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## Key findings

- Eleven cases of Grade 3–4 anaphylaxis in children were reported to NAP6.
- The incidence of perioperative anaphylaxis in children was 2.7 per 100,000: approximately a quarter of the rate in adults.
- The commonest presentation was bronchospasm or high airway pressure.
- All cases of anaphylaxis were promptly recognised and a consultant anaesthetist was involved in the management of all the cases.
- Treatment was started in the majority of cases within five minutes of the first clinical features.
- There were no cardiac arrests associated with any of the paediatric cases.
- There were no paediatric deaths reported.
- After physical recovery sequelae included withdrawal, anger and anxiety about future treatments.
- Antibiotics and neuromuscular blocking agents (NMBAs) are used about half as frequently in paediatric anaesthesia as in adult practice and this may partially explain relative rates of anaphylaxis.
- In paediatric practice, when an NMBA was used this was atracurium in 57% of cases.
- Atracurium accounted for three of eleven episodes of anaphylaxis.
- There were no reports of teicoplanin-induced anaphylaxis, but its use is almost ten-fold lower than in adults.
- Allergy clinic testing was generally rather poor, being frequently incomplete and with advice given to patients and families being inadequate. Some patients were left at risk of future anaphylaxis as a result.

## What we already know

Perioperative anaphylaxis is uncommon in children, and reported incidences vary considerably.

In 1993, a prospective paediatric study estimated the incidence to be 1 in 7,741 anaesthetics (Murat 1993). Latex was the main cause in that series, and the incidence of anaphylaxis caused by NMBAs was very low at 1 in 81,275 cases.

A French series in 2011 reported 122 cases of IgE-mediated hypersensitivity of any severity in patients younger than 18 years over an eight-year period (Mertes 2011). Latex accounted for the largest proportion of cases (42%), followed by NMBAs (32%) and antibiotics (9%). In patients of all ages NMBAs were the most common trigger agents (58%), followed by latex (20%) and antibiotics (13%).

More recently, the APRICOT study in 2017 reported three cases of anaphylaxis in 30,874 paediatric anaesthetic cases, giving an incidence of approximately 1 in 10,000 (Habre 2017).

Clusters of cases of latex allergy and anaphylaxis have been reported (Gold 1991, Kelly 1994). Children with spina bifida having multiple operations throughout childhood were identified as being particularly at risk. The insidious onset from between 40–290 minutes from induction makes this a particularly challenging diagnosis to make. Increased awareness of latex allergy and the avoidance of powdered latex gloves (Newsom 1997, Vandenplas 2009) has reduced latex exposure in the hospital setting.

Latex and NMBAs have historically been prominent triggers, with antibiotics less commonly cited. This is likely to have been influenced both by differences in procedures commonly undergone by children and by anaesthetic technique.

## Numerical analysis

A child was defined as a person aged less than 16 years. For the purposes of analysis, patients were age-banded as age 0–5 or 6–15 years. Methods are described in detail in Chapter 5.

The Activity Survey (Chapter 8) included 2,053 paediatric cases, all involving general anaesthesia, with an estimated annual caseload of 402,753 cases.

Eleven cases of perioperative anaphylaxis in patients <16 years were reported, three of which were emergency procedures. With an estimated 403,000 paediatric cases performed per annum, the incidence of Grade 3-4 anaphylaxis is 2.73 per 100,000 paediatric anaesthetics (95% Confidence interval 1.36-4.89 per 100,000). The incidence in paediatric patients is therefore lower than in adult patients (255 cases in 2,723,314 patients: 9.36 per 100,000, 95% CI 8.42-10.59 per 100,000, Fisher  $p < 0.001$ ).

### Patients

Of the eleven reported cases, one was younger than 5 years and ten were 6–15 years.

All cases had general anaesthesia: anaesthesia was induced with propofol in eight cases, with thiopental in one, and with an inhalational induction in two. Anaesthesia was maintained with a total intravenous technique in one case. There was an equal number of male and female patients where this information was recorded. Four cases were ASA 1, three ASA 2 three ASA 3, and one ASA 4 (ASA 3–4 36% vs 9.2% in the Activity Survey, (Chapter 8)). Four of ten in whom body habitus was recorded were reported to be overweight. Two patients had well-controlled asthma. All events occurred during normal working hours, with the exception of one night-time case and one weekend case.

### Features

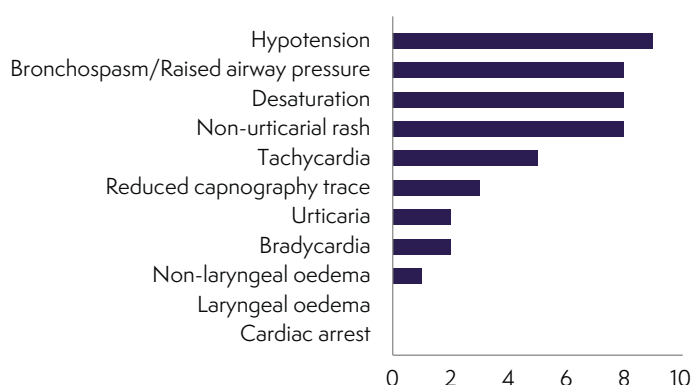
Six cases presented in the operating theatre, three in the anaesthetic room, one during transfer from the recovery room to the ward, and one in the radiology department. Seven cases presented after induction and before surgery.

A consultant anaesthetist was present from the start in eight cases, two were started by a career grade anaesthetist and one by an ST7 anaesthetist in training. A consultant anaesthetist was present during resuscitation in all cases.

The first clinical feature was bronchospasm and/or high airway pressures in seven (64%) cases, hypotension in two, tachycardia in one, and non-urticarial rash in the remaining case. Bronchospasm presented within five minutes, whereas hypotension was generally slower in onset. A decrease in end tidal carbon dioxide levels was noted in three cases, with an absent capnography trace in two of these at some point. Two cases exhibited non-laryngeal oedema, which was delayed in one case. There were no cardiac arrests and no fatalities in children.

Considering clinical features that appeared at any time during the anaphylactic episode, hypotension featured in nine cases, bronchospasm in eight, oxygen desaturation in eight, non-urticarial rash in eight, tachycardia in five, reduced capnograph trace in three, urticaria in two, bradycardia in two and non-laryngeal swelling in one (Figure 1). The lowest recorded systolic blood pressure was lower than 50 mmHg in four cases and the lowest recorded oxygen saturation was less than 85% in five cases. All cases were judged Grade 3 by the index anaesthetist, but on panel review, six were judged as Grade 4.

**Figure 1. Number of children exhibiting clinical features at any time during the anaphylactic episode**



### Resuscitation

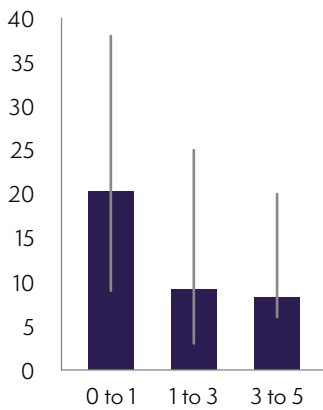
Specific treatment for anaphylaxis was started within five minutes in six of the seven cases where bronchospasm and/or high airway pressures were the presenting features. When hypotension or tachycardia were the presenting features, specific treatment tended to be started later. This finding was also seen in adults (Chapter 10, Clinical features). Anaphylaxis-specific treatment was delayed for more than 15 minutes in one case where flushing/non-urticarial rash was the presenting feature, and 11–15 minutes in one case where hypotension was the first feature.

All patients received intravenous (IV) adrenaline, with one exception where ephedrine and metaraminol alone were administered. Three patients received IV and intramuscular adrenaline and four patients received an infusion of adrenaline. The median number of doses of IV adrenaline was 2.5 (range 0–9). One patient received IV atropine and one required an infusion of noradrenaline to treat refractory hypotension. Two patients received inhaled salbutamol and one received magnesium sulphate for bronchospasm. No patients received phenylephrine, vasopressin, glucagon, glycopyrronium, aminophylline, or sugammadex for treating the reaction.

A child with hay fever presented for elective minor surgery. They received general anaesthesia which included atracurium and almost immediately became profoundly hypotensive, with bronchospasm and desaturation. Resuscitation required multiple boluses of adrenaline as well as chlorphenamine, salbutamol, magnesium, hydrocortisone and a substantial volume of fluid. The child was transferred to critical care for Level 3 care. Allergy clinic investigation confirmed atracurium-induced allergic anaphylaxis.

Eight patients received hydrocortisone, one patient received dexamethasone and one methylprednisolone. Two children did not receive a corticosteroid. Eight patients received chlorphenamine.

Ten patients received IV crystalloid, one IV gelatin, and one no IV fluid. The volume of IV crystalloid administered during the first five hours is shown in Figure 2.

**Figure 2. Volume of IV crystalloid (ml/kg) administered after the event (bar - median, line - range)**

AAGBI guidelines (Harper 2009) were used in 5 (45%) cases and Resuscitation Council UK guidelines (RCUK 2016) in one (9%) case. There was immediate access to a guideline in seven (63%) cases (all as a laminate) with none opting to access guidelines on a smartphone.

Surgery was abandoned in six cases and continued in five. Four of the abandoned cases were rescheduled. Three patients were admitted to critical care as a result of perioperative anaphylaxis, one of whom was transferred to a different hospital for Level 3 care. Hospital stay was extended as a result of anaphylaxis in seven cases (median 2 days, range 1–4). There were no further episodes of anaphylaxis during their stay.

The review panel judged the quality of clinical management in seven cases: good in four cases, good and poor in two cases and poor in a single case (where adrenaline was not administered). All cases were abandoned or proceeded with appropriately except for one case which, although there was a good outcome, the panel judged that it had been imprudent to proceed.

Following resuscitation and clinical recovery, psychological sequelae were reported including withdrawal, anger and anxiety about potential future anaesthesia.

### Referrals

Eight cases of eleven had at least one mast cell tryptase sample taken. All cases were referred to an allergy clinic. Eight patients were referred to the allergy clinic by the index anaesthetist, two by another anaesthetist and the final patient by someone other than an anaesthetist or surgeon.

Seven cases were reported through the trust's local critical incident reporting system, but only one case was recorded as being reported to the Medicines and Healthcare products Regulatory Agency (MHRA); two patients were issued with a hazard alert by the anaesthetist.

### Investigation

Four of eight mast cell tryptase series showed elevation or dynamic changes. The reaction was allergic anaphylaxis in three cases, non-allergic anaphylaxis in one case, anaphylaxis not-specified in two cases and uncertain in five. Culprit agents

were: atracurium in three cases and one each of; succinylcholine, aprotinin, cefuroxime, ibuprofen and cryoprecipitate. The trigger was not confidently-identified in the three remaining cases. The mechanism of the reaction to ibuprofen was judged to be non-allergic anaphylaxis.

### Identified allergens

The Allergen Survey (Chapter 9) identified that an NMBA was administered in 24.7% of paediatric cases and atracurium was chosen in 14% of cases (57% of paediatric NMBA uses). The next most frequently used NMBAs in children were rocuronium in 5.2% of children (21% of NMBA uses) and suxamethonium in 2.5% of cases (10% of NMBA uses).

In terms of exposure to the suspected trigger agents identified above, Table 2 shows the proportion of children receiving each across the Allergen Survey (Chapter 9).

**Table 2. Percentage of children in Allergen Survey cohort (n=2,053) exposed to agents identified as triggers in NAP6**

Agent	Exposures	Proportion of cases receiving (%)	No. of cases NAP6
Atracurium	282	14	3
Ibuprofen	358	17.4	1
Cefuroxime	70	3.4	1
Suxamethonium	52	2.5	1
Aprotinin	4	0.2	1
Cryoprecipitate	Unknown	–	1

A child received a non-steroidal analgesic orally as part of a premedication. The surgery was uneventful but the patient developed signs of anaphylaxis more than an hour later on the ward, most likely from the non-steroidal analgesic. The insidious onset, with no clear immediate culprit amongst many possibilities, makes this type of case difficult to recognise and thus promptly treat. The team did well to consider and correctly identify anaphylaxis in this case. Cases of latex allergy or chlorhexidine allergy may present similar challenges of slow and delayed onset.



### Allergy clinic investigation

The allergy clinic identified seven triggers and the panel eight. In one case the panel judged that the clinic had identified the wrong trigger agent. In seven of eight cases where this was assessed the clinic investigation had deviated from British Society for Allergy and Clinical Immunology (BSACI) guidelines. Problems included: failure to test for all possible triggers, failure to test for chlorhexidine or latex, failure to identify or provide advice on safe alternative drugs, excessively broad avoidance advice, and failure to establish a baseline mast cell tryptase level. In total, five of eight patients who were fully reviewed were judged by the panel to remain at risk of future anaphylaxis due to incomplete investigation or poor advice given to the patient or family.

Overall allergy clinic investigation, in eight cases fully reviewed as good in one, good and poor in three and poor in four.

An overweight child undergoing general anaesthesia received general anaesthesia including atracurium and developed profound bronchospasm, hypotension, desaturation and a rash two minutes after atracurium administration. A single dose of intravenous adrenaline and 1.5 L of crystalloid were sufficient for resuscitation. At allergy clinic investigation there was no mast cell tryptase rise. The drug suspected by the anaesthetist (atracurium) was not tested for but vecuronium intradermal skin testing was positive. Atracurium was not listed by the allergy clinic among the drugs to avoid despite it being judged the most likely agent by the anaesthetist. It was not clear whether testing for vecuronium (instead of atracurium) arose because of poor communication from the anaesthetist or misunderstanding at the allergy clinic.

### Discussion

The low incidence of paediatric perioperative anaphylaxis (about a quarter of that in adults) may have several causes. Latex exposure – previously a common trigger in children – has reduced significantly in recent years. It is also likely that children are both less sensitised prior to anaesthesia and less exposed to allergens during the perioperative period than adults. NAP6 indicates that NMBAs and antibiotics were used in 24.7% and 26.4% respectively of paediatric general anaesthetics, compared to 47% and 57% in adults (Allergen Survey, Chapter 9). When tracheal intubation is required in children, there is an increasing trend to achieve this without the use of NMBAs, which avoids exposure to a potent trigger for anaphylaxis (Simon 2002, Morton 2009, Sneyd 2010)

The Allergen Survey also showed that 14% of children received only sevoflurane, a low anaphylaxis-risk anaesthetic, for induction and maintenance of anaesthesia. Children are more likely than adults to receive general anaesthesia for non-surgical procedures and for diagnostic purposes. The APRICOT study, for example, found that 22% of their 30,874 cases had a general anaesthetic for an MRI procedure (Habre 2017).

Given the small number of cases reported in children, it is not possible to make confident conclusions concerning risk rates with different drugs. However, the number of cases of atracurium and suxamethonium appear to be proportionate to the number of exposures. Atracurium was the most-used NMBA in children (57%) by a large margin, followed by rocuronium and suxamethonium.

There was only one case of antibiotic-induced anaphylaxis in children (antibiotics are used less frequently in paediatric anaesthesia than in adults). Teicoplanin was a prominent trigger agent in the adult population (14% of all adult reactions and 19% of identified culprits in adults) but was not confirmed as a trigger in any paediatric case. Teicoplanin was administered in the perioperative period to 0.9% of children and 7.1% of adults – probably reflecting both lower rates of antibiotic use and lower rates of penicillin allergy in the younger age groups.

Allergic reaction to cryoprecipitate is rare and does not feature in recent Serious Hazards of Transfusion reports (SHOT 2016), although it is reported in the literature elsewhere (McVerry 1979).

There were no cases of latex-induced anaphylaxis, which may reflect its declining presence in the workplace (Newsom 1997) as well as an increased awareness of latex as a potential hazard following historical paediatric case clusters (Kelly 1994).

### Presenting features

Unlike in adult patients, bronchospasm and/or high airway pressures were the most common presenting features in children. Children are known to have more reactive airways with an incidence of laryngospasm 2–3 times that of adults (Gavel 2014). Anaphylaxis presenting in this manner was generally promptly recognised and treated.

Bradycardia was also more common in children compared with adults (18% vs 12.6%), although the degree of bradycardia was not reported. Strictly speaking, according to RCUK guidelines (Maconochie 2015), if there are no signs of life, and unless a pulse of greater than 60 beats per minute can be confidently palpated, cardiopulmonary resuscitation (CPR) should commence. Again, one must assume that each case was judged to have sufficient perfusion not to warrant CPR.



Cardiopulmonary resuscitation was not performed in any paediatric case. Four children had a recorded systolic blood pressure of less than 50 mmHg – the panel's threshold for designating a Grade 4 reaction in adults. However, unlike in adult patients, expert opinion did not favour setting a blood pressure below which CPR should be initiated.

### **Resuscitation**

All cases were resuscitated by an appropriate senior anaesthetist, and RCUK and/or AAGBI guidelines were generally well followed. All except one received adrenaline. Three received it intramuscularly, and in each of these cases they also received it intravenously. The AAGBI guideline (Harper 2009) advises intravenous administration, whereas the RCUK guideline (RCUK 2016) advises intramuscular except for 'experienced specialists'. The RCUK guidance is directed at a wider 'rescuer' population, many of whom will not have intravenous access, and it is clear that anaesthetists are relatively comfortable with the intravenous route here. However even paediatric anaesthetists encounter paediatric anaphylaxis only rarely: it is worthy of note that rehearsal of paediatric anaphylaxis drills in the simulator (Johnston 2017) or in a low-tech in-theatre setting (Kerton 2018) can improve adherence with guidelines and aid prompt management.

A single patient received ephedrine which is likely to be more readily available during routine anaesthesia. Ephedrine does have some beta-adrenoceptor agonist activity (Ma 2007) but is not included in any current guidelines. In general, there were omissions in case management in the administration of steroid and/or chlorphenamine as well as in the tryptase requests. Guidelines were not universally available or used in the paediatric cases, and no one opted to access them on a smartphone.

In one case gelofusine was used as the resuscitation fluid. Gelatin-containing fluids can themselves cause anaphylaxis – indeed, in one adult case in NAP6 the use of a gelatin-containing fluid to resuscitate from low blood pressure caused an anaphylactic reaction. There was also one adult death from a gelatin-containing fluid. There is no evidence to recommend gelatin-containing fluids over crystalloids, and the AAGBI guidelines specify use of crystalloids (Harper 2009), which NAP6 endorses.

### **Clinic investigation**

Investigation of paediatric allergy can be very difficult. In particular skin prick and intradermal testing may be difficult or impractical to perform. This was taken into account in assessing performance of allergy clinics. There were significant limitations to allergy-clinic investigation, which was frequently incomplete, and which frequently provided inadequate advice to patients/families. Some patients were left at risk of future anaphylaxis as a result. No clinic investigation was judged to have adequately explored all potential culprits. The majority were assessed as poor and only one of eight as good. This, together with the data presented in the Allergy clinic baseline survey (Chapter 13), provides evidence to support the contention that specialist paediatric investigation of perioperative anaphylaxis would be likely to benefit from improved network provision and the standardisation of approach.

## **Recommendations**

### **National**

- Consideration should be given at a national level to reconfiguring paediatric services for investigation of perioperative anaphylaxis in order to address a current shortfall in provision. In view of the small number of cases involved, collaboration with local hub services should be explored.

### **Institutional**

- Protocols and anaesthetic anaphylaxis treatment and investigation packs appropriate for children should be immediately available wherever paediatric anaesthesia is administered
- All anaesthetists administering anaesthesia to children should be trained in the management of paediatric anaphylaxis
- The preparation of drugs for management of paediatric anaphylaxis may be prone to error in the emergency setting. Paediatric anaesthetists should consider rehearsal of drills locally or in a simulation setting.

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