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**Anaesthesia, Surgery and Life-Threatening Allergic Reactions:
Management, outcomes and recommendations
in the 6th National Audit Project (NAP6) of the Royal
College of Anaesthetists.**

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For Peer Review

Anaesthesia, Surgery and Life-Threatening Allergic Reactions:**Management, outcomes and recommendations****in the 6th National Audit Project (NAP6) of the Royal College of Anaesthetists.**

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Running head: NAP6: Management, outcomes and recommendations

Abstract

The 6th National Audit Project on perioperative anaphylaxis collected and reviewed 266 reports of grade 3-5 anaphylaxis over one year from all National Health Service hospitals. This paper describes management, outcomes and subspecialty data: the full report is at <http://www.nationalauditprojects.org.uk/NAP6Report#pt>. Quality of management was assessed against published guidelines on management of anaphylaxis and cardiac arrest. All patients were resuscitated by anaesthetists of appropriate seniority. A management guideline was immediately available in 86% of cases. Immediate management was judged 'good' in 46% and 'poor' in 15% of cases. Recognition of and treatment of anaphylaxis were judged prompt in 97.3% and 83.4% of cases, respectively. Adrenaline was administered IV in 76% of cases, IM in 14% and both in 6%. No adrenaline was administered in 11%. The majority received other vasopressors (metaraminol, phenylephrine) before adrenaline. An IV infusion of adrenaline or noradrenaline was administered in 30.7% and 18.9% of cases, respectively. Two patients received vasopressin and one glucagon. Steroids and antihistamines were generally administered early. Careful examination of the role of antihistamines found no evidence of harm and could not exclude evidence of benefit. Sugammadex was given to treat anaphylaxis in 7.1% of cases. IV fluid administration was inadequate in 19% of cases. Cardiac arrests (15% of cases) were promptly treated; mean duration of cardiac compressions was 14 minutes, but cardiac compressions were performed in only 50% of patients with unrecordable blood pressure. The surgical procedure was postponed or abandoned in two thirds, and urgent surgery was delayed in 10% of all cases. More than half of patients required admission to critical care: 70% for level 3 care and most of these patients required catecholamine infusions after admission. Adverse sequelae were reported in a third of cases, including new anxiety, change in mood, impaired memory, impaired coordination, impaired mobility, symptoms of post-traumatic stress disorder, myocardial damage, heart failure and new renal impairment. Ten deaths (3.8%) were attributable to anaphylaxis, a per case mortality rate of 1 in 26.6 cases. Six per cent of survivors underwent uneventful surgery between the index event and the patient being seen in clinic.

Keywords: anaphylaxis; anaesthesia; outcomes; allergy; National Audit Project

Key findings

- All patients were resuscitated by an anaesthetist of appropriate grade and recognition of a critical event was prompt.
- Recognition of a critical event and of anaphylaxis was generally very prompt.
- There was delay in starting anaphylaxis-specific treatment in 25% cases, illustrating the potential difficulties inherent in recognition of perioperative anaphylaxis.
- Airway management was generally uncomplicated and without difficulty. A single front of neck airway was judged the only case of airway morbidity associated with anaphylaxis.
- When cardiac compressions were indicated there was delay starting them in more than half of cases.
- Vasopressin and glucagon were very rarely used.
- Sugammadex was administered in seven rocuronium-induced cases and no further pharmacological treatment was needed in four.
- Fluid administration was frequently judged to be insufficient and was inappropriate in 19%.
- The review panel judged management to be 'good' or 'good-and-poor-elements' in 85% of cases.
- Careful examination of the role of antihistamines found no evidence of harm and could not exclude evidence of benefit.
- More than half of patients required admission to critical care: 70% for level 3 care and most of these patients required catecholamine infusions after admission.
- Six per cent of survivors underwent surgery between the index event and the patient being seen in clinic. This was uneventful in every case.

1 Successful management of perioperative anaphylaxis is critically dependent on early recognition and
2 prompt initiation of specific treatment. Recognition that a critical event occurring during anaesthesia
3 is likely to be anaphylaxis may not be straightforward and the differential diagnosis is wide. The
4 onset may be immediate or delayed and the patient's medical history rarely provides any clues.
5 Rash, the classical sign of an allergic reaction, is present in approximately half of cases but may be
6 not visible under surgical drapes or delayed, especially in more severe cases. Hypotension is usually
7 the first sign of perioperative anaphylaxis.¹ A modest fall in blood pressure is a frequent
8 accompaniment of general anaesthesia² as well as during neuraxial anaesthesia, and vasopressor
9 drugs are often required during routine anaesthesia. It is only when the blood pressure does not
10 respond that less common causes of hypotension are sought, including ischaemic cardiac event,
11 cardiac arrhythmia, embolus, pneumothorax, covert haemorrhage and anaphylaxis.
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14 Similarly, bronchospasm, a not uncommon accompaniment of general anaesthesia, especially in
15 asthmatic patients is the first clinical feature in 18% of cases of perioperative anaphylaxis¹ and
16 anaphylaxis may not be the first differential diagnosis.
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19 It is generally agreed that adrenaline is the mainstay of management and is recommended in all
20 published guidelines.³⁻¹⁰ Having both alpha and beta agonist properties, adrenaline has compelling
21 theoretical advantages in the treatment of anaphylaxis by ameliorating many of the
22 pathophysiological processes (Figure 1)
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25 (Figure 1 near here)
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28 The beneficial actions of adrenaline include vasoconstriction which increases venous return,
29 reduced capillary permeability, increased cardiac contractility and cardiac output, bronchodilatation
30 and inhibition of mast cell and basophil mediator release. These benefits exceed the disadvantages
31 of vasodilatation in skeletal muscle and the potential risk of cardiac arrhythmias. Early
32 administration of adrenaline is associated with improved outcomes in out-of-hospital anaphylaxis.¹¹
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35 McLean-Tooke¹² concluded that adrenaline is not contra-indicated in patients with coronary artery
36 disease as continuing anaphylaxis likely further reduces coronary artery perfusion. However,
37 excessive dose or over-rapid IV administration can cause arrhythmias. Intravenous adrenaline is
38 more likely than intramuscular (IM) to result in cardiac complications in treatment of out-of-hospital
39 anaphylaxis in elderly patients¹³ but there is no published information regarding the perioperative
40 setting. The IV and IM routes are both recommended for the treatment of perioperative
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1 anaphylaxis; the IV route restricted to patients with continuous vital-signs monitoring, including
2 continuous ECG.⁹ The Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines
3 recommend an initial IV dose of 50mcg, repeated as necessary³. The Australian and New Zealand
4 Anaesthetic Allergy Group (ANZAAG) guidance for Grade 3 reactions recommend an initial IV dose of
5 100mcg followed, if necessary, by 100-200mcg every 1-2 minutes and a continuous infusion after 3
6 IV boluses.¹⁴

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12 Metaraminol is a second-line treatment in AAGBI guidelines³ but widely available in anaesthesia
13 settings. Several case reports describe survival after use of IV vasopressin 2-15 units (antidiuretic
14 hormone) in the management of intractable perioperative anaphylaxis,¹⁵⁻¹⁸ and this drug is included
15 in the ANZAAG guidelines.¹⁴ The benefit of adrenaline is likely reduced in the presence of beta
16 blockade. There are single case reports of glucagon use in beta-blocked patients leading to rapid
17 resolution of hypotension.^{19 20} European²¹ and ANZAAG¹⁴ guidelines recommend 1-2mg every 5
18 minutes until response, but it is not known how commonly glucagon and vasopressin are used to
19 treat perioperative anaphylaxis in UK practice.

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27 There are no published randomized controlled trials (RCTs) investigating the efficacy of
28 corticosteroids in the acute management of anaphylaxis. The rationale for their administration in
29 anaphylaxis appears to be down-regulation of the late-phase response by altering gene expression
30 and is an extrapolation of their effectiveness in the long-term management of allergic asthma²².
31 Hydrocortisone is recommended in published guidelines. Dexamethasone 7.5mg has an equivalent
32 glucocorticoid effect to hydrocortisone 200mg ([https://bnf.nice.org.uk/treatment-
33 summary/gluocorticoid-therapy.html](https://bnf.nice.org.uk/treatment-summary/gluocorticoid-therapy.html))

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40 The use of antihistamines in relatively minor out-of-hospital allergic reactions benefits urticaria and
41 pruritus. A Cochrane review of H1 anti-histamines for anaphylaxis was unable to make any
42 recommendations, as a result of lack of evidence.²³ This statement, together with side-effects of
43 promethazine, has resulted in some expert groups recommending anti-histamines should not be
44 administered.¹⁴ We aimed to establish whether administration of chlorphenamine, the most
45 commonly used antihistamine, influenced outcome.

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51 Several case reports may be considered supportive of administration of sugammadex during
52 rocuronium-induced anaphylaxis.^{24 25 26} The hypothesis that encapsulating the antigen may halt the
53 clinical features of anaphylaxis is unproven, despite in vitro and clinical studies.²⁷ Platt et al²⁸
54 reported sugammadex administration during immediate management of suspected rocuronium-
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1 induced anaphylaxis, in 13 cases, of which five were not rocuronium-induced. Clinical features
2 improved in six patients, including three without rocuronium-induced anaphylaxis: raising the
3 possibility that sugammadex may exert a vasopressor effect via a mechanism other than
4 encapsulating the antigen. We sought to determine to what extent sugammadex has been
5 incorporated in current management of perioperative anaphylaxis.
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11 Anaphylaxis is associated with an acute fall in actual and effective circulating blood volume as a
12 result of vasodilatation, increased vascular permeability and fluid sequestration, causing reduced
13 venous return and cardiac output (Figure 1) and there is consensus for rapid IV infusion of crystalloid
14 fluids. Recent guidelines emphasise the need to give rapid, repeated IV fluid challenges whilst
15 monitoring the response: ANZAAG guidelines¹⁴ recommend giving repeated boluses of 20ml/kg.
16 There is a paucity of information concerning IV fluid management in 'real life' management of
17 perioperative anaphylaxis but we support these recommendations.
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24 Little is known about the outcomes of perioperative anaphylaxis and we sought to establish the
25 influence of patient demographics, concomitant medication, co-morbidities and the quality of
26 resuscitation. Lastly, we aimed to characterise perioperative anaphylaxis in two important groups:
27 obstetric patients and children.
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31 **Methods**

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33 Methods are discussed in detail in an accompanying paper.²⁹ At panel review the quality of
34 immediate management was assessed and classified including factors such as timeliness, accuracy
35 and completeness. In doing this we also referred to current guidelines of the AAGBI and
36 Resuscitation Council of the United Kingdom (RCUK) on management of perioperative anaphylaxis³⁰
37 and cardiac arrest³¹ where relevant. The overall initial management was graded as 'good', 'good and
38 poor' or 'poor'.
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45 Although administration of adrenaline is the accepted standard for the immediate management of
46 perioperative anaphylaxis, the review panel recognised that anaphylaxis is an uncommon cause of
47 hypotension or bronchospasm during anaesthesia. It is therefore reasonable for anaesthetists to
48 start treatment with vasopressors and bronchodilators such as metaraminol, ephedrine and
49 salbutamol before instituting anaphylaxis-specific treatment, unless anaphylaxis was clinically-
50 obvious from the outset. Results here are based on a dataset of the 266 reviewed cases of confirmed
51 anaphylaxis. For some analyses a smaller dataset is used. The quality of delivered care is based on a
52 full panel review of 184 cases.²⁹
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Results

Resuscitation was performed by an anaesthetist of appropriate grade in all cases. The review panel considered that overall management was good in 46% cases; good and poor in 39%, and poor in 15% (Figure 2).

(Figure 2 near here)

Recognition of a critical incident and suspicion of anaphylaxis was within five minutes in 60% and 49% of cases, respectively. By 10 minutes, the corresponding figures were 78% and 74%.

Recognition of anaphylaxis and treatment were judged prompt in 97.3% and 83.4% of cases respectively (Figure 3).

(Figure 3 near here)

Specific treatment for anaphylaxis following the first clinical feature was started in <5 minutes in 64% of cases and <10 minutes in 83%. (Figure 4). Reported reasons for delay included confounding differential diagnoses such as pulmonary embolism, tension pneumothorax, gas embolism during abdominal endoscopy, primary cardiac events, surgical haemorrhage and neuraxial blockade associated hypotension.

(Figure 4 near here)

Pharmacological treatment was judged prompt and comprehensive in 83.9% and 98.8% of cases respectively. The vasoactive drugs administered are shown in Figure 5. Adrenaline was administered in 82.3% of cases; as IV boluses in 75.9% and was more likely to be given as severity increased. The median total dose was 0.2mg, 0.5mg and 4mg in severity-grades 3, 4 and 5 respectively. There was wide variation in the number of IV doses, ranging from one to thirty (median three doses).

Recognition of anaphylaxis was delayed in approximately one third of cases. The IM route was used in 14.1% of cases. Sixteen patients (6%) received both IV and IM adrenaline.

(Figure 5 near here)

1 An IV infusion of adrenaline was used in 30.7%, preceded by bolus doses in all except a single case.
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3 Adrenaline was judged not to have been given when indicated in 19.4% of cases; either not
4 administered (11%) or given late (8.4%).
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8 Metaraminol boluses were administered in 68.7% of patients of whom 73.6% also received
9 adrenaline. Phenylephrine was administered by IV bolus in 7.8% of cases and an infusion in 3.5%.
10 Most cases were obstetric. An IV infusion of noradrenaline was administered in 18.9% of cases. Only
11 two patients received vasopressin (antidiuretic hormone) and one received glucagon. In both cases
12 these drugs were given late in the resuscitation process and each was preceded by ephedrine,
13 metaraminol and adrenaline.
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19 Bradycardia was present in 13.2% of all cases, treated with glycopyrronium in 4.3% and atropine in
20 6.2%, a third in association with cardiac arrest. Tachycardia was rare, being treated once with
21 amiodarone, which was also used during the management of four cases of cardiac arrest.
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25 IV hydrocortisone was administered in 82.9% of cases (1-4 doses, median dose 200 mg) and
26 dexamethasone (administered after the event) in 16.1% of cases (median dose 6mg). Both drugs
27 were administered in 8.7% of cases. Two patients received methylprednisolone. Of note
28 dexamethasone was also given before the event in 19.2% of cases. Thirty-four patients (12.8%) did
29 not receive a steroid, including four fatalities.
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35 IV chlorphenamine was administered in 73.6% (median 10mg, 5-40mg) and IV ranitidine in 5.3% of
36 cases. Nine (3%) patients received both drugs (Table 1). We performed further analysis using a
37 logistic regression model to elucidate benefit/harm associated with chlorphenamine. Variables
38 included; initial resuscitation drugs, (adrenaline bolus, corticosteroids, metaraminol, ephedrine and
39 chlorphenamine); patient factors (age group intervals excluding children and over 75 yrs due to
40 small numbers) and ASA status (excluding ASA 5 due to small numbers). Outcome was level of harm
41 (no harm, low, moderate/severe harm or death) as defined in the accompanying paper.²⁹
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45 Chlorphenamine administration was associated with an increased probability of 'no harm' and
46 reduced probability of a 'moderate/severe' harm: odds ratios 2.20 (1.05-4.58) and 0.41 (0.18-0.91),
47 respectively. Chlorphenamine had no effect on the probability of 'low harm' or death. In order to
48 exclude chlorphenamine as a surrogate for good (as opposed to 'poor' or 'good and poor') clinical
49 management (noting that chlorphenamine administration was not used as a measure of quality of
50 care during panel discussions) we performed a Fischer exact test. This confirmed a significant
51 association between administration of chlorphenamine and care being judged as good (P<0.005).
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1 Thus, it was not possible to extricate any potential benefits of chlorphenamine from the presumed
2 benefits of good care.
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6 (Table 1 near here)
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8 9 *Sugammadex*

10 Sugammadex was administered during the first six hours following the event in nineteen (7.1%)
11 cases (median dose 300mg, range 150 – 1200mg). The suspected trigger agent was rocuronium in
12 nine cases, and the actual culprit in seven: Sugammadex did not terminate the reaction in three and
13 further vasopressors and bronchodilators were needed.
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18 19 *IV fluids*

20 IV fluid management was judged inappropriate, almost always as insufficient, in 19% of cases.
21 Ninety eight percent patients received IV crystalloids in the first hour after the reaction, 86% during
22 the subsequent 2 hours and 69% during the next 2 hours. The median volume administered during
23 each time period was 1L (range 0.1L to 6.0L); 1L (range 0.1 to 3.0L) and 0.5L (range 0.1L to 4.5L). The
24 only IV colloids administered during the first hour after the anaphylactic event were succinylated
25 gelatin products in 25 (9%) cases.
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30 31 *Airway*

32 Airway management was judged appropriate in 98.8% of cases (Figure 5); in 1.2% of cases it was
33 judged that tracheal intubation should have been performed. Airway swelling, airway difficulty and
34 complications were uncommon. Tracheal intubation was performed as part of resuscitation in 13.2%
35 of patients; in the majority this involved removal of a supraglottic airway and replacement by a
36 tracheal tube. In three (1.1%) cases the tracheal tube was removed and replaced as a result of
37 suspected oesophageal intubation as part of the differential diagnosis. A front of neck airway was
38 instituted in one patient who developed laryngeal oedema and stridor, but other details of this case
39 were scarce. In seven patients it was necessary to re-intubate the trachea after completion of the
40 primary surgical procedure; in no case was re-intubation difficult due to laryngeal swelling.
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49 *Guideline access*

50 A management guideline was immediately accessible in 86% of cases, mainly as a laminated sheet:
51 15% of immediately-available guidelines were contained in designated 'anaphylaxis-packs'. A
52 smartphone was not used to access guidelines in any cases.
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1 The AAGBI guideline was most commonly used (60.5% of cases). The RCUK guidelines on
2 management of anaphylaxis and on life support were used in 5.3% and 6.4% of cases, respectively
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4 Local or Trust guidelines accounted for 3.8% of cases. In 44 (18.6%) cases no specific guideline was
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6 used. The reporting anaesthetist judged that the theatre team contributed effectively to
7
8 management in 87% of cases and was partially-effective in a further 7.7%.

11 *Fatal cases*

12 Immediate management was prompt in all but one of the ten cases and all resuscitations followed a
13 guideline and were managed by a consultant. Resuscitation from cardiac arrest was prompt,
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15 prolonged and extensive. CPR took place for a median 39 mins and in all cases for >25 minutes.
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17 Resuscitation included Extra-Corporeal Membrane Oxygenation in one case and immediate cardiac
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19 catheterization to explore or manage an acute coronary syndrome in two cases. Adrenaline was
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21 administered IV in all cases including an infusion in five cases. A median of 5 doses (5mg) adrenaline
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23 was administered (range 2-13mg). No patient received IM or IO adrenaline. Ephedrine, metaraminol,
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25 glycopyrronium and atropine were used early in resuscitation. Five patients received noradrenaline,
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27 one vasopressin and one glucagon, administered at 65 minutes after the reaction. Approximately
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29 half of cases received chlorphenamine and hydrocortisone. Sugammadex was not used. Fluid
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31 resuscitation volumes were relatively modest 1-4.5L (median 1.5L) in the first hour and in the first
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33 five hours 1-9.5L, (median 1.5L); only one patient received >4L in total. Five patients did not survive
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35 initial resuscitation, while five did, of whom one died soon after. Of the four remaining patients, all
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37 were admitted to ICU and all survived at least one week, but all deaths occurred in <30 days. Four
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39 patients developed multiple organ failure.

40 A mast cell tryptase sample was sent in all cases and a dynamic change was identifiable in five cases.
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42 Mast cell tryptase results are discussed elsewhere.³² There were no episodes of recrudescence of
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44 anaphylaxis. Good elements of care were: appropriately senior resuscitators (10/10); prompt
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46 recognition of the critical event (9/10); prompt recognition of anaphylaxis (9/10); appropriate airway
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48 management (10/10) and prompt initiation of cardiac compressions (9/10, 1 uncertain). Inadequate
49
50 fluid administration was a recurrent theme.

51 *Cardiac arrests*

52 Cardiac arrest was reported in 40 (15%) patients – in 27% of these within 5 minutes of trigger
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54 administration, though others were preceded by prolonged hypotension. All these patients received
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56 cardiac compressions; the mean duration was 14 minutes (range 1 to 60 minutes). It was generally
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58 prolonged in those who died but brief in those who survived: median 8 minutes, IQR 2-8 minutes in
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1 survivors. The event was generally promptly recognised and treated. Delay in managing anaphylaxis
2 was due to slow diagnosis or uncertain diagnosis (one case each) and loss of IV access (one case).
3 Quality of resuscitation is summarized in table 2. On average five doses of IV adrenaline were
4 administered (mean 5mg, range 0-12 mg). Half of survivors received an adrenaline infusion after
5 initial resuscitation. Second line drugs included noradrenaline to 15 patients, vasopressin to two,
6 glucagon to one, intralipid to one and sugammadex to one. Chlorphenamine and steroid were given
7 to approximately 75% of patients during resuscitation. Fluid volumes were modest; median volume
8 1.75L (range 0-4.5L) during the first hour and 3.25L (range 0-9.5L) during the first 5 hours. Panel
9 judgements on quality of care are included in Table 2.
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16 *Profound hypotension*

17 CPR was initiated in 28 (50%) of those with an unrecordable blood pressure, in five (9%) with systolic
18 blood pressure <50mmHg and in two (3.8%) with lowest blood pressure of 50-59mmHg. The panel,
19 after taking external expert advice, used a threshold of <50mmHg as the point at which CPR was
20 indicated in adult patients. Deakin et al.³³ demonstrated using invasive BP measurement, which
21 overestimates systolic blood pressure compared with non-invasive methods,³⁴ that systolic blood
22 pressure <50mmHg was associated with pulselessness with a 90% positive predictive value. So,
23 when the lowest blood pressure was <50mmHg and CPR was not started, this was deemed to be
24 suboptimal care. There were 114 (42.9%) such cases. Overall prompt CPR (when the blood pressure
25 was <50mmHg or unrecordable) was reported in 23% of cases. Pharmacological treatment was
26 judged inadequate in 21% and adrenaline administration was judged inadequate in 17%. Fluid
27 administration was deemed inadequate in 24%. Patient characteristics, outcomes and quality of care
28 are summarised in Table 2.
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39 (Table 2 near here)
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42 *Discontinuation of the trigger agent*

43 The suspected trigger agent was discontinued in twenty-two of the twenty-six cases where this
44 would have been possible. Agents that were not discontinued comprised IV gelatin, a chlorhexidine-
45 coated central venous line, a second dose of co-amoxiclav and a second dose of protamine. The
46 actual trigger agent was not discontinued in four of the fourteen cases where this would have been
47 possible, comprising IV gelatin, administration of a second dose of protamine and two instances of
48 retained chlorhexidine-coated central venous line.
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55 *Continuation of surgery*

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1 In approximately one third of cases the procedure was unchanged but, in over half the cases, the
2 intended surgery was not started. In a small proportion of cases the procedure was modified or
3 abandoned. Median severity was Grade 4 in the abandoned cases and Grade 3 in continued cases. In
4 two cases cardiopulmonary bypass was used as part of the resuscitation process.
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8 9 *Unplanned hospital stay and critical care admission*

10 The median unplanned hospital length of stay (LOS) as a result of anaphylaxis was one day, but there
11 was a wide range: 18.4% >2 days; 11.7% >3 days; 8.3% >4 days and 6.6% > 5 days. The longest
12 unplanned LOS was 150 days.
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17 One hundred and forty-four (54%) patients were transferred to critical care: the majority (70%) for
18 level 3 care. The median duration of level 3 care was one day (range 1-9 days), and of level 2 care
19 was one day (range 1-25 days). Six patients required level 3 care and five level 2 care for >2 days. No
20 patient required an increase in their level of care after admission to critical care. While in Critical
21 care, 63% required inotropic support and 5.1% bronchodilator therapy. Of the patients requiring
22 inotrope infusions in ICU/HDU, 34.5% received adrenaline, 21.4% both adrenaline and
23 noradrenaline, 15.5% noradrenaline, and the remainder other inotropic drugs.
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30 *Outcomes (cases of all severity)*

31 The severity of physical harm (see accompanying paper for definitions)²⁹ identified by the review
32 panel was none in 8%; low in 51%; moderate in 34%; severe in 4% and uncertain in 3%. Concomitant
33 beta-adrenergic blocking drugs were associated with greater severity: 60% of fatalities were taking a
34 beta blocker compared with 18% of all cases.
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39 We asked about physical and psychological sequelae after the event. Data was recorded poorly, so
40 any estimates must be judged as minima. More complications were recorded in the section of the
41 case report form completed before allergy clinical referral (97 sequelae: 69 mild, 21 moderate and
42 seven severe) than in that completed after the allergy clinic visit (74 sequelae 41 mild, 27 moderate
43 and six severe). Anxiety about future anaesthetics was the most commonly reported consequence,
44 accounting for more than half of longer term consequences, in three cases this extended to
45 symptoms of post-traumatic stress disorder. Ten patients reported problems with mood, memory or
46 co-ordination. There were twelve reports of myocardial infarction, a cerebrovascular event, acute
47 kidney injury or new shortness of breath.
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1 As a result of anaphylaxis, cancer surgery was delayed in 19 (7.1%) cases, urgent non-cancer surgery
2 in eight (3%), non-urgent surgery in 76 (28.6%) and other treatment was delayed in nine (3.4%)
3 cases. Total hospital stay was extended as a result of anaphylaxis in 75% of patients (median 1 day,
4 range 0-150 days).
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8 9 *Obstetric cases*

10 We identified eight obstetric cases in NAP6, all of which were Grade 3. The NAP6 Activity Survey³⁵
11 estimated 233 886 obstetric anaesthetics are administered per annum in the UK, giving an incidence
12 of severe obstetric perioperative anaphylaxis of 3.4 per 100 000. Six patients received neuraxial
13 anaesthesia and two general anaesthesia. Six cases occurred in association with anaesthesia for
14 caesarean section, most commonly after delivery of the baby. There were no cardiac arrests,
15 maternal or neonatal deaths. All patients developed hypotension, in some cases profound. In four of
16 six patients who developed severe anaphylaxis during neuraxial anaesthesia, a common feature was
17 the patient complaining of feeling unwell before the onset of hypotension or other clinical signs.
18 Hypotension commonly developed at a time when spinal-induced hypotension would have been
19 anticipated to have settled.
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28 A consultant anaesthetist was involved in the management of all the cases. In five cases there was
29 prompt treatment but, in three cases, there was a delay in diagnosis and treatment was delayed.
30 Resuscitation drugs differed from those used in non-obstetric cases: six patients received
31 phenylephrine, four adrenaline, and three both drugs. Fluid management was appropriate in all
32 cases. An anaphylaxis pack was used to assist management in only two cases. In four cases overall
33 care was judged as good and in one good and poor. Identified culprits were chlorhexidine,
34 atracurium, suxamethonium and ondansetron and in four cases no trigger was identified. Maternal
35 and neonatal outcomes were good in all cases. None of the women who experienced anaphylaxis
36 during neuraxial anaesthesia required tracheal intubation. In three women hospital discharge was
37 delayed and one patient reported anxiety about future anaesthesia.
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47 *Paediatric cases*

48 Eleven cases of perioperative anaphylaxis in patients <16yrs were reported, three of which were
49 emergency procedures. With an estimated 403,000 cases performed per annum, the incidence of
50 grade 3-4 anaphylaxis is 2.73 per 100,000 paediatric anaesthetics. Two patients had well-controlled
51 asthma. Six cases presented in the operating theatre, three in the anaesthetic room, one during
52 transfer from the recovery room to the ward and one in the radiology department. Seven cases
53 presented after induction and before surgery. The first clinical feature was bronchospasm and/or
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1 high airway pressures in seven (64%) cases with hypotension being the presenting feature in two,
2 tachycardia in one and non-urticarial rash in the remaining case. Bronchospasm presented within
3 five minutes, whereas hypotension was generally slower in onset. A decrease in end tidal carbon
4 dioxide levels was noted in three cases with an absent capnography trace in two of these at some
5 point. Two cases exhibited non-laryngeal oedema, which was delayed in one case. There were no
6 fatalities in children. The clinical features present at any time during the reaction are shown in Figure
7 6. All cases were judged grade 3 by the index anaesthetist: on panel review, six were judged as grade
8 4.

14 (Figure 6 near here)

18 The review panel judged that clinical management was good in four cases, good and poor in two
19 cases and was poor in a single case (where adrenaline was not administered). A consultant was
20 present during resuscitation in all cases. AAGBI guidelines were used in five, and RCUK guidelines in
21 one. In seven cases, there was immediate access to a guideline as a laminated document.

26 Specific treatment for anaphylaxis was started within five minutes in six of the seven cases where
27 bronchospasm and/or high airway pressures were the presenting features. When hypotension or
28 tachycardia were the presenting features, specific treatment tended to be started later. Adrenaline
29 was administered in ten cases, either IV or IM and an infusion was required in four cases. Other
30 vasopressors were used in small numbers of cases. Eight patients received chlorphenamine and
31 eight hydrocortisone. Two patients did not receive a corticosteroid. One patient received atropine.
32 No patients received phenylephrine, vasopressin, glucagon, glycopyrrolate, sugammadex or
33 magnesium sulphate. Ten patients received IV crystalloid, one IV gelatin, and one no IV fluid. The
34 volume of IV crystalloid administered during the first five hours is shown in Figure 7.

41 (Figure 7 near here)

45 In six cases the procedure was abandoned and four of these were rescheduled, in all cases except
46 one judged to be appropriate. Three patients were transferred to HDU/ICU as a result of the event,
47 including one to a different hospital. Following resuscitation and clinical recovery, one child was
48 reported as being withdrawn and angry and one child reported anxiety about potential further
49 anaesthesia. Seven cases were reported through the Trust's local critical incident reporting system
50 but only one case was recorded as being reported to the Medicines and Healthcare products
51 Regulatory Authority (MHRA) and two patients were issued with a hazard alert by the anaesthetist.

1 The anaesthetist suspected the causal agent was atracurium in three cases, with single cases of each
2 of the following; lidocaine, suxamethonium, piperacillin/tazobactam, teicoplanin, aprotinin,
3 cefuroxime, ibuprofen and cryoprecipitate. The review panel identified atracurium in three cases
4 and one each of the following; suxamethonium, aprotinin, cefuroxime, ibuprofen and
5 cryoprecipitate. The trigger agent could not be confidently-identified in the remaining cases. The
6 mechanism of the reaction to ibuprofen was judged to be non-allergic anaphylaxis.
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16 *Concordance*

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18 Concordance between triggers suspected by the anaesthetist and identified by the panel is discussed
19 in greater detail in a paper exploring investigation of the NAP6 cohort.³²
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23 Amongst cases with an identified trigger, overall concordance was 75% between the anaesthetist
24 and the panel. However, anaesthetists were likely to over-identify NMBAAs as triggers and to fail to
25 recognise chlorhexidine -induced anaphylaxis.
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29 *Communication*

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31 The panel judged that there were considerable shortcomings in communication between the
32 anaesthetist and the patient following the event. Information given to the patient by the
33 anaesthetist about which drugs or other substances they should avoid before attending an allergy
34 clinic for investigation was oral in 26.6 %, written in 19.8 %, both in 39.2% and none in 14%. In 222
35 cases where this information was available, 29% were issued with a hazard warning card; 39% of
36 these by the index anaesthetist.
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44 **Discussion.**

45 *Obstetric cases*

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47 Anaphylaxis during pregnancy is very uncommon ($\approx 1.6-3.0$ per 100,000 maternities^{36 37 38}). The
48 predominant use of neuraxial techniques likely limits exposure to many of the trigger agents
49 associated with general anaesthesia. Previous studies have highlighted latex and suxamethonium as
50 culprits³⁹. The incidence during caesarean was reported as 2.1 per 100,000 with antibiotics
51 important triggers. Perioperative obstetric anaphylaxis is complicated by the need to ensure the
52 safety of both patients and of the potential impact of both maternal hypotension and adrenaline
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1 administered to the mother on uteroplacental haemodynamics. The literature is generally reassuring
2 with good maternal and neonatal outcomes, but it is notable that maternal outcomes may be less
3 good when anaphylaxis occurs during caesarean delivery and neonatal outcomes worse when
4 maternal anaphylaxis develops during labour. The placenta is metabolically active and metabolises
5 histamine and other endogenous mediators,⁴⁰ potentially protecting the fetus from mediator-
6 related morbidity.
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12 The overlapping clinical features of anaphylaxis with other acute obstetric morbidities can hinder the
13 diagnosis of anaphylaxis, particularly during the onset or in the presence of neuraxial block. In the
14 absence of vasopressor-prophylaxis, hypotension occurs in two thirds of patients during spinal
15 anaesthesia. However other conditions such as aortacaval compression, haemorrhage, and much
16 more rarely, amniotic fluid or thromboembolic embolus can lead to severe hypotension.
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22 Phenylephrine was the most commonly-used vasopressor. Phenylephrine infusions are
23 recommended to prevent and treat hypotension associated with spinal anaesthesia⁴¹ and are
24 therefore immediately available and familiar to the anaesthetist working on labour ward. In the
25 presence of spinal anaesthesia, hypotension from other causes can be exacerbated and require large
26 doses of vasopressor to treat effectively. Adrenaline is recommended for the management of
27 anaphylaxis and although there might be theoretical concerns about its potential effect on the
28 uteroplacental circulation, particularly when used to treat anaphylaxis before delivery, this effect is
29 short lived⁴² and any transient effect on uteroplacental circulation is likely to be less than the impact
30 of maternal hypotension. Thus, adrenaline should be first-line treatment in obstetric patients.
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38 *Paediatric cases*

39 Perioperative anaphylaxis is uncommon in children and reported incidences vary considerably.^{43 44 45}
40 Latex and NMBAs have historically been prominent triggers and antibiotics less commonly cited. This
41 likely is influenced by differences in both procedures commonly undergone by children and by
42 anaesthetic technique.
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47 The low incidence of paediatric perioperative anaphylaxis may have several causes. Latex exposure
48 has reduced significantly in recent years. It is also likely that children are both less sensitised and less
49 exposed than adults to allergens during the perioperative period. NAP6 indicates that NMBAs and
50 antibiotics were used in 24.7% and 26.4% of paediatric general anaesthetics, compared to 47% and
51 57% in adults³⁵ The Allergen survey also³⁵ showed that 14% of children received only sevoflurane
52 for induction and maintenance; a low anaphylaxis-risk anaesthetic.
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3 Unlike in adult patients, bronchospasm and or high airway pressures was the most common
4 presenting feature in children. Bradycardia was also more common in children compared with adults
5 (18% vs 12.6%). Cardiopulmonary resuscitation was not performed in any paediatric case: four
6 children's systolic blood pressure was <50mmHg, but expert opinion did not favour setting a blood
7 pressure below which CPR should be initiated in children.
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12 Given the small number of cases reported in children, it is not possible to make confident
13 conclusions concerning risk rates with different drugs. However, the number of cases of atracurium
14 and suxamethonium appear to be proportionate to the number of exposures. Atracurium was the
15 most-used NMBA in children (57%) by a large margin, followed by rocuronium (5.2%) and
16 suxamethonium (2.6%). Paediatric cases are increasingly intubated without an NMBA.⁴⁶
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22 There were no cases of latex-induced anaphylaxis which may reflect its declining presence in the
23 workplace⁴⁷ as well as an increased awareness as a potential hazard following historical paediatric
24 case reports.⁴⁸
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28 *Immediate management: all cases*

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30 It is reassuring that resuscitation involved a consultant or other career grade anaesthetist in all
31 cases. The majority (88.7%) of UK patients are anaesthetised by consultant or career grade
32 anaesthetists:⁴⁹ nevertheless, trainees were willing to call for help and the theatre team contributed
33 effectively to management in almost 90% of cases. Recognition of perioperative anaphylaxis may be
34 difficult but nevertheless was prompt in 83% of cases.
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39 Overall quality of management was judged 'good' in slightly less than half of the cases. The deficits
40 were multi-factorial and included insufficient IV fluids (19% of cases), non-administration (17.7%) or
41 late administration of adrenaline, delays in recognising anaphylaxis and starting specific treatment,
42 and lack of cardiac compressions where the BP was <50mm Hg or unrecordable. An apparent
43 reluctance to give adrenaline has been previously reported.⁵⁰ We suggest four factors operate. First,
44 anaphylaxis is very uncommon: an anaesthetist will see perioperative anaphylaxis on average only
45 once every 7.25 years.⁵¹ Second, when faced with hypotension, it has been the anaesthetist's
46 previous experience that repeated doses of the 'usual' vasopressors will eventually restore the blood
47 pressure, encouraging a 'more of the same' approach. An analogous behaviour is the 'task fixation'
48 sometimes observed when managing a difficult intubation. Third is the phenomenon of crisis-denial
49 and the realisation that giving adrenaline will affirm that a crisis exists. Fourth, unless the
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1 anaesthetist has a critical care background, administration of adrenaline may be outside their
2 previous experience. It is also possible that the anaesthetist may have, unfounded, concerns that
3 adrenaline is contra-indicated in patients with coronary artery disease or in obstetric patients. In
4 addition to immediate availability of management guidelines, overcoming these barriers to
5 adrenaline administration requires frequent practice drills and, ideally, simulator training.⁵²
6 Reluctance to administer large volumes of IV fluids was also observed, particularly in patients with
7 cardiac disease, perhaps through misplaced fears of causing fluid overload and precipitating heart
8 failure.

9 Vasopressin is recommended for intractable hypotension in several guidelines^{5,10} but was
10 administered in only two cases despite the presence of persistent hypotension, evidenced by the
11 administration of noradrenaline infusion in almost 1 in 5 cases. Several cardiac arrests were
12 preceded by prolonged hypotension. Of note, earlier guidelines omitted this drug³ and it likely that
13 awareness is limited. It is also likely that vasopressin is unavailable in many anaesthetising sites, a
14 situation addressed by our recommendations. Similar comments apply to glucagon.

15 We sought to be in a position to make firm recommendations about the administration of
16 chlorphenamine. Using level of harm as the outcome and including all putative factors, logistic
17 regression identified chlorphenamine administration was associated with increased probability of
18 'no harm' and reduced probability of 'moderate/severe' harm. However, the confidence intervals
19 were wide and a Fischer exact test demonstrated that anaesthetists who gave overall good care as
20 determined by the review panel were more likely to have administered chlorphenamine,
21 presumably as a result of following UK guidelines, i.e. we were unable to demonstrate causality. The
22 review panel considered that chlorphenamine should continue to be recommended, though mainly
23 to reduce angioedema/urticaria.

24 Our data do not support efficacy of sugammadex in rocuronium-induced anaphylaxis. Of seven
25 proven cases, in four no further pharmacological treatment was needed after sugammadex was
26 given, but three required further vasopressor and or bronchodilator therapy.

27 Patients with profound hypotension had less good quality of care than any other patient group. They
28 were more likely to have delayed diagnosis and administration of adrenaline, and CPR was a rarity:
29 significant numbers of patients came to harm. Early recognition of these patients as at high risk of
30 harm, early management with adrenaline, fluids and CPR provides an opportunity to improve
31 outcomes.

1 Treatment and referral to allergy clinics might be improved by provision of specific Anaesthetic
2 anaphylaxis treatment packs and Anaesthetic anaphylaxis investigation packs. These are described in
3 Supplementary materials A and B respectively.
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8 The majority of patients in our cohort required transfer to critical care, mostly for level 3 care and
9 half of patients required catecholamine infusions and a substantial number of patients were harmed
10 by their anaphylactic event. While the decision to abandon or continue surgery needs to be a
11 balanced one based on individual circumstances, the review panel were of the view that it is
12 inadvisable for surgery to proceed after life-threatening anaphylaxis (grades 3 and 4) unless there
13 are over-riding reasons to do so. Sadleir⁵³ demonstrated that patients with Grade 3 anaphylaxis who
14 continued with surgery (42.2%) did not require more intra-operative adrenaline or longer
15 postoperative ventilation than those in whom the procedure was abandoned. However, surgery was
16 more likely to be abandoned in the more severe Grade 3 cases. The authors attempted to control for
17 this effect by using the degree of mast cell tryptase rise as a surrogate for severity but NAP6 data
18 demonstrated no relationship between acute mast cell tryptase levels and indices of clinical
19 severity.⁵⁴ In Sadleir's study, surgery was continued in a small proportion of cases of grade 4
20 anaphylaxis.
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30 The potential risks of patients undergoing surgery without adequate precautions before they have
31 attended an allergy clinic are underlined by a case in which an NMBA was the suspected culprit but
32 chlorhexidine was demonstrated to be the cause on allergy testing. In most circumstances urgent
33 surgery can be performed before allergy clinic assessment by applying some simple, cautious rules:
34 we have developed a management plan (Appendix 1) for patients in whom surgery is needed before
35 a clinic diagnosis has been obtained.
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41 Gibbison et al demonstrated that perioperative anaphylaxis accounts for a third of all cases of
42 anaphylaxis admitted to critical care units;⁵⁵ a similar proportion to that admitted from the
43 emergency department following community anaphylaxis. Our data, 144 admissions over a one year
44 period, are compatible with Gibbison's. Almost two thirds of patients admitted to ICU/HDU required
45 continuing inotropic support, but only 5% needed continuing bronchodilator therapy; we believe this
46 is a novel finding. Of note, there were no cases of so-called biphasic anaphylaxis.
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52 The mortality rate (3.8%) observed in NAP6 corresponds with other large series. A significant finding
53 was the association with increased age, increased ASA, morbid obesity, coronary artery disease and
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1 beta blocker and ACEI medication. These factors are likely to interact and may not each be
2 independent predictors of poor outcome but are worthy of further research.
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6 We are not aware of other studies which investigated a wide range of physical and psychological
7 adverse sequelae. Severe anxiety and mood changes, mild/moderate memory impairment and
8 impaired mobility were observed. Physical harm was uncommon but did include one front of neck
9 airway and a small number of patients who experienced myocardial infarction, stroke, acute kidney
10 injury or new shortness of breath as a consequence of perioperative anaphylaxis or during their
11 recovery. It is likely these sequelae are underdiagnosed. We recommend that all patients should be
12 followed-up after perioperative anaphylaxis.
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19 In order to facilitate this and the many other tasks that are needed for a department of anaesthesia
20 to be 'institutionally prepared' to manage perioperative anaphylaxis we recommend that all
21 departments of anaesthesia should have a 'Departmental Lead for Anaphylaxis'. The suggested roles
22 and responsibilities are set out in Supplementary materials C.
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27 In appendix 2 we list a series of recommendations intended to improve care. They are numerous and
28 some simply reinforce known good practice. However, each recommendation is founded on the
29 direct and indirect findings of NAP6. We hope that (as with previous NAPs^{56 57}) the many
30 recommendations we have made will be largely implemented. Others may stimulate discussion or
31 provide hypotheses for future research. We hope this will both increase awareness of the topic and
32 improve institutional and individual preparedness for these infrequent but potentially life-
33 threatening events. This will have the potential to make inroads into avoiding avoidable anaphylaxis,
34 improving the quality of care patients receive when it occurs and afterwards, both by anaesthetists
35 and in allergy clinics.
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49 **Declaration of interest**

50 TMC: is an associate editor of the British Journal of Anaesthesia. He is not aware of any financial
51 conflicts.
52

53 NJNH, TG, DNL, MT, HK, K-LK, SM, SK, KFe, JH, HT, AW, WE, SN, NMcG, KFI, MB, LF and SF all have no
54 conflicts to declare.
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Authors' contributions and authorship

NJNH – Co-designed methodology of the study. Analysed results. Collated draft sections, wrote all drafts of the paper and the final draft.

TMC – Co-designed the methodology of the study. Analysed results. Reviewed and revised drafts of the paper and the final draft.

TG, SF, NL, MT, K-L K, SK, SM, JH, KF, MB, HT Co-designed methodology of the study. Analysed results and wrote draft sections of the paper.

All other panel members contributed to the design and methodology of the study, reviewed the results and took part in review of draft manuscripts leading to finalisation.

LF - Contributed to design and methodology of the study. Administered study. Took part in review of draft manuscript leading to finalisation.

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Appendix 1: Urgent surgical intervention after suspected perioperative anaphylaxis and prior to allergy investigations: NAP6 suggested management plan

It is possible to provide safe anaesthesia in almost every case and unnecessary to postpone urgent surgery.

- ✓ It is important to discuss the case with a consultant Allergist or Clinical Immunologist as soon as possible after the suspected anaphylactic event
- ✓ Regional anaesthesia, where practical, may be a sensible option to enable avoidance of most drugs suspected to have caused anaphylaxis during previous general anaesthesia
- ✓ If anaesthesia was induced with propofol and general anaesthesia is required, the choice of induction agents includes inhalational agents, thiopental, etomidate (non-lipid formulation) and ketamine.
- ✓ If tracheal intubation is required and an NMBA is contra-indicated:
 - A remifentanil infusion, magnesium sulphate and topical anaesthesia are helpful adjuncts to deep anaesthesia in facilitating laryngoscopy and intubation
 - Where remifentanil was used in the previous anaesthetic, consider the use of alfentanil
 - Awake intubation under topical anaesthesia is an alternative
- ✓ If local anaesthetics are not contra-indicated, sufficient surgical muscle relaxation can usually be provided if necessary with an adequate depth of anaesthesia and adjunct neuraxial block, transversus abdominis blocks, rectus sheath blocks or other peripheral nerve block
- ✓ Pre-warn the theatre team beforehand, and be prepared to diagnose and treat anaphylaxis promptly. Consult appropriate guidelines in advance
- ✓ Premedication with antihistamines and steroids may reduce the severity of reactions caused by non-specific histamine release but will not prevent anaphylaxis.

Avoid the following if administered/exposed during the 60 minutes prior to the suspected anaphylactic event:

- All drugs to which the patient was exposed, with the exception of inhalational anaesthetic agents
- All antibiotics of the same class that was administered (beta lactams; macrolides; fluoroquinolones; aminoglycosides; monobactams; carbapenems). The surgical and anaesthetic team should discuss antibiotic choice with a microbiologist

- If an NMBA was administered during this period, all NMBAs should be avoided unless it is absolutely impossible to do so, due to the risk of cross-sensitivity
- Chlorhexidine (including chlorhexidine antiseptic wipes, medical gel (e.g. used before catheter insertion) and chlorhexidine-coated intravascular lines/catheters)
- IV colloids
- Radiological contrast and dyes used for lymph node identification
- Latex
- Local anaesthetics of the same class (amides; esters)
- Histamine-releasing drugs (morphine and codeine) as the previous reaction may have been due to non-specific histamine-release

If past anaesthetic records are not available, in addition to the above:

- Assume that the patient previously received an antibiotic. Antibiotics are the most common cause of perioperative anaphylaxis in the UK. Discuss antibiotic prophylaxis with a microbiologist beforehand
- Assume that the patient was previously exposed to propofol, morphine, chlorhexidine, latex, IV colloid, and an NMBA
- If possible, use local or regional anaesthesia in patients who have had a previous suspected anaphylactic event during general anaesthesia, and vice versa

Appendix 2. NAP6 Recommendations for anaesthetists

Recommendations regarding allergy clinic investigations can be found in the accompanying paper (Bill CEA) and all recommendations including those for research are in the main report at <http://www.nationalauditprojects.org.uk/NAP6Report#pt>.

DEPARTMENTAL ORGANISATION & IMMEDIATE MANAGEMENT

National

1. Relevant standard setting and examining organisations should ensure that the detection, management and referral for investigation of perioperative anaphylaxis is a core curriculum content for anaesthetists and intensivists.
2. Allergy history-taking should be included in core curricula for medical and nursing training. Nurses in pre-operative assessment clinics require particular skills and training.

Institutional

3. Procedures should be in place to ensure that an appropriate patient allergy history is sought and recorded before anaesthesia is administered.
4. There should be a *departmental lead for perioperative anaphylaxis* in each department of anaesthesia. This role should be supported by appropriate time and DCC/SPA allocation.
5. Department leads and their local allergy clinic should liaise directly to ensure current phone numbers and email contacts for the clinic are readily available to anaesthetists in their department, and kept up to date.
6. Departments of anaesthesia should have protocols for the detection, management and referral for investigation of perioperative anaphylaxis. These should be readily accessible to all departmental members, widely disseminated and kept up to date.
7. Clinical Directors of anaesthetic departments should ensure their anaesthetists have been trained in the management of perioperative anaphylaxis.
8. Perioperative anaphylaxis guidelines and/or a management algorithm should be immediately available wherever anaesthesia is administered.
9. *Anaesthesia anaphylaxis treatment packs*, including an anaphylaxis management algorithm, adrenaline pre-filled syringes suitable for IV administration, hydrocortisone and details of the location of glucagon and vasopressin should be immediately available wherever anaesthesia is administered.
10. *Anaesthesia anaphylaxis investigation packs*, including tryptase sampling tubes and paperwork that describes (a) details of blood tests required and their timing (b) instructions on referral for

1 further investigation and allergy clinic details (c) documentation for the patient, should be
2 available in all theatre suites.
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5 11. Vasopressin and glucagon for the management of intractable perioperative anaphylaxis should
6 be available within 10 minutes, wherever anaesthesia is administered.
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8 12. Referrals to allergy clinics for investigation of perioperative anaphylaxis should include full
9 details of the patient's medication, the event and timings of all drugs administered prior to the
10 event. A standardised form (e.g. the AAGBI proforma) should accompany the referral.
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12 13. Investigation of perioperative anaphylaxis should include follow-up, either in hospital or in
13 primary care, to detect adverse sequelae such as new anxiety, impairment of cognition or
14 activities of daily living or deterioration in cardiorespiratory or renal function. The anaesthetic
15 department lead should co-ordinate this.
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20 **Individual**

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22 14. All anaesthetists responsible for perioperative care should be trained in recognition and
23 management of perioperative anaphylaxis and relevant local arrangements.
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25 15. Adrenaline is the primary treatment of anaphylaxis and should be administered immediately
26 anaphylaxis is suspected. In the perioperative setting this will usually be IV.
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28 16. Where a critical perioperative hypotensive event occurs, and perioperative anaphylaxis is one of
29 several differential diagnoses, treatment for anaphylaxis should start promptly as there is little
30 to be lost and much to be gained.
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32 17. If IV access is not immediately available intramuscular or interosseous routes should be used
33 promptly, until IV access is established.
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35 18. A rapid IV crystalloid (not colloid) fluid challenge of 20ml/kg should be given immediately. This
36 should be repeated several times if necessary.
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38 19. During anaphylaxis with a systolic blood pressure <50mmHg in adults, even without cardiac
39 arrest, CPR should be started simultaneously with immediate treatment with adrenaline and
40 liberal IV fluid administration.
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42 20. If an IV colloid is being administered at the time of the anaphylactic event, it should be
43 discontinued, and the IV administration set replaced.
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45 21. Administration of IV vasopressin 2 Units, repeated as necessary, should be considered when
46 hypotension due to perioperative anaphylaxis is refractory
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48 22. During perioperative anaphylaxis in patients taking beta blockers early administration of IV
49 glucagon 1 mg should be considered, repeated as necessary.
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51 23. When anaphylaxis occurs following recent insertion of a chlorhexidine-coated central venous
52 catheter, this should be removed and, if appropriate, replaced with a plain one.
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24. A corticosteroid should be administered as part of resuscitation of perioperative anaphylaxis.
 25. Chlorphenamine may be given as part of the resuscitation process, but NAP6 found no evidence of either benefit or harm. It may reduce angioedema and urticaria.
 26. Blood samples for mast cell tryptase (MCT) should be taken in accordance with national guidelines.
 - a. 1st sample as soon as the patient is stable.
 - b. 2nd sample as close to 1 -2 hours as possible after the event.
 - c. 3rd (baseline) at least 24 hours after the event
 27. All patients experiencing suspected perioperative anaphylaxis should be referred for specialist investigation in an allergy clinic. This is the responsibility of the consultant anaesthetist in charge of the patient at the time of the event: i.e. the consultant anaesthetising or supervising the case.
 28. Where a trainee refers a patient to an allergy clinic the contact details of a consultant anaesthetist should be included in the referral.
 29. If there is a need for urgent referral, the anaesthetist should phone the allergy clinic for advice, as well as making a written referral.
 30. Where perioperative anaphylaxis has led to deferment of urgent surgery, alternative anaesthesia should be feasible by following simple rules.

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Research

31. There remains uncertainty about the benefits or potential harm of administering antihistamine drugs during resuscitation of perioperative anaphylaxis. Clinical trials would provide valuable evidence.
32. There remains uncertainty about the benefits or potential harm of administering sugammadex during resuscitation of perioperative anaphylaxis and for management of rocuronium induced anaphylaxis specifically. Clinical trials would provide valuable evidence.

PATIENT EXPERIENCE

Institutional

33. Consent should always be informed. Therefore, patients should be informed of the risk of anaphylaxis pre-operatively. Patient information leaflets may be suitable as part of this process.
34. Following a peri-operative anaphylactic event and before discharge from hospital the patient should be provided with a letter from their anaesthetist. This letter should be in addition to the discharge summary and a copy should be sent directly to the patient's GP.

Research

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35. The effect of a perioperative anaphylactic event on a patient's physical and physiological well-being in both the medium and the long term is not well understood. Research into this topic and dissemination of the outcomes could be of great benefit to patients.

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CLINICAL FEATURES

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36. All anaesthetists responsible for perioperative care should be trained in recognition and management of perioperative anaphylaxis and relevant local arrangements.

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Individual

37. Perioperative anaphylaxis can present with a single clinical feature, in particular isolated hypotension. Anaesthetists should exercise a high index of suspicion in recognising perioperative anaphylaxis and commence treatment promptly.
38. In patients with asthma, the occurrence of bronchospasm or high airway pressures should not automatically be attributed to acute asthma as, in these patients this is frequently the presenting feature of life-threatening anaphylaxis.
39. As anaphylaxis may be delayed, particularly with some oral drugs, referrals to allergy clinics should include details of all agents that the patient has been exposed to within at least the previous 120 minutes
40. During perioperative anaphylaxis in patients taking beta blockers early administration of IV glucagon 1mg should be considered, repeated as necessary.

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Research

41. Further studies are required to clarify the role of a fall in end-tidal CO₂ concentration in the early recognition and management of severe perioperative anaphylactic reactions.
42. The role of glucagon and vasopressin in refractory anaphylaxis (particularly in high risk groups such as the elderly, and those taking beta blockers or ACE inhibitors) needs further investigation.
43. Studies are indicated to establish the influence of mast cell activation disorders on the severity and clinical presentation of perioperative anaphylaxis.
44. Research would be of value to investigate the effect of corticosteroids, both given prior to anaphylaxis and for its treatment.

DEATHS, CARDIAC ARREST and PROFOUND HYPOTENSION

Severe perioperative anaphylaxis here refers to perioperative anaphylaxis requiring CPR or with profound hypotension (e.g. systolic blood pressure <50mmHg).

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45. In patients who experience perioperative anaphylaxis with a high risk of adverse outcome (elderly, obese, ASA \geq 3, patients taking beta blockers or ACEI, prolonged CPR), anaesthetists should be prepared to escalate treatment early.
 46. During anaphylaxis with a systolic blood pressure <50mmHg in adults, even without cardiac arrest, CPR should be started simultaneously with immediate treatment with adrenaline and liberal IV fluid administration.
 47. During perioperative anaphylaxis in patients taking beta blockers early administration of IV glucagon 1mg should be considered, repeated as necessary.
 48. Administration of IV vasopressin 2 Units, repeated as necessary, should be considered when hypotension due to perioperative anaphylaxis is refractory.
 49. The need for a vasopressor infusion should be anticipated after severe perioperative anaphylaxis.
 50. Non-essential surgery should not be started after severe perioperative anaphylaxis.
 51. Where severe perioperative anaphylaxis occurs during non-essential surgery the operation should be curtailed unless there is an overriding reason to continue.
 52. Patients with severe anaphylaxis should be admitted to critical care (HDU/ICU).
 53. While it is not possible to be definitive about how long a patient should be observed after Grade 3-4 perioperative anaphylaxis, it would seem imprudent for them to be discharged on the same day as the event.
 54. All cases of severe perioperative anaphylaxis, including fatalities, should be discussed with an allergy clinic at the first available opportunity.

REPORTING

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55. MHRA should improve communication with clinicians; for example, providing an annual report which includes perioperative anaphylaxis

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56. The departmental lead should ensure all cases have been reported to the Trust incident reporting system.
 57. The departmental lead should ensure all cases are reported (by the anaesthetist encountering the reaction, or the departmental lead) to the MHRA as soon as possible after the event and record the MHRA case identifier for future reference.

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58. The department lead should (using the MHRA case identifier) ensure the MHRA record is updated after allergy clinic investigation is completed, to ensure the information held is accurate.

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59. The departmental lead should be informed of the case.
60. The MHRA case identifier should be included in the referral to the allergy clinic.
61. All cases of grade 3-5 perioperative anaphylaxis should be presented and discussed at local morbidity & mortality meetings, for purposes of education and familiarisation.

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NMBA

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62. Except in cases of known or suspected allergy to specific NMBAs, the risk of anaphylaxis should not be an over-riding factor in choice of NMBA, as this varies little between NMBAs.

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Research

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63. Further research on population sensitisation by pholcodine is needed. If a causal association is confirmed, withdrawal of pholcodine-containing medicines from the UK market should be formally considered.
64. There remains uncertainty about the benefits or potential harm of administering sugammadex during resuscitation of perioperative anaphylaxis and for management of rocuronium-induced anaphylaxis specifically. Clinical trials would provide valuable evidence.

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ANTIBIOTICS

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65. Patients with reported allergy to a beta-lactam antibiotic and at least one other class of antibiotics should be referred for specialist allergy investigation, before elective surgery, in line with *NICE CG183: Drug allergy: diagnosis and management*.
66. If antibiotic allergy is suspected despite negative skin tests, challenge testing should be performed.
67. Trust guidelines on antibiotic prophylaxis for surgery should be immediately available to anaesthetic and surgical teams in theatre.

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68. Antibiotic administration should strictly follow national or local guidelines.
69. A test dose of antibiotic should not be used, as it will not prevent or reduce the severity of anaphylaxis.
70. Ninety per cent of anaphylaxis due to antibiotics presents within ten minutes of administration. When perioperative antibiotics are indicated they should be administered as early as possible, where practical at least 5-10 minutes before induction of anaesthesia, providing this does not interfere with their efficacy.
71. The anaesthetist should consider co- amoxiclav or teicoplanin amongst the likely culprits when anaphylaxis occurs after their administration.
72. Broad beta lactam avoidance advice should be discouraged, and patients should be further investigated to clarify the drug(s) to avoid and to identify safe alternatives.

CHLORHEXIDINE

National

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73. The MHRA should work with manufacturers of medical devices, e.g. central venous (and other intravascular) catheters to ensure that products are labelled clearly and prominently, to identify whether they contain chlorhexidine or not.

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74. Operating theatres should have an accessible list of chlorhexidine-containing items. Appropriate alternatives should be available for patients with suspected or confirmed chlorhexidine allergy.
75. Investigation of suspected perioperative anaphylaxis should include chlorhexidine.

Individual

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76. Chlorhexidine allergy should be included in the allergy history taken by anaesthetists, nurses and other healthcare professionals.
77. Clinical teams should be aware of 'hidden chlorhexidine' such as in urethral gels and coated central venous catheters and should consider this as a potential culprit if perioperative anaphylaxis occurs.
78. When anaphylaxis occurs following recent insertion of a chlorhexidine-coated central venous catheter, this should be removed and, if appropriate, replaced with a plain one.

PATENT BLUE DYE

Individual

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79. If administration of Patent Blue dye is planned during surgery, the surgical team should discuss the risk of anaphylaxis as part of the consent process for surgery.
80. If anaphylaxis occurs in a patient who has received Patent Blue dye, it should not be assumed that this is the culprit, and the patient should be referred for specialist allergy investigation.
81. Where pulse oximeter saturations fall during anaphylaxis in a patient who has received Patent Blue dye, hypoxia should be assumed to be real. A blood gas sample should be taken, when the patient is stable enough for this.

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INVESTIGATION

82. Specialist perioperative allergy clinics should adopt an MDT approach, including where practical having an anaesthetist with a special interest in the allergy clinic. Where this is not practical cases should be discussed with an anaesthetist before the patient attends the clinic.
83. Referrals to allergy clinics for investigation of perioperative anaphylaxis should include full details of the event and a full list of the patient's medication and drugs administered prior to the event. A standardised form (e.g. the AAGBI proforma) should accompany the referral.

Individual

84. All patients experiencing suspected perioperative anaphylaxis should be referred for specialist investigation in an allergy clinic. This is the responsibility of the consultant anaesthetist in charge of the patient at the time of the event: i.e. the consultant anaesthetising or supervising the case.
85. The anaesthetist referring the patient for investigation of perioperative anaphylaxis should explain the importance of attending and allay any fears to improve uptake of allergy clinic appointments.

OBSTETRIC

Institutional

86. Obstetric units should ensure immediate availability of anaesthetic anaphylaxis treatment and investigation packs wherever general or regional anaesthesia is administered

Individual

87. An allergy history should be taken even when there is extreme urgency to deliver the baby.
88. Anaesthetists should be vigilant to non-obstetric causes of hypotension in obstetric patients.
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89. Anaphylaxis in obstetric patients should be managed following the same principles as in non-obstetric patients. Adrenaline should not be withheld for fear of a detrimental effect on placental perfusion.
90. Anaphylaxis should be actively considered where the cause of maternal hypotension or collapse is unclear, and mast cell tryptase levels should be measured.
91. Anaesthetists should be aware that hypotension due to anaphylaxis can be exacerbated by neuraxial blockade and or aortocaval compression.

PAEDIATRIC

Institutional

92. Protocols and anaesthetic anaphylaxis treatment and investigation packs appropriate for children should be immediately available wherever paediatric anaesthesia is administered
93. All anaesthetists administering anaesthesia to children should be trained in the management of paediatric anaphylaxis.
94. 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.

CRITICAL CARE

95. Patients with severe anaphylaxis should be admitted to critical care (HDU/ICU).
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Table 1 ASA grade, level of care and outcomes in patients receiving chlorphenamine or no chlorphenamine for grade 3-5 perioperative anaphylaxis.

	CHLORPHENAMINE n = 195	NO CHLORPHENAMINE n = 65
	52.3%	46.2%
	45.1%	46.2%
	3%	8%
Prompt cardiac compressions	46%	50%
Level 2 care	11%	11%
Level 3 care	33.8%	13.9%
Inotropes needed in ICU	31.8%	12.3%
Physical harm: None	3.6%	12.3%
Physical harm: Low	39%	24.6%
Physical harm: Moderate	26.2%	16.9%
Physical harm: Severe	2.6%	7.7%

Table 2. Quality of resuscitation and outcomes in patients who died, compared to those who survived cardiac arrest, or experienced profound hypotension or did not experience profound hypotension.

	Deaths (n=10)	Non-fatal cardiac arrest (n=31)	BP <50 but not cardiac arrest or death (n=79)	All others (n=135)
Quality of resuscitation				
Appropriate resuscitator	100%	100%	100%	98%
Prompt recognition	100%	91%	98%	99%
Prompt diagnosis of anaphylaxis	88%	82%	80%	85%
Prompt treatment of anaphylaxis	70%	83%	65%	78%
Adrenaline administered as needed	90%	100%	76%	77%
Prompt CPR when indicated	90%	91%	2%	67%
Appropriate fluid	67%	81%	78%	83%
Good initial management	60%	65%	8%	58%

Poor initial management	0%	9%	34%	8%
Outcomes				
Outcomes where known (median)	Severe	Moderate	Moderate	Low
% experiencing any harm	100%	74%	59%	60%
ICU for vasopressors (% of all cases)	n/a	67%	32%	23%
Time on ICU (median, all cases)	n/a	2	0	1
Unplanned hospital length of stay	n/a	2	1	1

For Peer Review

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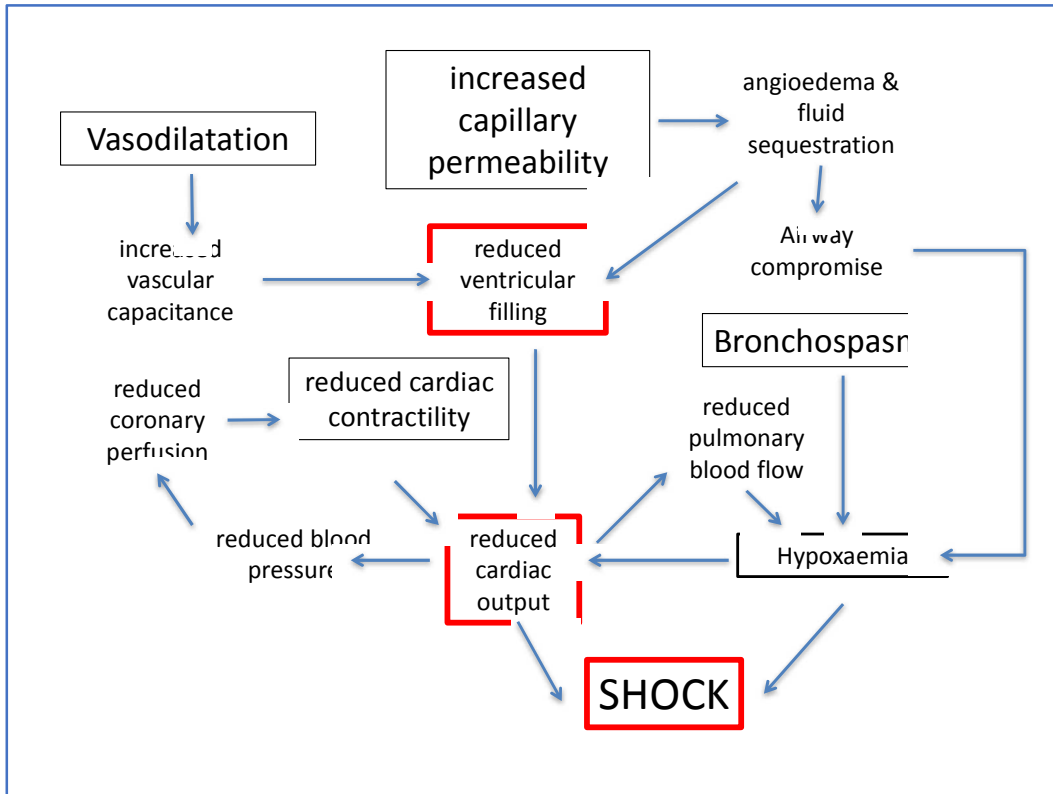


Figure 1. Pathophysiological mechanisms responsible for anaphylactic shock

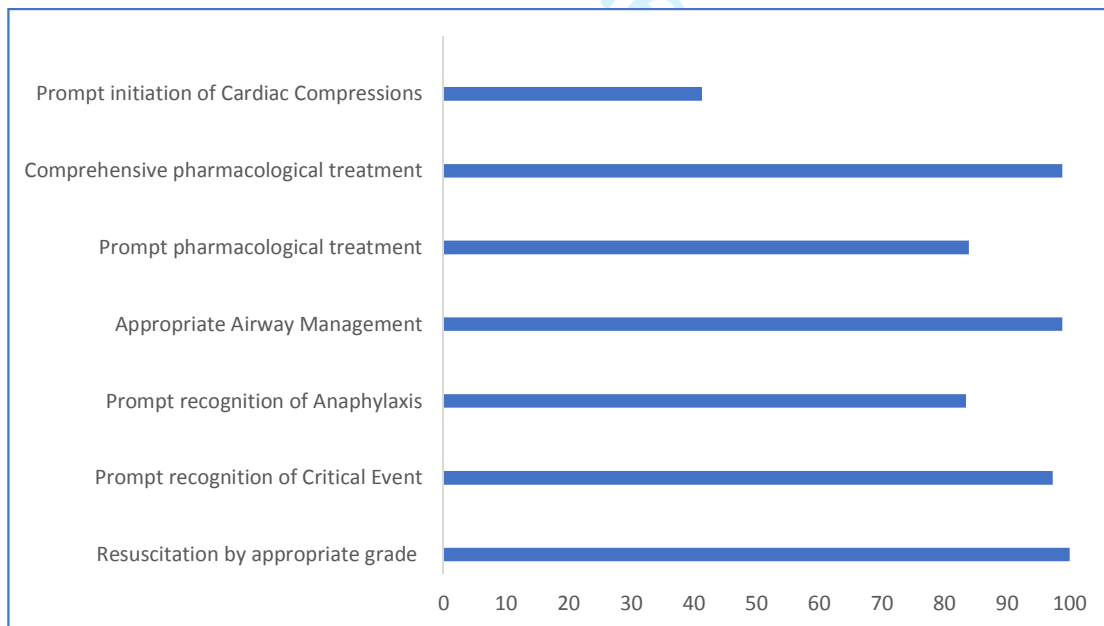


Figure 2 Quality of management of perioperative anaphylaxis by anaesthetists (% of cases)

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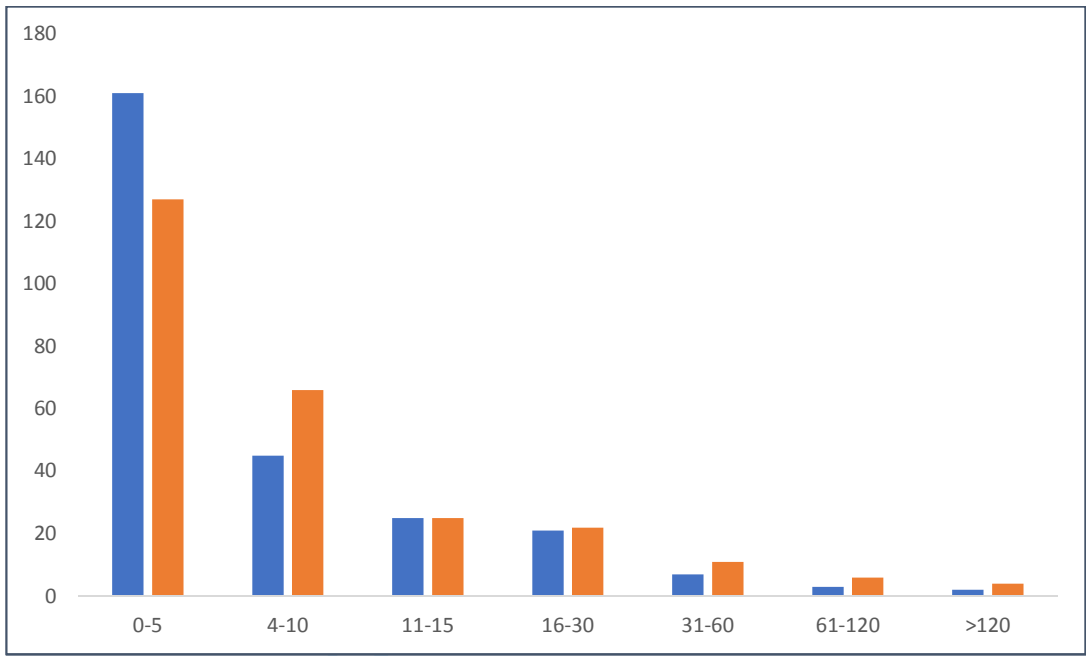


Figure 3 Elapsed time (minutes) between drug administration (suspected trigger agent) and recognition of a critical incident and suspecting anaphylaxis. Blue – Time to recognise critical incident, orange, time to suspect anaphylaxis.

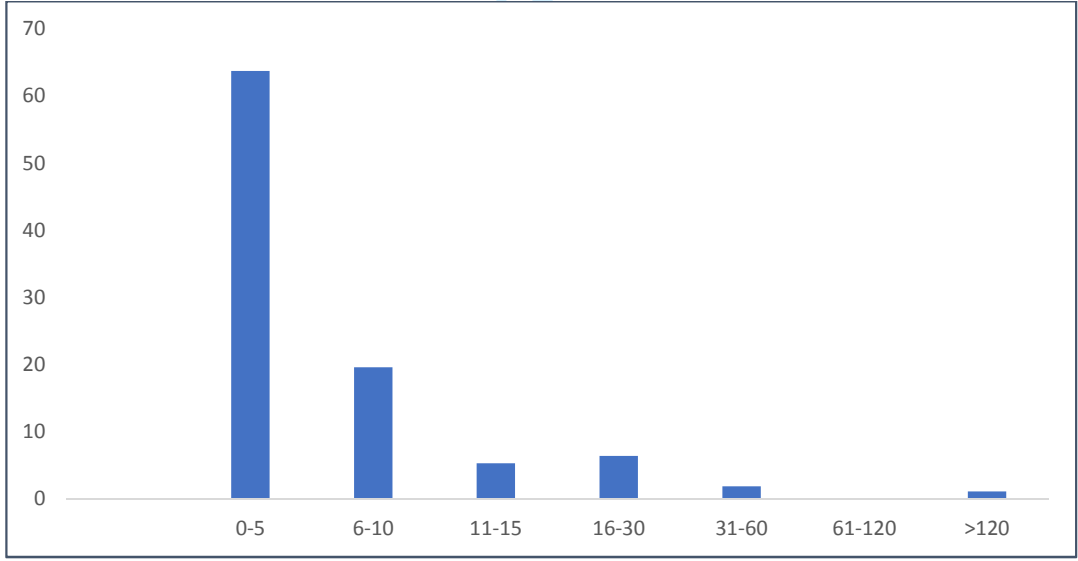


Figure 4. Speed of starting anaphylaxis-specific treatment after first clinical feature (% of cases).

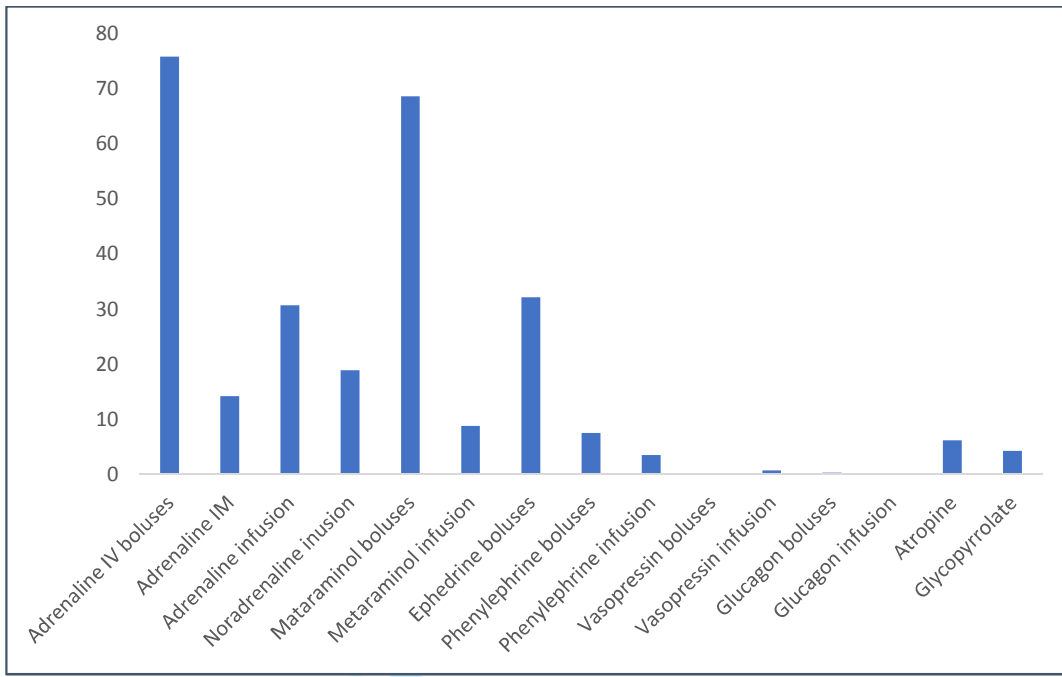
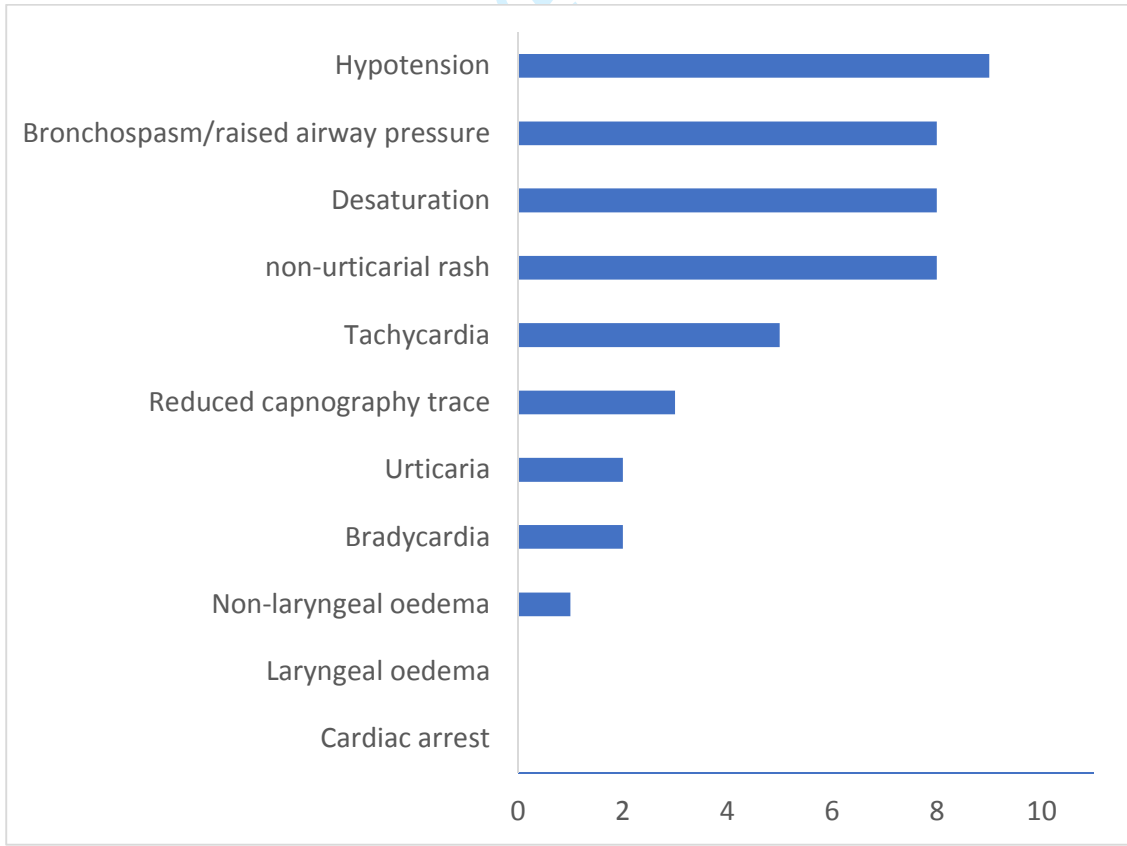


Figure 5. Vasoactive drugs administered during initial management of perioperative anaphylaxis (% of cases).



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Figure 6. Number of children exhibiting clinical features at any time during the anaphylactic episode.

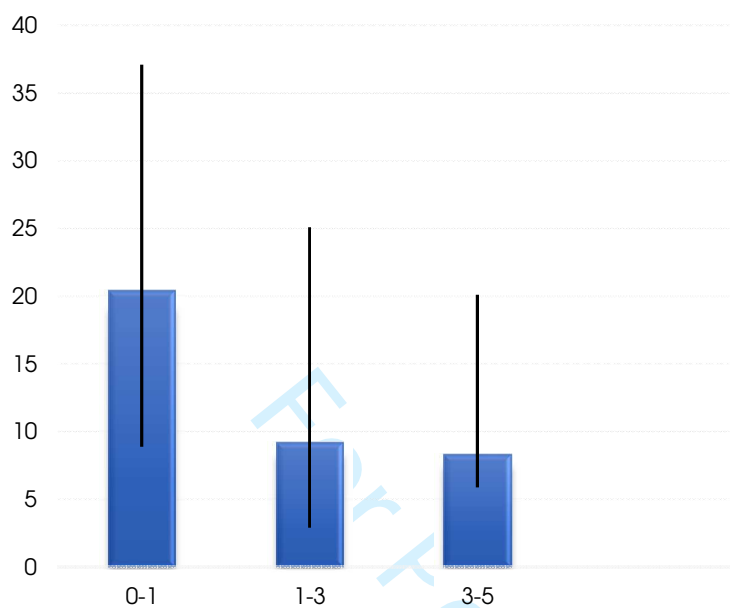


Figure 7. Volume of IV crystalloid (ml/kg) administered to children during the first five hours after an anaphylactic event (median, range).