CONSENSUS GUIDELINES

Emergency medical treatment of anaphylactic reactions

Project Team of the Resuscitation Council (UK)

1. Objective of document

Anaphylaxis seems to be increasingly common, almost certainly associated with appreciable increase in prevalence of allergic disease over the last two or three decades. Although the drug treatment and management of anaphylaxis is described elsewhere,[1] anaphylaxis continues to be poorly managed. There are two main problems. First, epinephrine (adrenaline) is greatly under-used: chlorpheniramine and hydrocortisone injections are more often given. Second, there has been a vogue for inappropriate use of intravenous epinephrine (adrenaline), both by paramedics and in accident and emergency (A&E) departments, when epinephrine (adrenaline) should have been given intramuscularly. Published recommendations for the management of anaphylaxis also vary. This document provides a broad consensus on the appropriate emergency management of acute anaphylactic reactions by first medical responders who are unlikely to have specialised knowledge.

No definitive clinical trials have been performed to provide an unequivocal evidence base: moreover such evidence is unlikely to be forthcoming. A wealth of experience does, however, exist. This has been integrated through the wide membership of the Project Team which was convened under the aegis of the Resuscitation Council of the United Kingdom with representation from four royal colleges and three specialist associations: other members were coopted because of their individual expertise. Consensus was achieved after two meetings and multiple circulation of working papers. An earlier document from broadly the same group (but at that time representing the Joint Royal Colleges and Ambulance Liaison Committee) has dealt with the management of anaphylaxis by paramedics—who are often the first to attend out of hospital emergencies.[2] This complementary document offers guidance to general practitioners and A&E staff who are usually the first physicians to become involved. Anaphylactic reactions may occur *within* hospital as a result of attempted hyposensitisation, the administration of drugs including anaesthetic agents, or contrast materials. Some specialist groups have issued recommendations for the management of emergencies that occur under these specific circumstances.[3–5] The present guidance is not intended to replace existing advice for defined groups in hospital nor to influence the essential individual advice and management provided in specialist clinics.

2. Recognition of anaphylactic and anaphylactoid reactions

2.1. There are no universally accepted definitions of anaphylactic and anaphylactoid reactions. Disparate mechanisms can lead to serious symptoms and signs due to sudden activation of mast cells and basophils. The term anaphylaxis is usually used for hypersensitivity reactions typically mediated by immunoglobulin E (IgE). Anaphylactoid reactions are similar, but do not depend upon hypersensitivity. For simplicity the term anaphylaxis will be used here for both types of reactions unless there is an important distinction to be made. Their manifestations and management are similar so that the distinction becomes important only when considering the follow up management. Both may present clinically with angio-oedema, urticaria, dyspnoea, and hypotension. But some patients may die from acute irreversible asthma or laryngeal oedema with few more generalised manifestations. Other symptoms include rhinitis, conjunctivitis, abdominal pain, vomiting, diarrhoea, and a sense of impending doom. There is also usually a colour change: the patient may appear either flushed or pale. Cardiovascular collapse is a common manifestation[6] especially in response to intravenous drugs or stings, and is caused by vasodilatation and loss of plasma from the blood compartment. Cardiac dysfunction or arrhythmias are due principally to hypotension, or rarely to underlying disease,[7 8] or to epinephrine (adrenaline) that has been administered intravenously.[9] Anaphylactic reactions vary in severity and progress may be rapid, slow, or (unusually) biphasic.[10] Rarely manifestations may be delayed by a few hours (adding to diagnostic difficulty), or persist for more

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than 24 hours.[7] Reactions may follow exposure to a variety of agents—with insect stings, drugs or contrast media, and some foods being the most common. Peanut and tree nut allergy has recently been recognised as particularly dangerous.[11] Muscle relaxants may cause anaphylaxis while anaesthetic agents are important causes of anaphylactoid reactions.[3 12] β Blockers may increase the severity of an anaphylactic reaction and antagonise the response to epinephrine (adrenaline).[13] They may also increase the incidence of anaphylaxis, but the data are limited and inconsistent.[13 14] The complex nature of anaphylaxis has been described in reviews.[15–17]

2.2. The lack of any consistent clinical manifestation and a wide range of possible presentations may cause diagnostic difficulty. Clinical experience has shown that many patients with genuine anaphylaxis do not always receive appropriate medication. Rarely, patients have been given injections of epinephrine (adrenaline) inappropriately for vasovagal reactions or panic attacks. Diagnostic problems have arisen particularly in children. Guidelines for the management of shock from anaphylaxis must therefore take into account the inevitability of some diagnostic errors, with an emphasis on the need for safety of any recommended measures.

2.3. In each case, a full history and examination should be undertaken as soon as circumstances permit. The history of previous allergic reactions is important as well as that of the recent incident. Special attention should be paid to the condition of the skin, the pulse rate, the blood pressure, the upper airways, and auscultation of the chest. Peak flow should be measured where possible, and recorded.

2.4. No investigations can prove anaphylactic sensitivity to an allergen other than giving a challenge with the suspect agent. But an attempt should always be made retrospectively to assess the likelihood that a severe reaction was genuinely of an anaphylactic nature. While this is a matter for a specialist clinic rather than part of emergency management, a possible anaphylactic emergency provides an opportunity for specific blood tests. Some rely on measurements of specific IgE antibody: these are useful but must be interpreted carefully. Measurement of mast cell tryptase can also assist with retrospective diagnosis.[18] Both of these tests can be performed on 10 ml of clotted blood which hospitals can send to a reference laboratory. Ideally blood should be taken 45 to 60 minutes after the reaction, but in any case not later than six hours after the event. The use of blood tests is to be encouraged because future management can be helped by increased diagnostic certainty.

2.5. No reliable epidemiological data are available on the incidence of anaphylaxis partly because of the difficulty defining anaphylactic reactions, but one study found an incidence of 1:2300 attendees at an A&E department (equivalent to one episode per 15 000 of the population per annum) and fourfold more (approximately one in 3500 per annum) in the second part of the study the following year.[19] Even the mortality is unknown. Some allergens may cause short lived sensitivity. Second attacks are by no means invariable in response to penicillin[20] or contrast agents, and approximately half remain vulnerable after insect stings.[21] Peanuts on the other hand, may leave patients with a persistent predisposition to anaphylaxis after a first attack, but eventual resolution occurs in some.

3. Considerations in relation to treatment

3.1. Epinephrine (adrenaline) is generally agreed to be the most important drug for any severe anaphylactic reaction,[6 22] although there has been no standard recommendation for dose or route. As an α receptor agonist, it reverses peripheral vasodilation and reduces oedema. Its β receptor activity dilates the airways, increases the force of myocardial contraction, and suppresses histamine and leukotriene release. Epinephrine (adrenaline) works best when given early after the onset of the reaction[22] but it is not without risk, particularly when given intravenously.[9] Epinephrine (adrenaline) when given intramuscularly is very safe. Adverse effects are extremely rare, and the only case of myocardial infarction reported after its intramuscular administration had numerous risk factors for coronary disease.[23] Sometimes there has been uncertainty as to whether complications (for example myocardial ischaemia) have been due to the effects of the allergen itself or to epinephrine (adrenaline) given as treatment for it.

3.2. Epinephrine (adrenaline) may rarely fail to reverse the clinical manifestations of anaphylaxis, especially in late reactions or in patients treated with β blockers. Other measures then assume greater importance, particularly volume replacement.

3.3. Antihistamines (H_1 blockers) should be used routinely in the management of all anaphylactic reactions to help counter histamine mediated vasodilatation. They may be unhelpful for at least some anaphylactoid reactions that depend in part on other mediators but have the virtue of safety. Their use alone is, however, unlikely to be lifesaving.

3.4. Corticosteroids are considered as slow acting drugs and may take up to 4–6 hours to have an effect even if given intravenously. They may, however, help in the emergency treatment of an acute attack, and they also have a role in preventing or shortening protracted reactions. They form an essential part of management in recurrent idiopathic anaphylaxis[24 25] and are also of special importance to asthmatics especially those who have been treated recently with corticosteroids. Although some authors have expressed cautions about steroids,[25] and the contribution of individual drugs when several are given is difficult to prove, clinical experience shows that parenteral hydrocortisone is of value in anaphylaxis. The safest practice is to use corticosteroids for all victims likely to be suffering from a severe anaphylactic reaction.

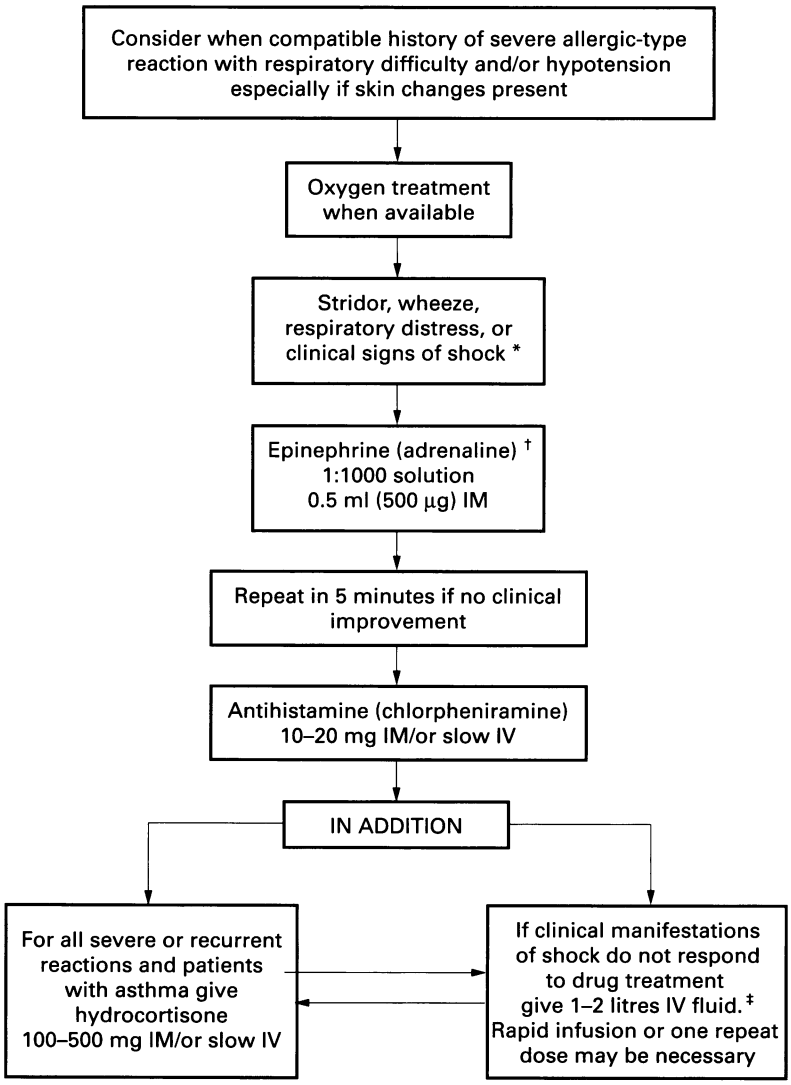

*Figure 1 Anaphylactic reactions for adults: treatment by first medical responder. *An inhaled β_2 agonist such as salbutamol may be used as an adjunctive measure if bronchospasm is severe and does not respond rapidly to other treatment. †If profound shock is judged* immediately *life threatening give cardiopulmonary resuscitation/advanced life support if necessary. Consider* slow *intravenous (IV) epinephrine (adrenaline) 1:10 000 solution. This is* hazardous *and is recommended only for an experienced practitioner who can also obtain IV access without delay. Note the different strength of epinephrine (adrenaline) that is required for IV use. ‡A crystalloid may be safer than a colloid.[26] IM = intramuscular.*

4. Recommendation for management

4.1. The recommendations are summarised in algorithms shown in fig 1 (for adults) and fig 2 (for children).

4.2. All victims should recline in a position of comfort. Lying flat with or without leg elevation may be helpful for hypotension but unhelpful for breathing difficulties. If available, oxygen should be administered at high flow rates (10–15 litres/min). Cardiopulmonary resuscitation must be performed if the need arises.

4.3. Epinephrine (adrenaline) should be administered intramuscularly to all patients with clinical signs of shock, airway swelling, or definite breathing difficulty,[6] and will be rapidly absorbed. Manifestations such as inspiratory stridor, wheeze, cyanosis, pronounced tachycardia, and decreased capillary filling alerts the physician to the likelihood of a severe reaction. For adults, a dose of 0.5 ml epinephrine (adrenaline) 1:1000 solution (500 µg) should be administered intramuscularly, and repeated after about five minutes in the absence of clinical improvement or if deterioration occurs after the initial treatment especially if consciousness becomes—or remains—impaired as a result of hypotension. In some cases several doses may be needed, particularly if improvement is transient.

The doses of epinephrine (adrenaline) recommended for children are as follows: >11 years, up to 500 µg intramuscularly (0.5 ml 1:1000 solution); 6–11 years, 250 µg intramuscularly (0.25 ml 1:1000 solution); 2–5 years, 125 µg intramuscularly (0.125 ml 1:1000 solution); and <2 years: 62.5 µg intramuscularly (by additional dilution 1:1000 solution).

As for adults, doses may be repeated after five minutes if necessary.

Devices for home use currently known as the EpiPen or Anapen and the EpiPen Jr or Anapen Junior that can inject 300 µg or 150 µg respectively are available. The drug may therefore have been administered by parents before medical help is available. The doses can be regarded as equivalent to the 250 µg and 125 µg more generally recommended. Other self administration devices include Min-I-Jet Adrenaline which contains 1 mg (1000 µg) of epinephrine (adrenaline). This allows incremental dose selection, but it should not be used in children because of the risk of overdose.

4.4. Intravenous epinephrine (adrenaline) in a dilution of at least 1:10 000 (*never* 1:1000) is hazardous and must be reserved for patients with profound shock that is immediately life threatening and for special indications, for example during anaesthesia. The injection should be given as slowly as seems reasonable while monitoring heart rate and the electrocardiogram. Electrocardiographic monitoring is mandatory if epinephrine (adrenaline) is given intravenously. Note also that a further 10-fold dilution to 1:100 000 epinephrine (adrenaline) allows finer titration of the dose and increases its safety by reducing the risk of unwanted adverse effects and dangerous complications.[9 25]

4.5. An antihistamine (chlorpheniramine) should be administered. Caution is needed to avoid drug induced hypotension: administer either by slow intravenous injection or by intramuscular injection. Its use may be helpful and is unlikely to be harmful. The dose for children and adults is determined by age as follows: >11 years , 10–20 mg intramuscularly; 6–11 years, 5–10 mg intramuscularly; and 1–5 years: 2.5–5 mg intramuscularly.

4.6. Hydrocortisone (as sodium succinate) should be administered after severe attacks to help avert late sequelae. This is of particular importance for asthmatics (who are at increased risk of severe or fatal anaphylaxis) if they have been treated with corticosteroids previously. The dose of hydrocortisone should be given by slow intravenous or intramuscular injection—care being taken to avoid inducing further hypotension. The dose for adults and children is determined by age as follows[4]: >11 years, 100–500 mg; 6–11 years, 100 mg; and 1–5 years, 50 mg.

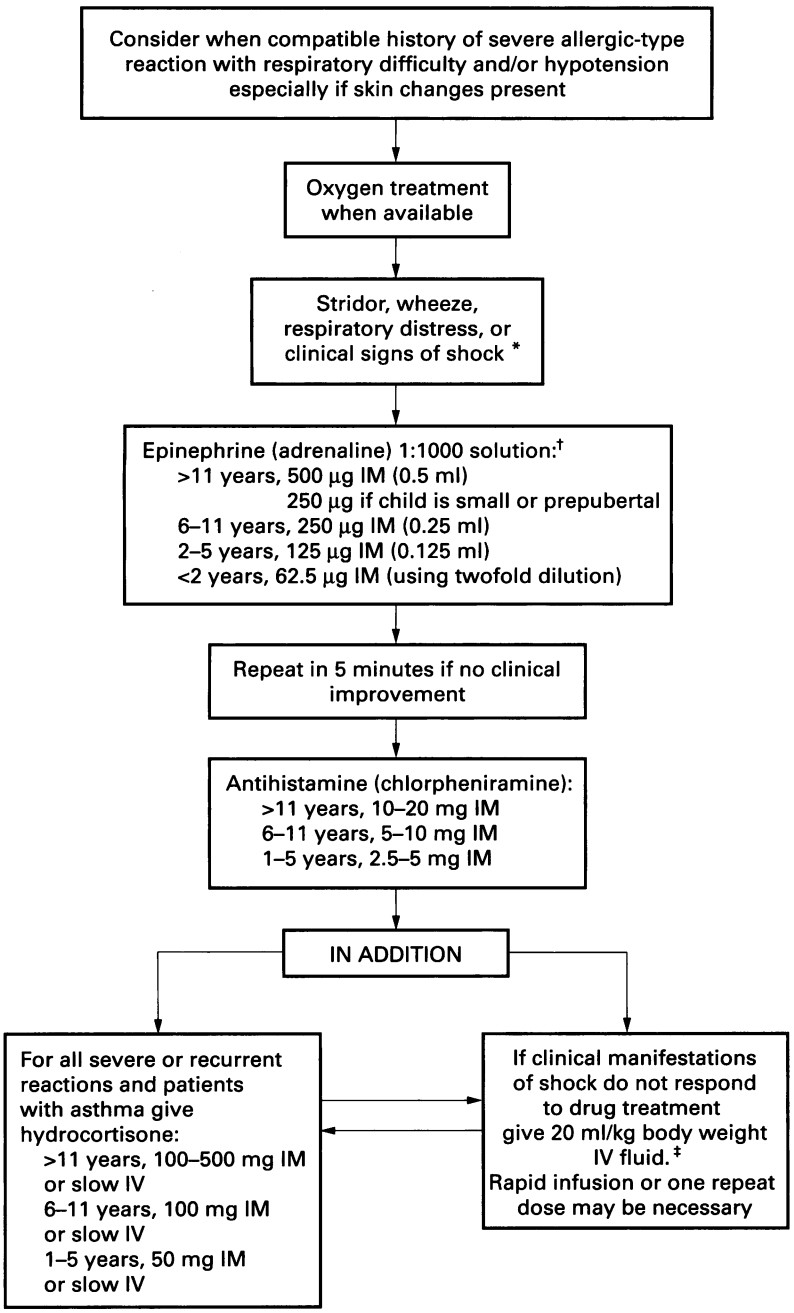

*Figure 2 Anaphylactic reactions for children: treatment by first medical responder. *An inhaled β_2 agonist such as salbutamol may be used as an adjunctive measure if bronchospasm is severe and does not respond rapidly to other treatment. †If profound shock is judged* immediately *life threatening give cardiopulmonary resuscitation/advanced life support if necessary. Consider* slow *intravenous (IV) epinephrine (adrenaline) 1:10 000 solution. This is* hazardous *and is recommended only for an experienced practitioner who can also obtain IV access without delay. Note the different strength of epinephrine (adrenaline) that is required for IV use. ‡A crystalloid may be safer than a colloid.[26] IM = intramuscular.*

4.7. If severe hypotension does not respond rapidly to drug treatment, fluid should be infused. A crystalloid may be safer than a colloid.[26] A rapid infusion of 1–2 litres may be needed. Children should receive 20 ml/kg rapidly, followed by another similar dose if there is no clinical response.

4.8. Patients with even moderately severe attacks should be warned of the possibility of an early recurrence of symptoms and in some circumstances should be kept under observation for 8–24 hours. This caution is particularly applicable to:

- Severe reactions with slow onset due to idiopathic anaphylaxis.
- Reactions in severe asthmatics or with a severe asthmatic component.
- Reactions with the possibility of continuing absorption of allergen.
- Patients with a previous history of biphasic reactions.

4.9. An inhaled β_2 agonist such as salbutamol is useful[27] as an adjunctive measure if bronchospasm is a major feature that does not respond rapidly to other treatment.

4.10. All sufferers from anaphylaxis should be advised of the benefits of wearing some device such as a bracelet that will inform bystanders at the time of any future attack. Precautions should be taken, where practicable, to avoid exposure to the suspected allergen.

4.11. Investigation and assessment at a specialist allergy clinic is recommended for all patients who have suffered a severe reaction.

5. Cautions

5.1. In patients who are taking tricyclic antidepressants or monoamine oxidase inhibitors the dose of epinephrine (adrenaline) should be much reduced because of an interaction which is potentially dangerous. Some fluorohydrocarbons used as refrigerants as well as cocaine sensitise[28] the heart to epinephrine (adrenaline) and are contraindications to its use.

5.2. The use of epinephrine (adrenaline) by the intravenous route in the special circumstances given in paragraph 4.4 should usually be reserved for medically qualified personnel who have experience of it, who know that it must be administered with extreme care, and who are aware of the hazards associated with its use.

5.3. The subcutaneous route for epinephrine (adrenaline), sometimes recommended for children on anecdotal evidence only, has no role in anaphylaxis because its absorption is appreciably slower.[29] Unnecessary delay in achieving adequate plasma concentrations is inappropriate when dealing with this emergency.

5.3. Warnings must be given, when appropriate, in relation to the two strengths of epinephrine (adrenaline) that are available for injection. For anaphylaxis, epinephrine (adrenaline) is used in a dilution of 1:1000 intramuscularly whereas a dilution of 1:10 000 is used intravenously principally for cardiac arrest (with the rare additional indications outlined in paragraphs 4.4 and 5.2).

5.4. All who treat anaphylaxis should be aware of the potential for confusion between anaphylaxis and a panic attack. Victims of previous anaphylaxis may be particularly prone to panic attacks if they think they have been re-exposed to the allergen that caused a previous problem. The sense of anxiety and breathlessness leading to hyperventilation are symptoms that resemble anaphylaxis in some ways. While there is no hypotension, pallor, wheeze, or urticarial rash/swelling, there may sometimes be an erythematous rash associated with anxiety which adds to the diagnostic difficulty.

A mild anaphylactic reaction that triggers panic causes particular diagnostic difficulty. Problems can also arise with vasovagal attacks after immunisation procedures, but the absence of rash, breathing difficulties, and swelling is a useful distinguishing feature as is the slow pulse of a vasovagal attack compared with the rapid pulse of a severe anaphylactic episode.

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