

## Anaphylaxis; recognition and management

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### INTRODUCTION

Anaphylaxis has been defined as 'a serious allergic reaction that is rapid in onset and may cause death'.<sup>1</sup> Rates of allergy and anaphylaxis in low-income countries appear to be low compared to high-income settings, although the incidence appears to be increasing worldwide, and anaphylaxis is becoming more common in children. A survey by the World Allergy Organisation (WAO) found that essential drugs used in the assessment and management of anaphylaxis, with the exception of adrenaline, are not universally available to healthcare providers, and clinical guidelines were in use in only 70% of surveyed nations.<sup>2</sup> This article will describe recognition and management of anaphylaxis in children, with reference to the UK Resuscitation Council Guidelines.

### EPIDEMIOLOGY

Accurate information on the prevalence of perioperative anaphylaxis in children is difficult to find. The condition is likely to be both under-diagnosed and under-reported. The incidence of all anaphylactic reactions in children and adolescents has been estimated as 10.5 in 100,000 or higher.<sup>3</sup> Perioperative anaphylaxis is thought to occur in around 1 in 10,000 anaesthetics in children. Asthma, family history, multiple surgeries, latex exposure and food allergy are all risk factors.<sup>4</sup> Mortality rates can be significant, with up to 10% of all reported anaesthesia-related reactions having fatal outcomes, although it is likely that less severe reactions go unreported.<sup>5</sup> Asthma is an important risk factor for both the occurrence and severity of reaction. Most fatal cases of anaphylaxis are seen in patients with asthma. Variations in diagnostic criteria and reporting rates raise doubts over the true incidence and outcomes in anaphylaxis treatment. Certainly, the incidence of allergy and the number of prescriptions for self-administered adrenaline (e.g. EpiPen) is increasing.<sup>6,7</sup>

### PATHOPHYSIOLOGY

Anaphylaxis is an IgE mediated type I hypersensitivity reaction, which occurs after exposure to a foreign molecule/antigen, and results in mast cell degranulation and histamine release. The clinical syndrome of anaphylaxis is much more complex

and comes from the cascading release of many vasoactive substances including histamine, tryptase, leukotrienes, cytokines, platelet activating factor and prostaglandins.

Initial antigen exposure results in the formation of specific IgE antibodies on mast cells. Second exposure allows binding of an antigen with IgE antibodies on the presensitised mast cells. The resulting antigen-antibody complex leads to the degranulation of mast cells and massive chemical mediator release, which results in the classical features of:

- Airway oedema
- Bronchoconstriction
- Increased vascular permeability
- Vasodilatation/hypotension

Other mechanisms are described, with 'non-IgE mediated' responses often being labelled as anaphylactoid reactions. These reactions do not require antigen pre-sensitization, and can involve direct mast cell/basophil interactions or complement activation, but still result in massive chemical mediator release. IgE and non-IgE reactions are clinically indistinguishable in their presenting features and do not differ in their management. The term 'anaphylactoid' has now largely been abandoned.

### COMMON ALLERGENS IN CHILDREN

#### Food

Food allergy is the commonest cause of anaphylaxis in children.<sup>8</sup> A 5-year retrospective study in Australia found 85% of paediatric admissions to the emergency department for an allergic reaction were following exposure to a food related allergen.<sup>9</sup> Peanuts, fish, milk, eggs and shellfish are most commonly identified triggers, although any food can be implicated. Worldwide variation in common food allergens is seen. Of particular interest to the anaesthetist is the association between egg allergy and propofol (discussed below). Some children outgrow their food allergy; hypersensitivity to allergens such as nuts and shellfish remain throughout life and are commonly associated with more severe reactions.<sup>10</sup>

### SUMMARY

Anaphylaxis is a life threatening condition

Prompt recognition and optimal management reduces adverse outcomes

Follow basic life support and anaphylaxis guidelines

Avoid further allergen exposure, administer oxygen and intravenous fluid and raise the patient's legs. These simple measures are useful in the management of anaphylaxis

Prompt administration of adrenaline is the most effective treatment in anaphylaxis

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## COMMON PERIOPERATIVE ALLERGENS

Common allergens encountered in the perioperative period include neuromuscular blocking agents, antibiotics and latex. These account for the majority of perioperative reactions. Radiological contrast, colloid based intravenous fluids, dye and chlorhexidine anti-septic solutions are all potential causative agents.

### Neuromuscular blocking agents

Neuromuscular blocking agent (NMBA)-related reactions account for more than 60% of anaphylactic reactions in the perioperative period. All NMBAs are potentially allergenic, and cross-reactivity amongst them is common.<sup>11</sup> Suxamethonium is more likely to cause anaphylaxis than any of the non-depolarising agents. The risk of anaphylaxis with different NMBA has been suggested to be as follows<sup>12</sup>:

- High risk: suxamethonium, rocuronium
- Intermediate risk: vecuronium, pancuronium
- Low risk: atracurium and its isomer, cisatracurium

Controversy surrounds the risk of anaphylactic reaction to rocuronium. Some studies claim it to be a high-risk allergen while others suggest that it is an intermediate risk agent and that increased reaction rates merely reflect increased frequency of use.<sup>13</sup> Non-immune histamine release is seen with atracurium and other benzylquinolonium compounds. Anaphylaxis during first time exposure to NMBAs is also common. Sensitisation is thought to be due to exposure to other compounds with a quaternary ammonium ion, found in common household products such as cosmetics, toothpaste, cough syrup and detergent.

### Antibiotics

Antibiotics account for up to 15% of all reactions occurring under anaesthesia and up to a third of all adverse drug reactions in the paediatric population. Rates seem to be increasing.<sup>12, 14</sup> Penicillins and cephalosporins are commonly used in perioperative care and are the most frequent cause of drug-related hypersensitivity reactions in children. The two agents have a shared  $\beta$ -lactam ring, and cross-reactivity rate of 10% between the two classes of drug is often quoted, but is now discounted by many experts.<sup>15</sup> It is prudent to avoid cross-exposure in those with previously documented anaphylaxis to either agent. Fortunately, anaphylactic reactions to other broad-spectrum antibiotics such as clindamycin and gentamicin are rare.

### Induction agents

Propofol is formulated in a lipid emulsion of soya oil, glycerol and egg phosphatide and is a commonly used induction agent. The egg-based constituent of propofol is a highly purified phosphatide, lecithin, whilst the allergens responsible for hypersensitivity reactions are the egg white proteins: ovoalbumin, ovotransferrin and ovomucoid. Propofol allergy is well documented, but a direct causal relationship between propofol and egg allergy has not been demonstrated. Manufacturers suggest a cautious approach is best in those with egg-related anaphylaxis, but propofol has been widely administered to egg allergic patients without incident.<sup>16</sup>

Thiopentone related anaphylaxis is recognised and becomes more

likely with repeated usage. Etomidate hypersensitivity is exceedingly rare. Ketamine use is increasing in hospital and pre-hospital settings and has been a common sole anaesthetic agent in the developing world for many years. Allergic reaction to ketamine is also rare. Thus both ketamine and etomidate provide a good anaesthetic option for patients with previous anaphylaxis from an unidentified agent.

### Other anaesthetic agents

Local anaesthetic allergy is rare. Reported reactions are more likely to be caused by accidental intravascular injection or reaction to preservative. Inhalational anaesthetic agents are the only agents in perioperative practice not to have associated immune-mediated allergic reactions.

### Latex

Latex hypersensitivity is increasingly reported, and as a result, many healthcare institutions have moved to a latex free clinical environment. Perioperative reaction rates are now falling in areas where this has been achieved. The following groups of children are at high risk for latex allergy:<sup>17</sup>

- Multiple operations
- Surgery in the neonatal period
- Atopic children
- Spina bifida
- Cerebral palsy.

There is also recognised cross reactivity between latex and food such as kiwi, banana and avocado.<sup>18</sup> Hospitals should have clear policies for latex allergic patients. Staff should have good knowledge of latex products and the latex-free alternatives. Medical staff should use latex free products where possible to avoid sensitisation of themselves and their patients.

### Chlorhexidine

Chlorhexidine is a chemical antiseptic used for skin preparation in surgery, and is also present in a number of different household products such mouth washes, antiseptic wipes, eye drops, and as a coating for medical devices such as urinary catheters, central lines and antiseptic dressings. Anaphylaxis to chlorhexidine has been reported in those with a known allergy to chlorhexidine, but where the presence of chlorhexidine was not recognised, for instance in a medical device.

## RECOGNITION OF ANAPHYLAXIS

Anaphylaxis is an acute, severe multisystem disorder. It varies in its presentation and severity and so a high index of suspicion is required. Clinical diagnosis is aided by history and clinical context. It is important to recognise that anaphylaxis can occur on the first exposure to a drug and within seconds of administration, particularly if given by the intravenous route. The vast majority of anaphylactic reactions occur around induction of anaesthesia. Symptoms and signs evolve within seconds or minutes of allergen exposure. The chief difficulty in managing perioperative anaphylaxis has often been to distinguish it from other serious adverse reactions during surgery and anaesthesia, shown in Table 1. Anaphylaxis must always

be considered in the event of perioperative airway obstruction, bronchospasm and hypotension.

Dermatological signs may be the first to appear and can include pruritis, urticaria, erythema, flushing or angioedema. Over 80% of paediatric reactions have skin manifestations. In the absence of skin manifestations the diagnosis can be overlooked in favour of an alternative event. Even when present, these classical signs may be missed as access for examination is limited by surgical drapes or impeded by poor theatre lighting. Signs may also be less obvious in pigmented skin.

Respiratory manifestations occur in over 90% of children and are the most worrying. Laryngeal swelling and bronchospasm may rapidly cause hypoxia. If the child is conscious, they may initially develop hoarseness or complain of a tingling throat. They can rapidly develop stridor and upper airway obstruction.

Cardiovascular effects such as hypotension are less common signs in children, only found in between a quarter and a third of cases. Tachycardia and hypotension indicate more severe reactions. Cardiovascular collapse is a late sign, which occurs peri-arrest. It is usually due to hypovolaemia due to both profound vasodilatation and increased capillary permeability leading to fluid leakage.

Gastrointestinal symptoms such as abdominal pain, nausea, vomiting and diarrhoea may also be seen in non-anaesthetised children.

A diagnostic tool has been proposed to improve identification of patients with anaphylaxis.<sup>1</sup> This is outlined in Table 2. It is proposed that following these criteria will identify over 90% of reactions, leading to early treatment and thus improved outcome.

## ALGORITHMS AND GUIDELINES

There are many published guidelines and management algorithms in the literature. Many nations adopt those produced by their own national societies and expert panels. In 2011, the World Allergy Organisation (WAO) Anaphylaxis guideline was created following a lack of a single global template for anaphylaxis management

**Table 1. Differential diagnosis of anaphylaxis**

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- Depth of anaesthesia (too deep i.e. hypotension)
  - Depth of anaesthesia (too light i.e. bronchospasm)
  - Inhaled foreign body
  - Acute asthma
  - Drug induced histamine release (opioids, atracurium etc)
  - Flushing syndrome (red man syndrome with vancomycin)
  - Pulmonary /air embolism
  - Vagal syncope
  - Hypovolaemic shock
  - Septic shock
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**Table 2. Clinical criteria for diagnosing anaphylaxis (adapted with permission from Sampson HA,<sup>1</sup> included with permission of Sampson HA & Elsevier)**

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**Anaphylaxis is highly likely when any ONE of the following three criteria is met:**

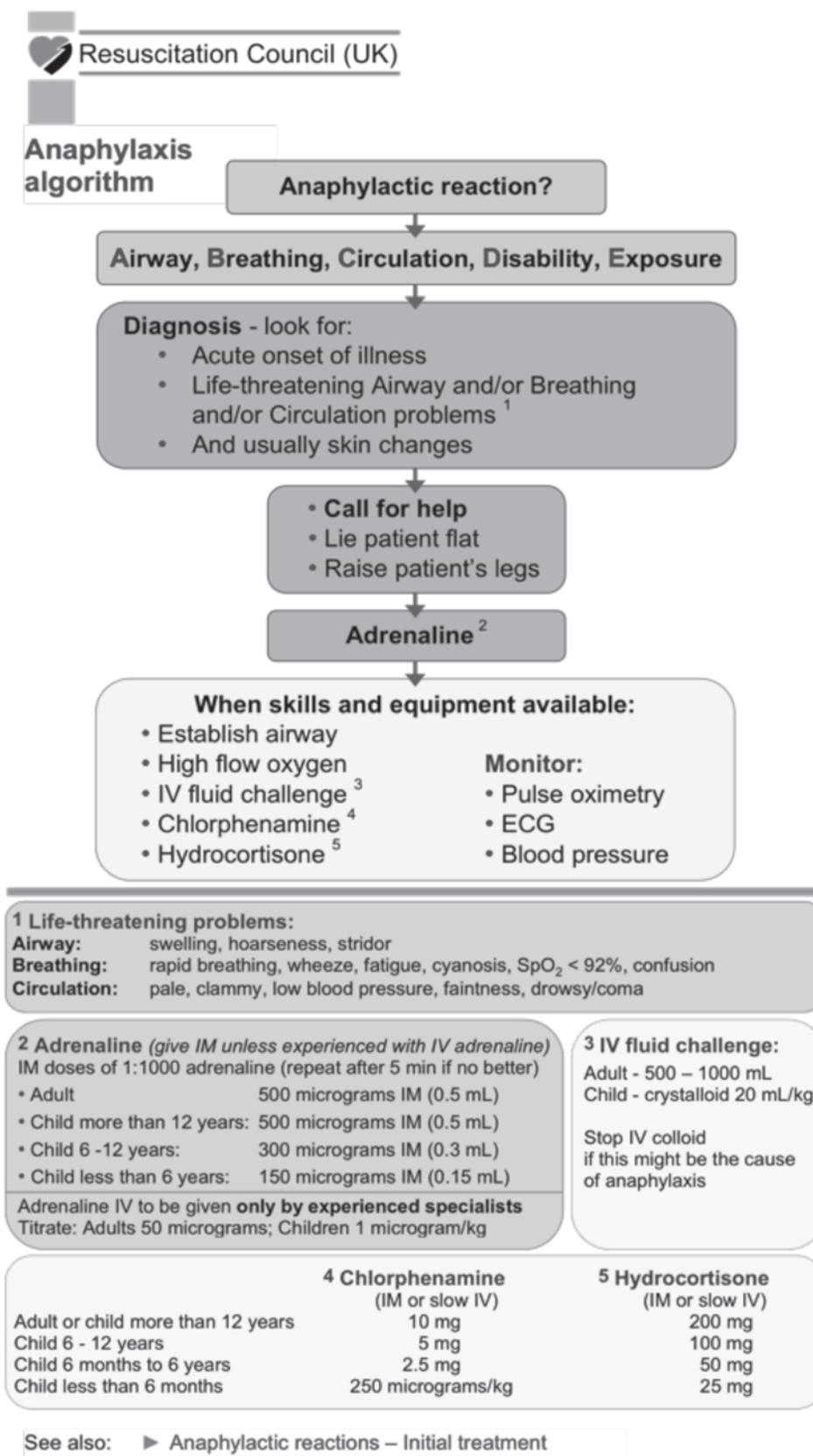
1. Acute onset of illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalised urticaria, itching or flushing, swollen lips-tongue-uvula) and at least ONE of the following:
    - Respiratory compromise (e.g. dyspnoea, wheeze, bronchospasm, stridor, reduced PEF, hypoxaemia)
    - Reduced blood pressure or associated symptoms of end organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
  2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    - Involvement of skin-mucosal tissue (e.g. generalised urticaria, itch-flush, swollen lips-tongue-uvula)
    - Respiratory compromise (e.g. dyspnoea, wheeze, bronchospasm, stridor, reduced PEF, hypoxaemia)
    - Reduced blood pressure or associated symptoms (e.g. hypotonia [collapse] syncope, incontinence)
    - Persistent gastrointestinal symptoms (e.g. abdominal pain, vomiting)
  3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours)
    - Infants/ children: low age - specific systolic blood pressure or greater than 30% decrease in systolic pressure
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and is an excellent resource.<sup>19</sup> The algorithm produced by the UK Resuscitation Council is well presented and concise, making it ideal for display in clinical areas.<sup>20</sup> This is shown in Figure 1. The choice of guideline in itself is not important. Of greater importance is that clinical staff are aware and have access to the guideline. They must also have opportunity to rehearse critical incident scenarios in the management of anaphylaxis.

## Immediate management

Use an ABCDE approach for assessment. This approach, combined with knowledge of presenting symptoms/signs and implementation of diagnostic criteria, aids a prompt diagnosis. Once anaphylaxis has been recognised, you should also follow an ABCDE approach in management, combined with the rapid implementation of basic measures of care as outlined below (see Figure1). For life threatening or severe reactions, you must do this together with the prompt administration of intramuscular adrenaline. A rapid decision is needed as to whether the surgical procedure is able to continue. It is recognised that many healthcare providers may have limited resources and limited access to drugs and monitoring equipment. It is important to recognise that many reactions can be treated successfully with implementation of simple measures and the early administration of adrenaline alone.

**FIGURE 1.** Treatment algorithm for anaphylaxis (with permission from Resuscitation Council UK<sup>20</sup>)



## Basic measures

Stop further administration of potential causative agents, administer supplementary oxygen and place the patient supine with legs raised. These are simple measures to implement. These can be instituted whilst extra help, equipment and adrenaline is obtained. If not already in place, obtain appropriate airway management and vascular access. Treat cardiac arrest using the standard resuscitation protocols.

## Early adrenaline

The early use of adrenaline is the most important factor in achieving a good outcome. Adrenaline acts on alpha and beta adrenoreceptors and increases systemic vascular resistance, coronary perfusion pressure, cardiac contractility whilst causing bronchodilatation and inhibiting inflammatory mediator release.

Adrenaline 1:1000, at a dose of 0.01ml.kg<sup>-1</sup> intramuscularly (IM), is the drug of choice and should be injected into the antero-lateral thigh. Some algorithms have simplified adrenaline dosing to include EpiPen use, with a range of 150micrograms (0.15ml 1:1000 adrenaline) to 500micrograms (0.5ml 1:1000 adrenaline) depending on age (see Figure 1). The IM route is preferred as it confers a better safety profile in the hands of most health professionals.

The intravenous (IV) route should be used with caution. Arrhythmias can be induced if adrenaline is given IV (VF/VT), so ECG monitoring is essential. The intraosseous (IO) route can also be used, using the same dose as the IV route. IO adrenaline should be followed by a saline flush. Ongoing clinical assessment is essential. If ineffective, the IM adrenaline can be repeated at 5-minute intervals with further doses indicated until clinical improvement is achieved.

## Airway

It is essential to maintain a clear airway and give oxygen. Early endotracheal intubation is advised if there is any suggestion of upper airway obstruction developing. A range of endotracheal tube sizes should be available to allow for any developing laryngeal oedema and intubation difficulty. Surgical cricothyroidotomy may be required if there is severe oedema or if mask ventilation is not possible.

## Breathing

Bronchospasm may be alleviated by IM adrenaline through its action on beta-2 adrenoreceptors. Treatment with a nebulised beta-2 agonist, such as salbutamol 2.5-5mg is useful, although this should not delay administration of adrenaline if it is required. Administration to an anaesthetised patient is described elsewhere (page 61 and reference 21).

## Circulation

Obtain vascular access, if not already secured, and begin fluid resuscitation. Change to the IO route if IV access is difficult. Give 20 ml.kg<sup>-1</sup> IV bolus of crystalloid (0.9% saline or balanced salt solutions) if the child is hypotensive. Give further fluids titrated to blood pressure, urine output and heart rate. Position the child head down if hypotension persists. This increases venous return, and is useful if IV access has yet to be achieved or if access to IV fluids is limited. If more than 40ml.kg<sup>-1</sup> IV fluid is required, consider inotropic support and invasive ventilation.

Manage fluid resistant hypotension with an adrenaline infusion rather than continuing IM injections or intermittent IV boluses of

adrenaline. Titrate IV adrenaline to effect, starting from 0.1mcg.kg<sup>-1</sup>.min<sup>-1</sup> (range 0.1-1.0mcg.kg<sup>-1</sup>.min<sup>-1</sup>) to achieve a normal blood pressure. Although adrenaline can be infused peripherally initially, it should be administered via a central venous catheter if possible. An adrenaline infusion can be made by adding 0.3mg.kg<sup>-1</sup> adrenaline to 50ml of 0.9% saline or 5% dextrose; an infusion of 1ml.hr<sup>-1</sup> = 0.1mcg.kg<sup>-1</sup>.min<sup>-1</sup>.

Dopamine, noradrenaline and phenylephrine are acceptable alternatives; noradrenaline has a powerful alpha-receptor agonist effect and should be considered if hypotension is unresponsive to adrenaline. Specialised equipment, monitoring and appropriately trained staff are required if a vasopressor infusion is used: the child should be looked after in an intensive care unit or high dependency unit if possible. Mortality can be high in this patient group, even in well-resourced clinical settings.

## Secondary management

Adrenaline is the drug treatment of choice for severe anaphylaxis. Antihistamines and steroids are useful adjuncts for the management of anaphylaxis, but their administration should not delay the use of adrenaline. There is concern that inclusion of agents other than adrenaline in guidelines risks their use as inappropriate first line agents.<sup>23</sup>

Histamine (H1) antagonists such as chlorpheniramine (2.5-10mg IM or slow IV, see Figure 1) are useful in minor allergic reactions but their speed of action means they are not appropriate as first line agents. Some guidelines omit them entirely as there is a lack of strong evidence for their use, their effect on outcomes, or in prevention of biphasic reactions.

Steroids, such as hydrocortisone (25-200mg IV depending on age, see figure 1), are often given IV in the treatment of anaphylaxis, but offer little benefit in the acute phase. Intravenous methylprednisolone (1mg.kg<sup>-1</sup>) has been used in less severe reactions, or where the oral route is still available, prednisolone 1mg.kg<sup>-1</sup> PO. Steroids are thought to reduce the risk of biphasic reactions. Biphasic reactions can occur in up to 20% of cases, with most occurring in the first 6 hours. A period of close observation is recommended in a well-staffed and monitored environment. They are more often seen in those patients who have delayed administration of adrenaline, or in those who require repeated doses, so a period of observation is required after stability is achieved.<sup>20</sup> A recently published systematic review showed that there is no good quality evidence to support the use of glucocorticoids in this setting, although use in patients with coincidental asthma is still advisable.<sup>23</sup>

## Investigations and follow-up

Correct identification of triggers for anaphylactic reaction in the perioperative period can be difficult as patients are exposed to multiple drugs and potential causative allergens in a brief period.

Specialist laboratory assays are required to confirm the diagnosis. At present serum tryptase is the only useful blood test commonly available in most modern laboratories.

The half-life of tryptase is approximately 2 hours; levels increase after mast cell activation, peaking rapidly and falling again. It is important that a sample of clotted blood is taken as soon as possible during

the reaction and a second sample 1 to 2 hours later to show the rise and fall in serum tryptase. A third sample is taken at 24 hours to determine baseline tryptase levels and allow interpretation of the earlier results. It is essential to record the times that samples are taken for analysis purposes. Samples that require transfer to another centre for analysis should be refrigerated at +4°C.

Patients who have experienced anaphylaxis under anaesthesia should undergo investigation prior to repeated exposure to anaesthesia. Make detailed records of all drugs, timings and events surrounding the reaction. Ideally, the child should undergo further investigation and immunological testing to identify the causative agent under the guidance of a specialist allergist. This may include skin testing utilising dilute concentrations of drugs. Skin pricks or intradermal injections can be used to look for signs of sensitisation. Specific immunological assays, looking for antigen-specific IgE, are available for a number of drugs. Tests are available for suxamethonium, latex and many commonly used antibiotics, but this is often only available in specialist laboratories. For many this is not achievable due to lack of resource and access to a certified allergist. The Association of Anaesthetists of Great Britain and Ireland (AAGBI) have produced guidelines for anaesthetists detailing the immediate investigation and more specialist tests that may be warranted.<sup>5</sup>

A strategy for any future anaesthesia is very important as patients are at increased risk of another reaction. Future operations should occur in a latex free environment where possible. Regional anaesthesia is ideal and avoidance of NMBAs and any drug previously used or those with recognised cross-reactivity is strongly recommended.

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