. Hourihane JO, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. BMJ 1996; 313:518-521.
10. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. Clinical and Experimental Allergy 2000; 30:1144-1150.
11. Camargo C. Anaphylaxis: A look at the oldest of allergic problems: Emergency department perspective on anaphylaxis. Program and abstracts of the American College of Allergy, Asthma & Immunology 2004 Annual Meeting; November 12-17, 2004; Boston, Massachusetts.
12. Kemp SF, Lockey RF, Wolf BL, Lieberman P. Anaphylaxis: A review of 266 cases. Arch Intern Med 1995; 1749-1754.
13. Clark S, Bock SA, Gaeta TJ, et al. Multicenter study of emergency department visits for food allergies. J Allergy Clin Immunol 2004; 113:347-352.
14. Sampson HA, Munoz-Furlong A, Bock SA, Schmidt C, Bass R, Chowdhury BA, et al. Symposium on the definition and management of anaphylaxis: Summary report. J Allergy Clin Immunol 2005; 115:571-574.
15. Sampson HA, Munoz-Furlong, et al. Second symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol 2006; 117:391-397.
16. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1997; 1:466-469.
17. Sampson HA, Mendelson LM, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med 1992; 327:380-384.
18. Simmons FER. Anaphylaxis: A look at the oldest allergic problems: Adrenaline; past, present, and future. Program and abstracts of the American College of Allergy, Asthma & Immunology 2004 Annual Meeting; Nov12-17, 2004; Boston, Mass.
19. Bautista E, Simons FE, Simons KJ, et al. Adrenaline fails to hasten haemodynamic recovery in fully developed canine anaphylactic shock. Int Arch Allergy Immunol 2002; 128:151-164.
20. Simons FE, Gu X, Simons KJ. Adrenaline absorption in adults: intramuscular versus subcutaneous injection. J Allergy Clin Immunol. 2001; 108:871-873.
21. Simons FE, et al. Outdated EpiPen and EpiPen Jr autoinjectors: past their prime? J Allergy Clin Immunol. 2000; 105:1025-1030.
22. Gold MS, Sainsbury R. First aid anaphylaxis management in children who were prescribed an adrenaline autoinjector device (EpiPen). J Allergy Clin Immunol 2000; 106:171-176.
23. Korenblat P, Lundie MJ, et al. A retrospective study of adrenaline administration for anaphylaxis: How many doses are needed? Allergy and Asthma Proc 1999; 20:383-386.
24. Sampson H. Clinical practice. Peanut allergy. N Engl J Med. 2002; 346:1294-1299.
25. Johnston SL, Unsworth J, et al. Adrenaline given outside the context of life-threatening allergic reactions. BMJ 2003; 326:589-590.
26. Bautista E, Becker A, Duke K, Simons FE, et al. Limited utility of intramuscular adrenaline in the treatment of haemodynamic collapse in experimental anaphylactic shock. Am J Respir Crit Care Med 2000; 161:A549.

Urological Emergency

'Priapism is a condition characterised by a persistent painful erection that is not related to sexual desire.

Most cases of priapism, if seen early enough in their evolution, will respond to conservative measures. Asking the patient to climb stairs (arterial "steal" phenomenon), or the application of ice packs, may often bring about detumescence. Should these measures fail then the corpora should be aspirated with a butterfly needle and syringe. The needle should be introduced into the lateral aspect to avoid both the urethra (ventrally) and the neurovascular bundle (dorsally). The amount of blood that needs to be aspirated to bring about detumescence is variable.

In the most common type of priapism—"low flow" (anoxic) priapism—the aspirated blood will be dark and deoxygenated. Should corporal aspiration fail in this type of priapism then slow infusion of an (alpha) agonist such as phenylephrine may be tried. Aspiration of bright red blood is diagnostic of "high flow" priapism. Infusion of phenylephrine is contraindicated in this type because the drug will rapidly leak into the circulation, causing severe systemic hypertension. Should conservative measures fail, surgery may be needed. Winter's procedure creates a communication between the engorged corpora cavernosa and the glans penis, allowing blood to be shunted away from the penis by the corpus spongiosum.'

Dawson C, Whitfield H. ABC of Urology: Urological emergencies in general practice. BMJ 1996;312:838-840.