# Anaphylaxis: a study of the condition and treatment

**Neil Allen**
Faculty of Education, Health and Community
School of Nursing and Allied Health
Liverpool John Moores University

**Abstract**

Anaphylaxis is a sudden, severe and life threatening hypersensitivity reaction following exposure to a foreign protein. The majority of anaphylactic deaths are caused by envenomation from stings followed by adverse reactions to drugs and food.

Treatment tends to be through the use of intramuscular adrenaline, nebulised salbutamol, anti-histamines and steroids, although evidence has shown that the time required for the anti-histamines and steroids to work shows little benefit for the patient in the early treatment stage.

Given the nature of anaphylaxis, research on human subjects is fraught with ethical dilemmas and a status quo in treatment regimes is likely for the foreseeable future.

**Keywords**

anaphylaxis; treatment; guidelines; allergen; adrenaline

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The term anaphylaxis literally means ‘against protection’, but anaphylaxis has no universally agreed definition however, Johansson et al. (2004, p.835) proposed the following: ‘Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction’. Originally identified in 1902 by Portier and Richet, anaphylaxis is an immunological response following exposure to a foreign protein that has previously been seen by the patient’s immune system.



This protein can be introduced to the immune system through a number of channels, mainly food, drugs and venom. Alves and Sheikh (2001) noted that foodstuff triggers greatly affected children, whereas medicinal triggers were more common in older people. There are also a significant number of idiopathic triggers.

The epidemiology of anaphylaxis is difficult to ascertain, mainly due to diagnostic uncertainty; in a review of allergy services, the Department of Health (2006) identified an increase in admission rates from 7 to 12 per 100,000 people, with a threefold increase since 1994. This may be an underestimation, because anaphylaxis can be misdiagnosed as severe asthma, while many cases are treated in the emergency department and not admitted to a ward. The problem of diagnosis is not exclusive to the United Kingdom, a retrospective analysis by Klein and Yocum (1995) in the United States of America of patient records in an emergency department over a four month period revealed that 13 out of 17 patients fitted the criteria for anaphylaxis but were diagnosed with other conditions.

The Resuscitation Council's (UK) clinical guidelines (2008) state that a diagnosis of anaphylaxis is more likely when a patient is exposed to a trigger and then develops a sudden illness with rapidly progressing skin changes and life-threatening airway and/or breathing and/or circulation problems. However, a single set of criteria will not identify all anaphylactic reactions; Brown (2004) identified certain combinations of symptoms that facilitate diagnosis such as a sudden onset and rapid progression of symptoms, exposure to a known allergen, life-threatening airway, breathing and/or circulatory problems. The issue of misdiagnosis is also seen in death records: Pumphrey (2000, 2004) and Pumphrey and Roberts (2000) found an average of 20 deaths per year attributed to anaphylaxis since 1992 in the United Kingdom. These were identified by setting up a register from the certified cause of death and other sources such as hospital treatment records, which detailed the patient's medical history and allergic reactions that suggested anaphylaxis. The findings revealed that two-thirds of deaths were caused by envenomation (stings); four-fifths of those dying from medicinal anaphylaxis had no previous indication of an allergy; and many dying from food allergies had previously experienced non-severe reactions. Pumphrey (2000) found that whereas 86% of food-related fatalities resulted from respiratory arrest, shock was more common in iatrogenic and venomed reactions.

In the United States, the estimated number of deaths per year is around 1500, with 1300 being iatrogenic and approximately 100 attributed to each of food and stings (Neugut et al. 2001). However, given its larger population compared with the United Kingdom, and the difficulties in diagnosing anaphylaxis, these numbers could be higher.

As explained earlier, anaphylaxis is an immunological response to exposure to a foreign protein previously seen by the immune system. The reaction occurs rapidly, within minutes, although the onset time will depend on the trigger: reactions are quicker to intravenous triggers than to a sting, and slower to orally ingested triggers. Pumphrey (2000) stated that onset is almost always within two hours of exposure to a trigger.

At the initial exposure, the immune system will provide Immunoglobin E (IgE) antibodies specific to that allergen, which will cause an exaggerated immunological response on subsequent exposures, manifesting as an anaphylactic reaction. Individuals report any of the following: urticaria, angioedema, stridor, hoarse voice, confusion, lethargy, shortness of breath, cyanosis, wheeze, hypotension, tachycardia, gastrointestinal problems (abdominal pains, incontinence, vomiting), erythema, rhinitis, conjunctival swelling, laryngeal swelling, respiratory/cardiac arrest. The rapid progression to life-threatening airway obstruction and asphyxia is an obvious concern, due to the angioedema of the uvula, tongue and soft palate. Netzel (1986) identified that 75% of deaths resulted from asphyxia due to upper airway oedema and severe bronchospasm. Where indicated, early intubation should be carried out; however, nasal intubation may be necessary if the swelling prevents a clear view of the vocal chords. If an endotracheal intubation is not possible, Atkinson and Kaliner (1992) and Brown (2009) have suggested securing a surgical airway via a cricothyroidotomy. It is important to identify the signs and symptoms of any potential compromise to the airway early and act promptly to prevent further deterioration in the patient.

The signs and symptoms of anaphylaxis are produced by the rapid release of chemical mediators following exposure. These chemical mediators are histamine, heparin and tryptase granules, which fill the cytoplasm of mast cells. The mast cells – located in regions that come into contact with the external environment, such as beneath the skin's surface, outer surface of the eyes, respiratory tract linings and connective tissue in all organs except the brain – play an important role in the body's inflammatory response (Jones 2002). They are activated by an allergen, degranulating and releasing the chemical mediators into the surrounding tissues. This process results in increased vascular permeability, leading to systemic capillary leak syndrome, which is characterised by hypotension and hypovolaemia. A chain reaction is then set in motion, whereby mast cells synthesise and reproduce new granules, which in turn degranulate (Pareham 2000).

Bird (1996) states that an IgE hypersensitivity reaction depends on the method of ingestion, and the rate of administration and absorption of the allergen. The reactions can also vary in severity; although onset is generally rapid, it can be delayed. Further, reactions can be biphasic – a secondary reaction occurs – which is quite common, especially in patients requiring higher doses of adrenaline (Brazil and MacNamara 1998).

Owing to the immediate threat to life, patients who are diagnosed as anaphylactic are prescribed an auto-injector containing either 0.15 mg or 0.3 mg of adrenaline for intramuscular self-administration. Adrenaline is widely recognised as the most effective first-line treatment for anaphylaxis; Fisher (1995) and McLean-Tooke et al. (2003) state that it is the most important drug. As an alpha-receptor agonist, it reverses peripheral

vasodilation and reduces oedema; as a beta-receptor agonist, it dilates the bronchial airways, increases myocardial contractions and supresses histamine release. Mast cells also have beta-2 adrenergic receptors that inhibit their activation and thus reduce the severity of the IgE hypersensitivity reaction. Intramuscular administration of 500 µg (0.5ml of 1:1000 solution) adrenaline is recommended, preferably into the outer aspect of the thigh (Simons et al. 2001), as intravenous administration is more hazardous and carries the risk of hypotension, cardiac arrhythmias and myocardial infarction (Barach et al. 1984).

Other medications that can be prescribed for a life-threatening anaphylactic reaction include:

Oxygen – It is recommended that 10–15 litres/minute are administered via a reservoir mask to maintain oxygen saturation levels at 94–98% (British Thoracic Society 2008). However, oxygen is also administered via a nebuliser mask when a bronchodilator is used, at a rate of 6–8 litres/minute.

Fluids – Large volumes of fluid can be lost in interstitial spaces (capillary leak syndrome), causing a drop in circulatory body fluids followed by hypotension, vasodilation and shock. Over half of anaphylactic deaths occur within the first hour, and in 25% of cases, death is related to hypotension and circulatory failure (Netzel 1986). There is no evidence as to whether a colloid or crystalloid solution is more effective; however, one concern is that colloids, especially polygeline (Haemaccel), are known to cause anaphylactic reactions (Duffy et al. 1994). Fisher and Baldo (1988), though, have concluded that colloids rarely produce anaphylactic reactions in patients already in shock, possibly because of the

protective effects of the patients' own sympathoadrenal response. Once intravenous access is gained and there is evidence of hypotension, fluids should be started immediately, but not to the detriment of the early use of intramuscular adrenaline.



Antihistamines –These are a secondary treatment for anaphylaxis and despite the weak evidence base, there is a logical reason for their use (Sheikh et al. 2007). H1-antihistamines may help counter histamine-mediated vasodilation and bronchial constriction, but alone, they are unlikely to be life-saving; owing to the time taken to diagnose anaphylaxis, the concentration levels of histamine around a mast cell after degranulation means a competitive blocker has little effect (Brown 1995).

Steroids – Smith et al. (2003) have reported the benefits of early corticosteroid treatment for asthma, but, as with antihistamines, there is little evidence on its benefit in anaphylaxis. Moreover, when administered intravenously, steroids may take up to 4–6 hours to become fully effective. Although they are believed to shorten, or even prevent, protracted reactions, both Fisher (1987) and Bochner (1991) report that there is no guidance as to the best steroid to use: hydrocortisone or prednisolone.

Bronchodilators – As the presentation of anaphylaxis resembles asthma (except for hypotension), bronchodilators are considered useful for bronchoconstriction. Nebulised salbutamol 2.5–5 mg is recommended but only considered beneficial when bronchoconstriction is a prominent feature and not responding to conventional adrenaline treatment. On the other hand, Pumphrey and Nicholls (2000) found that magnesium sulphate could reverse an otherwise irreversible bronchospasm.

Glucagon – Toogood (1988) and Thomas (2005) report glucagon as a recommended treatment secondary to adrenaline for patients prescribed β-blockers. This is because

glucagon increases intracellular levels of cyclic adenosine monophosphate that results in bronchodilation, with some anti-inflammatory effects, by using a calcium-dependent stimulant to bypass β-adrenergic receptors (Strober and Gottesman 2009). The recommended dosage for glucagon is 1 mg administered intravenously and then repeated every five minutes at 5–15 µg/min.

Naloxone – Hypotension caused by shock is believed to be partly due to the effects of opiates released by the body after major blood loss (loss of circulating body fluids in interstitial spaces during anaphylaxis). Amir (1984) found that naloxone improved the survival rate of mice in experimental anaphylaxis by blocking opiate receptors in the central nervous system. However, Boeuf et al. (2009) concluded that although naloxone may improve blood pressure, more trials were required to prove whether it prevented death. Consequently, naloxone is not currently used as an anaphylactic treatment.

Currently, Olivera et al. (2010) are undertaking research to identify a possible drug target to counteract vasodilation. The protein SPHK1 has been shown to produce the molecule S1P that affects blood vessels and the immune system.

NICE guidelines (2011) suggest that following a diagnosis of anaphylaxis and liaison with a specialist allergy service, patients should be prescribed an auto-injector; however, Unsworth (2001) warns against the overprescribing of adrenaline in the community. Patients should therefore be provided with information about the condition, what to do in the event of a reaction, the risks of a biphasic reaction and information on patent support groups, such as the Anaphylaxis Campaign (www.anaphylaxis.org.uk). When a patient is diagnosed as anaphylactic to an identified allergen or trigger, they should obviously take

action to avoid exposure, but this raises issues for patients whose trigger is a foodstuff. The Food Safety Act 1990 (amended 2004) provides a framework for food legislation in the United Kingdom, and the main responsibilities for businesses are to ensure that:



- food will not be detrimental to the health of the consumer
- food is labelled, advertised and presented in a way that is not false or misleading
- food served or sold is of a nature, substance or quality expected.

However, this does not include specific labelling for allergies, which is outlined in the European Directive 2003/89/EC; this legislation covers 14 food allergens that must be declared when they are used at any level in pre-packed foods, as follows:

Eggs

Milk

Fish

Crustaceans (e.g. crab, lobster, crayfish, shrimp, prawn)

Molluscs (e.g. mussels, oysters, squid)

Peanuts

Tree nuts (almonds, hazelnuts, walnuts, cashews, pecans, Brazil nuts, pistachios, macadamia nuts, Queensland nuts)

Sesame seeds

Cereals containing gluten (i.e. wheat, rye, barley, oats, spelt, kamut, or their hybridised strains)

Soya beans

Celery and celeriac

Mustard

Lupin

Sulphites at a concentration of ten parts per million



A study by Akeson et al. (2007) revealed that adolescents typically perceive anaphylaxis as 'no big deal', stating that it has a low impact on their daily life. Unsurprisingly, parents reported anxiety about handing over responsibility for avoidance and emergency management to their children; in fact, Akeson et al. found that having a child with anaphylaxis could have a significant long-term psychological impact on parents. One reason for the attitude of 'no big deal' among adolescents may be because they cannot remember ever having a reaction, which would contribute to a reduced perception of risk and increased self-confidence.

Broome-Stone (2012) does state that healthcare providers must take into account the psychosocial impact of food allergies on families; however, current literature does not provide evidence of how to provide healthcare access appropriate to the needs of families, and specific research is required to assist in understanding not only the patients' but also the families' psychosocial needs.

Patients need to be able to recognise the early symptoms of anaphylaxis, self-medicate with an adrenaline auto-injector and make family and friends aware where they keep their auto-injector. It is also useful for patients to wear a medical alert, so that if they collapse, the possible reason can be identified early. Those not yet diagnosed as anaphylactic need

to receive emergency medical treatment and assistance as soon as possible, which will include a range of medications and fluids.



As mentioned earlier, a wealth of research indicates adrenaline as the first drug of choice for anaphylaxis, although other drugs have been investigated. However, anaphylaxis is notoriously difficult to study, being an immediately life-threatening, often un-anticipated event, and most research has relied on death records, past medical history and hospital treatment records. Incidents of anaphylaxis are rising year on year (Resuscitation Council 2008), although misdiagnosis is contributing to the figures. This can be seen in possibly the earliest record of an anaphylactic death in 2640 BC, that of King Menes of Memphis, an Egyptian Pharaoh, on whose sarcophagus hieroglyphs depicted him being stung by a wasp (Donald and Redford 2001), although the interpretation of the hieroglyph is challenged by Krombach et al. (2004). Thus, a definitive diagnosis of anaphylaxis is difficult, as is research, due to the unexpected occurrence of a reaction, and treatment recommendations have to be based on clinical observation, interpretation of the pathophysiology and animal studies.

In conclusion, being potentially life–threatening raises ethical issues that make human studies difficult. As such, the status quo will continue in emergency anaphylactic treatment for the foreseeable future; prophylactic treatments may improve, but the emphasis must be on educating patients' relatives, and the general public, along with minimising the risk of exposure to a trigger.

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