# ABC OF ALLERGOLOGY

## DIAGNOSIS AND MANAGEMENT OF ANAPHYLAXIS

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***Anaphylaxis, or anaphylactic shock, is a sudden catastrophic allergic reaction affecting multiple systems in the body. It usually occurs within minutes of exposure to the offending allergen (insect stings, nuts and medicines being the most common causes).***

The first-line treatment of anaphylaxis is the immediate intramuscular injection of adrenaline (epinephrine). Failure to administer adrenaline probably constitutes medical negligence.

### What causes anaphylaxis?

Allergy to venom from bee and wasp stings can cause anaphylaxis, as can allergy to latex and drugs such as penicillin, codeine and aspirin.

The most common cause of anaphylaxis in the community is eating a food to which the person is allergic such as peanuts, tree nuts, fish and shellfish. These foods account for 90% of cases of food-induced anaphylaxis.[1]

***Allergic anaphylaxis (mainly IgE-mediated)***

Foods: Peanuts, tree nuts, sesame, fish, shellfish, egg, milk

Medication: Penicillin, sulfamethoxazole, cephalosporin, aminoglycoside

Insect stings: Bee, wasp, hornet including Royal Jelly

Anaesthetic agents: Thiopentone, suxamethonium, alcuronium

Allergen desensitisation immunotherapy ('allergy shots'). Latex, hormones (insulin), tetanus toxoid

Animal or human proteins: Semen, enzymes, colourants (insect derived)

Exercise-associated food allergy (wheat, celery, shellfish)

***Non-allergic anaphylaxis (previously anaphylactoid reactions)***

Aspirin sensitivity (including NSAIDs: ibuprofen, diclofenac, pyrazoles)

Opiates, ACE inhibitors, dextran, **radio contrast media,** streptokinase

Local anaesthetics (sulphites, parabens), chlorhexidine, gelatine

***Idiopathic (no apparent cause)***

This accounts for 30% of all anaphylaxis.

Even eating a minute amount of a particular food can trigger anaphylaxis. Some people are so sensitive that merely breathing in the food essence can trigger a reaction (as may occur in a restaurant when someone at another table is eating fish, or by kissing someone who has recently eaten peanuts). Subsequent allergic reactions are highly unpredictable and could manifest as milder, similar or more severe reactions.

Anaphylaxis may occur while exercising shortly after eating certain foods such as celery, shrimps, wheat, apple, hazelnut, squid and chicken (exercise-induced anaphylaxis).[1]

Iatrogenic anaphylaxis in hospital is commonly attributed to anaesthetic agents (muscle relaxants), antibiotics, radio contrast media, streptokinase, tetanus toxoid, latex and colloid (dextran) infusions.

Allergic anaphylaxis mediated by IgE requires prior sensitisation, while non-allergic anaphylaxis (previously called non-IgE or anaphylactoid reactions) may occur on the first exposure.[2] Both groups are clinically indistinguishable and their treatment is the same.

In about 30% of cases, a cause for the anaphylactic reaction may not be identified. The term '*idiopathic' anaphylaxis* was proposed in 1978 to describe this subgroup.

### Mediators of anaphylaxis

Biochemical mediators of anaphylaxis can be measured and are useful markers for both severity and confirmation that anaphylaxis has indeed taken place. This helps clarify the situation when the diagnosis of anaphylaxis is in doubt, such as under anaesthesia, in sudden infant death and at postmortem.

Beta-tryptase is released from tissue mast cells, and if possible should be measured at 1 hour and up to 5 hours after anaphylaxis. Tryptase may remain elevated for up to 12 hours in bee, drug- and anaesthetic-induced anaphylaxis but is rarely elevated in food anaphylaxis. Tryptase levels may even be elevated up to 15 hours post mortem.[3]

Remember that serum specific IgE will be depressed immediately after an anaphylactic reaction because it is 'used up' or tissue bound. RAST testing should therefore be deferred for a few weeks after the anaphylactic reaction; otherwise artificially low levels will be documented. In documented insect-venom anaphylaxis, 10% of patients may have no detectable venom-specific IgE despite being highly sensitive. In these cases, the cellular allergen stimulation test (CAST) which measures leukotriene release, is an alternative method of measuring venom-specific sensitivity.[4]

Intradermal injection skin testing is more sensitive than skin-prick testing to identify the culprit drug in anaphylaxis to anaesthetic agents and antibiotics.[5]

### Symptoms and signs of anaphylaxis

Anaphylaxis comprises a group of symptoms and features, which lead to a generalised severe allergic reaction with respiratory difficulties and circulatory shock.

Prodromal palmar and scalp itching with agitation is rapidly followed by generalised urticaria and angioedema. Skin signs are the most common initial manifestation in over 90% of anaphylactic reactions. However, cutaneous manifestations may occasionally be delayed or absent in rapidly progressive anaphylaxis. The next

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***Clinical grading of anaphylaxis (from Sampson[1])***

| *Grade* | *Skin* | *GI tract* | *Respiratory tract* | *Cardiovascular* | *Neurological* |
|---|---|---|---|---|---|
| 1 | Localised pruritus, flushing, urticaria, angioedema | Oral pruritus or tingling | | | |
| 2 | Generalised pruritus, flushing, urticaria, angioedema | Any of above plus nausea and/or emesis | Nasal congestion and/or sneezing | | Change in activity level |
| 3 | Any of above | Any of above plus repetitive vomiting | Any of above plus **sensation of throat pruritus or tightness** | Tachycardia | Change in activity level plus anxiety |
| 4 | Any of above | Any of above plus diarrhoea | Any of above plus **hoarseness, 'barky' cough, difficulty swallowing, dyspnoea, wheezing, cyanosis** | Any of above plus ***dysrhythmia and/or mild hypotension*** | 'Light headedness', feeling of *'impending doom'* |
| 5 | Any of above | Any of above plus loss of bowel control | Any of above plus **respiratory arrest** | **Severe bradycardia and/ or hypotension or cardiac arrest** | **Loss of consciousness** |

All symptoms are not mandatory. The severity grading should relate to the organ system most affected. Symptoms in 'bold face' are absolute indications for use of intramuscular adrenaline.

most common symptoms are dizziness, respiratory, gastrointestinal, and circulatory events with collapse and loss consciousness. The more rapid the onset of symptoms, the more likely they are to be life-threatening.[3]

Traditionally anaphylaxis has been categorised as mild, moderate or severe, but Sampson's grading utilising the organ affected and grading from 1 to 5 offers a more useful algorithm for assessment and treatment.[1]

Remember that anaphylaxis may recur hours after initial treatment (called a *late phase or biphasic response*), so all people who are treated for anaphylaxis should be monitored in an emergency unit for at least 4 hours after their reaction, even if they appear to have made a full recovery. *Protracted anaphylaxis* which persists for 3 to 21 days has occasionally been reported.[2]

***Risk factors for severe anaphylaxis***

**Previous severe reaction**

History of increasingly severe reactions

Coexistent asthma

Elderly on beta-blockers or ACE inhibitors

**Likely to develop anaphylaxis**

Peanut or tree nut allergy

Personal and family history of extreme atopy

Mastocytosis

## *Treatment of anaphylaxis*

Anaphylaxis needs to be treated as a matter of urgency as the symptoms of respiratory obstruction and shock develop rapidly. Emergency treatment always consists of basic cardiopulmonary support and simultaneous intramuscular injection of adrenaline (epinephrine) into the anterolateral thigh. The recommended dose in children is 0.01 ml/kg of 1:1000 adrenaline up to a maximum of 0.3 ml (0.3 mg) per dose and for adults 0.2 ml (0.2 mg) to 0.5 ml (0.5 mg) of 1:1000 adrenaline.

The subcutaneous route is no longer recommended as absorption is too slow, and intravenous administration may trigger arrhythmias and hypertension. Absorption from the thigh muscle is better than the deltoid muscle after intramuscular injection. No harm will be done by giving unnecessary adrenaline to a healthy individual but withholding administration may prove fatal in anaphylaxis.[6]

This initial treatment with adrenaline should be immediately followed by administering a fast-acting antihistamine and a short course of oral steroids to prevent a recurrence. Oral or intravenous steroids play no immediate role in anaphylaxis management, as they will take at least 2 hours to exert their effect, but do help reduce the risk of persistent or biphasic anaphylaxis.

Following anaphylaxis, all patients should proceed to and be monitored in a hospital emergency unit.[7] After all cases of Sampson Grades 3 to 5 anaphylactic reactions, two preloaded adrenaline auto-injectors (Epipen) should be prescribed for self-administration and a MedicAlert bracelet issued. Patients or their caregivers must be carefully instructed on how to use the Epipen! A major drawback of the Epipen in South Africa is that the only available dose is 300 µg which is suitable for an older child or small adult (30-50 kg). Adrenaline ampoules and syringes may often be 'fumbled' by caregivers and erroneous dosages can be given in the midst of panic associated with a sudden anaphylactic reaction. Caregivers should therefore practise and rehearse the procedure of adrenaline administration.[1]

For the generalised urticarial rash associated with 'mild' anaphylaxis (Sampson Grades1 & 2), fast-acting oral $H_1$ antihistamine medication should suffice. But injectable adrenaline should always be available in case a moderate to severe generalised reaction (Sampson Grades 3 to 5) occurs with signs of respiratory difficulty (including laryngeal oedema, 'staccato' cough and/or wheeze).[1]

Promethazine (0.5 mg/kg in children and 25-50 mg in adults) is quick acting and readily available in South Africa, while diphenhydramine and chlorpheniramine are also equally effective $H_1$ antihistamines and can be

prescribed via oral, slow intravenous or intramuscular routes.[8]

$H_2$-blockers such as ranitidine and cimetidine probably offer no additional benefit over high-dose $H_1$ antihistamines.

Venom immunotherapy (VIT) for bee and wasp venom anaphylaxis is highly effective, but treatment needs to be maintained for 5 years. Bee keepers are the most at-risk group for severe life-threatening anaphylaxis. Elderly patients (especially those with cardiovascular disease on beta-blockers and ACE inhibitors) are more at risk for anaphylaxis while 70% of children will outgrow their venom anaphylaxis. The risk of a severe reaction will decline the longer the interval between stings. There is a greater risk for bee stings (50%) than for vespid stings (25%) in patients with respective allergies to these insects.[4]

## *Other rare conditions can mimic anaphylaxis*

Systemic mastocytosis is a rare condition where there is a 20-fold increase in mast cells in the skin or internal organs – these can suddenly release enormous amounts of histamine and tryptase after minimal traumatic provocation thus mimicking anaphylaxis. The serum tryptase levels remain elevated even between attacks. Systemic mastocytosis is usually associated with a deeply freckled skin (urticaria pigmentosa) and associated flushing, headaches, urticaria, asthma, diarrhoea, hepatomegaly and osteoporosis with bone pain (a bone marrow biopsy with mastocytosis is diagnostic). The skin typically develops urticarial lesions upon firm stroking – Darier's sign. This condition is more common in children but most outgrow the disease by adolescence.

### *Treating anaphylaxis*

**Immediate intervention**

Remove the allergen!

Provide airway and basic life support.

- **Intramuscular adrenaline** (0.01 ml/kg of 1:1000) injected into anterolateral thigh muscle. Adults: 0.2 ml to 0.5 ml of 1:1000. Dose repeated at 5-minute intervals if necessary.

Followed by intravenous, oral or intramuscular:

- **Antihistamine: Promethazine** 0.5 mg/kg in children and 25-50 mg in adults
- **Hydrocortisone** (children 4 mg/kg and adults 200 mg) or prednisone (children 1 mg/kg and adults 50 mg).

**Other measures**

- **Laryngeal stridor:** Nebulised **adrenaline** 5 ml 1:1000 repeated every 10 mins (inhaled racemic adrenaline is less effective than intramuscular adrenaline)
- **Wheeze:** Nebulised **salbutamol 2.5 mg** if less than 5 years, **5 mg** for children over 5 years and adults. Consider aminophylline 5 mg/kg IVI over 15 minutes or salbutamol 15 µg/kg
- Administer **oxygen** 10 l/min via face mask if available
- **Hypotension:** Intravenous normal saline 20 ml/kg by rapid infusion
- On beta-blocker therapy: Administer **glucagon** 1-5 mg IVI over 5 minutes (children: max 1 mg).

**Discharge treatment:** Should include 3-day course of non-sedating antihistamine and prednisone.

Prescribe two emergency Epipen adrenaline auto-injectors and oral antihistamine, give written emergency treatment plan, and issue MedicAlert bracelet.

If symptoms do not correlate with those of typical anaphylaxis, reconsider the differential diagnosis:

- Panic attacks
- Vaso-vagal syncope
- Globus hystericus
- Aspiration of foreign body
- Epileptic seizures
- Flushing from histamine-rich foods
- Scombroid toxicity from fish
- Pulmonary embolism, hypoglycaemia, arrhythmia and acute myocardial infarct may closely resemble anaphylactic reactions

**Hereditary angioedema** (HAE) is a familial condition that occurs in 1 in 80 000 people. The typical symptoms begin in adolescence (more common in females). The painful angioedema lasts for 2-3 days and involves the face, neck and limbs with debilitating non-itchy swelling and breathing difficulties. This is due to a deficiency or underactivity of the C1 esterase inhibitor enzyme and is associated with a low serum complement C4.

**Carcinoid syndrome** can be confused with anaphylaxis as there is usually flushing, diarrhoea and wheezing, but also an associated right heart murmur with high levels of hydroxy indole acetic acid (HIAA) in the urine.

**Phaeochromocytoma** is a benign tumour that secretes adrenaline-like catecholamines which can mimic anaphylaxis with flushing but is associated with dangerous hypertension.

*The author would like to thank Professor Cas Motala for reviewing the manuscript and for his invaluable input.*

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