

ORIGINAL ARTICLE

Clinical Allergy

Specialist perioperative allergy clinic services in the UK 2018: Results from the Royal College of Anaesthetists Sixth National Audit Project (NAP6) investigation of perioperative anaphylaxis

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Summary

Background: The Royal College of Anaesthetists 6th National Audit Project examined Grade 3-5 perioperative anaphylaxis for 1 year in the UK.

Objective: To describe the causes and investigation of anaphylaxis in the NAP6 cohort, in relation to published guidance and previous baseline survey results.

Methods: We used a secure registry to gather details of Grade 3-5 perioperative anaphylaxis. Anonymous reports were aggregated for analysis and reviewed in detail. Panel consensus diagnosis, reaction grade, review of investigations and clinic assessment are reported and compared to the prior NAP6 baseline clinic survey.

Results: A total of 266 cases met inclusion criteria between November 2015 and 2016, detailing reactions and investigations. One hundred and ninety-two of 266 (72%) had anaphylaxis with a trigger identified, of which 140/192 (75%) met NAP6 criteria for IgE-mediated allergic anaphylaxis, 13% lacking evidence of positive IgE tests were labelled “non-allergic anaphylaxis”. 3% were non-IgE-mediated anaphylaxis. Adherence to guidance was similar to the baseline survey for waiting time for clinic assessment. However, lack of testing for chlorhexidine and latex, non-harmonized testing practices and poor coverage of all possible culprits was confirmed. Challenge testing may be underused and many have unacceptably delayed assessments, even in urgent cases. Communication or information provision for patients was insufficient, especially for avoidance advice and communication of test results. Insufficient detail regarding skin test methods was available to draw conclusions regarding techniques.

Conclusion and Clinical Relevance: Current clinical assessment in the UK is effective but harmonization of approach to testing, access to services and MHRA reporting is needed. Expert anaesthetist involvement should increase to optimize diagnostic yield and advice for future anaesthesia. Dynamic tryptase evaluation improves detection of tryptase release where peak tryptase is $<14 \mu\text{g/L}$ and should be adopted. Standardized clinic reports containing appropriate details of tests, conclusions, avoidance, cross-reactivity and suitable alternatives are required to ensure effective, safe future management options.

KEYWORDS

anaphylaxis, clinical immunology, drug allergy, IgE, latex

1 | INTRODUCTION

UK Allergy Specialist Peri-operative Anaphylaxis Clinics are few and distributed unequally.¹ The 2016 NAP6 baseline survey identified the self-reported clinical activity and perceived adherence to national guidance from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the British Society for

Allergy and Clinical Immunology (BSACI) on investigation of anaphylaxis during general anaesthesia and the National Institute for Clinical Excellence (NICE) CG183 “Drug allergy: diagnosis and management of drug allergy in adults, children and young people”.¹

We compared the actual performance in the NAP6 data set with that of the NAP6 baseline survey.

What we knew about investigations in perioperative anaphylaxis before NAP6

- Tryptase release is seen in most but not all cases of perioperative anaphylaxis, most commonly in the higher grades of reaction (Grade 3-5).²⁻⁹
- There is a poor correlation with reaction grade individually, but higher medians are seen in more severe reactions.³
- Tryptase levels plateau between 30 and 90 minutes post-reaction.⁹
- Dynamic tryptase results may identify tryptase release in more cases than exceeding fixed thresholds of 11.4 or 14 µg/L.^{3,10}
- Exposure to opioids such as pholcodine may correlate with neuromuscular blocking agent (NMBA) anaphylaxis. NMBA anaphylaxis is rarely diagnosed in Denmark, where it is banned, unlike Norway (historically) and the UK.^{11,12}
- Basal tryptase levels may correlate with severity of anaphylaxis in non-perioperative settings.¹³
- The incidence of latex allergy is probably decreasing.^{4,14}
- Rocuronium may now be a leading cause of NMBA reactions.¹⁵
- Chlorhexidine and teicoplanin are triggers on the rise.^{4,15-19}
- There is considerable variation in skin testing and no consensus on the best panel and sequence of testing.

2 | METHODS

NAP6 did not require National Research Ethics Service approval as a Health-Regulatory-Authority-defined service evaluation. All UK NHS and private hospitals undertaking surgery in the UK were invited. Anaesthetists reported cases in 2 web-based forms: Part A before allergy clinic investigation and Part B after allergy clinic assessment and follow-up. Only cases with both Part A and B were included.

Reports were assessed by the panel in an expert consensus analysis of imputability in exactly the same way as in an allergy clinic, but in a structured process involving consensus between multiple experts in allergy and anaesthesia and a multistage review as described in the NAP6 papers (Table 1). This is similar to Bayesian approaches to assigning drug imputability^{20,21}.

The clinical history and experience of the panel members led the diagnosis and test results were utilized as supporting evidence as is normal practice, but utilizing defined criteria.²¹ The outcomes for this paper were classified as "allergic anaphylaxis" when parameters strongly supported the diagnosis included relevant IgE sensitization, and as "non-allergic anaphylaxis" when relevant IgE sensitization

TABLE 1 Criteria used for classifying the mechanism of anaphylaxis and the level of diagnostic confidence

Class of event In addition to history of reaction Grade 3, 4 or 5	High certainty: all criteria Intermediate certainty: 3 of 4 criteria
1. Allergic anaphylaxis (IgE-mediated)	1. Timeline—within 60 min 2. Evidence of mast cell mediator release—tryptase 3. Evidence of positive sIgE (blood or skin tests)* 4. Differential diagnoses excluded
2. Anaphylaxis—non-allergic (no evidence of relevant IgE sensitization)	1. Timeline—within 60 min 2. Evidence of mast cell mediator release—tryptase 3. No evidence of positive sIgE (blood or skin tests) 4. Differential diagnoses excluded
3. Anaphylaxis—not allergic	As above, with no evidence of specific IgE but differential diagnoses more likely: Airway management Drug side effect Drug overdose Cardiac disease/event
4. Uncertain	Insufficient information to judge

*essential, except where a patient had died and could not be tested or where the history was very suggestive of a typical allergic reaction in the opinion of the panel

could not be demonstrated as summarized in Table 1. Seventeen cases where testing was not available but the reactions had a high probability of allergic aetiology were included in the allergic group despite lack of evidence of sensitization. It is acknowledged that the lack of ability to demonstrate sensitization is not an indication that the reaction was not IgE-mediated, due to the influence of time and the known deficiencies of all the tests, including tryptase sampling. In all other respects, "allergic" and "non-allergic" cases were identical.

The panel attributed a level of certainty to their diagnosis (Definite; Probable; Possible; Low/Unable to identify). Only Definite or Probable culprits were used for numerical analysis. This structured process was used in an attempt to avoid "outcome bias" (where the known poor outcome leads to an unreasonably harsh judgement), "hindsight bias" (where retrospective review leads to a tendency to believe that an adverse outcome was predictable or avoidable) and "groupthink" (where a desire to agree within groups leads to a lack of independent scrutiny).

In judging quality of care, we referred to guidelines from AAGBI²², NICE CG183²³ and BSACI²⁴ to measure deviation from standards of care.¹ Overall quality of care (management, clinic referral and allergy clinic investigation) were judged as "good," "poor," "good and poor" or "unassessable" based on adherence to guidelines and ultimately by panel consensus.

Grade of reaction was reviewed against criteria in the NAP6 epidemiology paper, consistent with WAO definitions.²⁵ Grade 3, bronchospasm or hypotension (systolic nadir ≥ 50 mm Hg) together with

any other features suggestive of anaphylaxis (rash, angioedema). Grade 4, as Grade 3 but requiring cardiopulmonary resuscitation (CPR) or where the lowest systolic BP was <50 mm Hg. Grade 5, Fatal reaction. The optimum minimum panel of NMBA (the NAP6 Panel) was defined to establish a safe NMBA for routine and emergency anaesthesia, constituting the suspected trigger plus suxamethonium, rocuronium and atracurium (or cis-atracurium).¹

Clinic assessment and referral was graded by the panel as "Good" (no deviation from guidance), "Good and Poor" (minor deviation unlikely to affect diagnosis) and "Poor" (major deviation likely to affect future risk). Kruskal-Wallis and Mann-Whitney nonparametric comparisons of medians and distributions were used to compare results using the IBM SPSS statistical programme at significance limit of $P < .05$.

3 | RESULTS

3.1 | Anaphylaxis cases

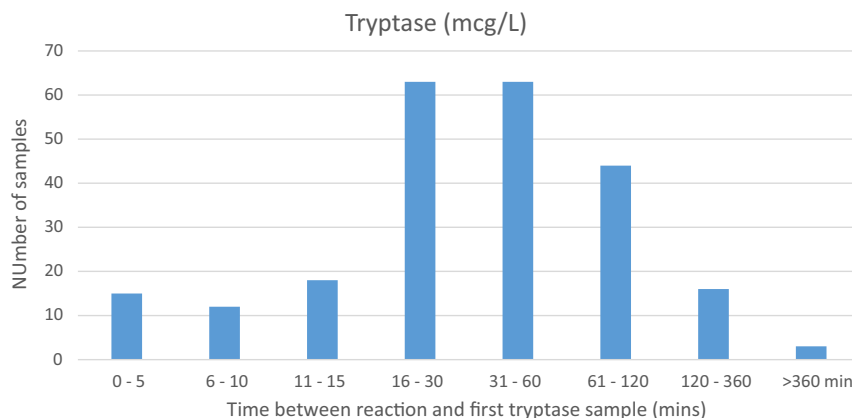
Of 504 submitted reports, 266 met inclusion criteria. One hundred and ninety-two of 266 (72%) cases had anaphylaxis with at least

one trigger identified, of which 140/192 (75%) met all NAP6 criteria for IgE-mediated allergic anaphylaxis, 15% (25) judged "non-allergic" anaphylaxis were identical in all parameters with the exception of a lack of relevant demonstrable IgE sensitization and 3% (6) cases did the panel feel that there was a reaction mediated by a non-IgE mechanism. In 16, the panel could not determine the type of reaction (uncertain). Most triggers were single agents but 5 of these cases had 2 potential triggers of equal probability. There was no difference in the trigger profile, clinical phenotype and grade, tryptase results, test utilization or ranges between the anaphylaxis groups.

3.2 | Tryptase sampling

Peak tryptase (Tp) above 14 µg/L were seen in 71% of cases. At least 3 Tryptase samples (T1, T2 and T3) were available in 178/266 (67%) of cases, 2 in 51 (19%) and one in 22 (8%). In 8 (3%), samples were taken but not received/reported and 7 (3%) had no samples taken. Eighty-one % of 184 reviewed cases had interpretable dynamic tryptase samples (≥ 2 samples within 6 hours of the reaction).^{3,22,24}

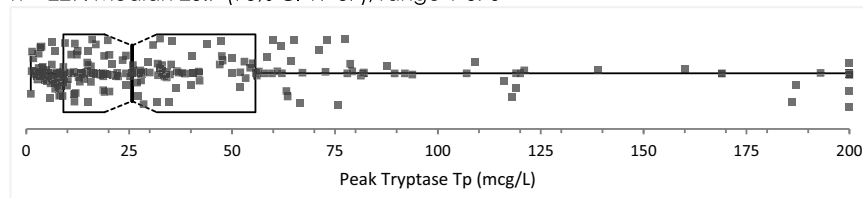
(A) Timings of First Tryptase (T1) samples



(B) Peak (Tp) and T1 Tryptase results are not significantly different ($p > 0.05$)

Peak Tryptase (maximum value in series, all grades).

$n = 229$. Median 25.7 (95% CI 19-37), range 1-576



T1 Tryptase (first value in series, all grades).

$n = 245$. Median 21.9 (95% CI 18-29), range 0.1-576

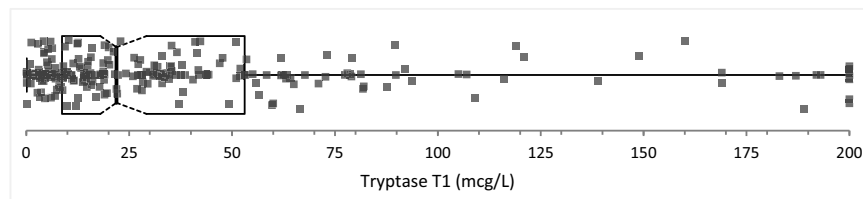


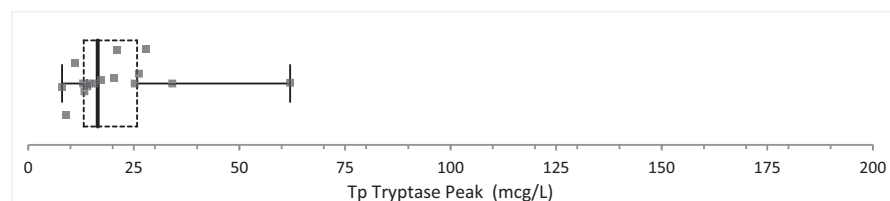
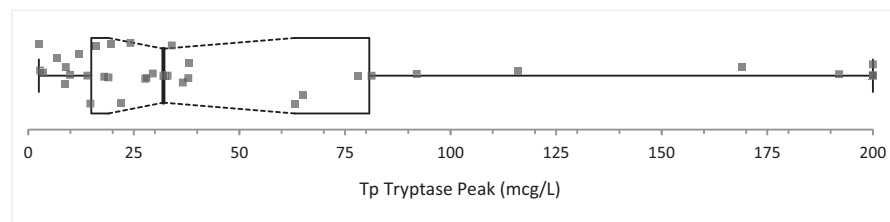
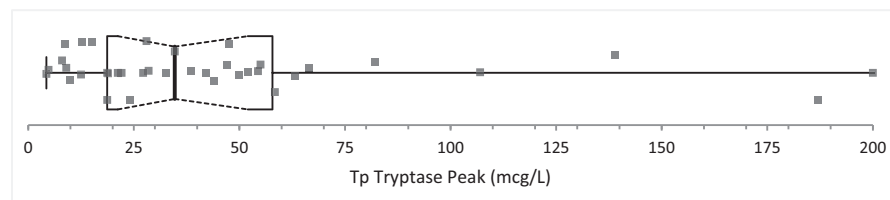
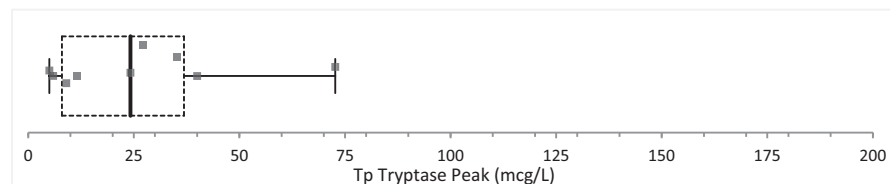
FIGURE 1 Timing and levels of first tryptase (T1) and peak tryptase (Tp) samples. A, Timings of First Tryptase (T1) samples. B, Peak (Tp) and T1 Tryptase results are not significantly different ($P > .05$). The scattergram represents all individual results. The black bar represents the median value, and the dotted indents represent the 95th confidence interval of the median. The solid line box represents the 25th and 75th centiles of the distribution, and the whiskers represent the maximum and minimum values. Where no confidence interval indent is shown, it is too large to plot

TABLE 2 Median tryptase values by reaction grade

Reaction grade	Number (n)	T1 median ($\mu\text{g/L}$)	95% CI ($\mu\text{g/L}$)	Tp median ($\mu\text{g/L}$)	95% CI ($\mu\text{g/L}$)
3	125	14.9	12-19	17.5	14-25
4	110	32.8	23-41	35.3	26-48
5	10	134 ^a	10-200	11.6 ^a	n/a

^aPeak tryptase can only be estimated where 2 or more samples are available; hence, T1 is a more accurate reflection of levels in Grade 5. Grade 3 and 4 medians are significantly different, $P = .001$.

Forty-five percent met BSACI guidance for "immediate" sampling; 45 (17%) at <15 minutes post-reaction, 64 (28%) at 16-30 minutes. One hundred and seventy-five (76%) were taken within the hour, consistent with the ANZAAG (Australian and New Zealand Anaesthetic Allergy Group) guidelines (Figure 1A).^{1,14,22-24} Twenty-three (3%) T2 samples were taken within 60 and 74 (32%) at <120 minutes, consistent with BSACI guidance, rising to 43% within 3 and 71% within 6 hours. One hundred and sixty-eight (73%) had satisfactory T3 >24 hours baseline samples, 12% were too early <20 hours.

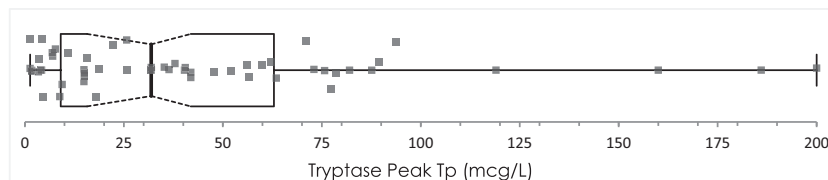
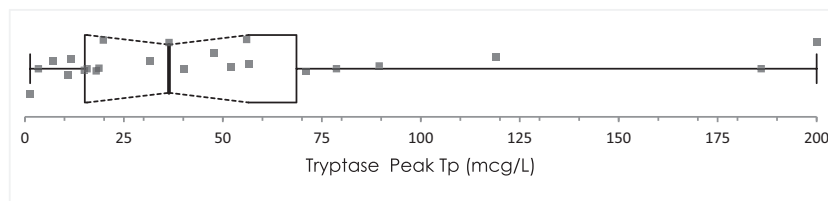
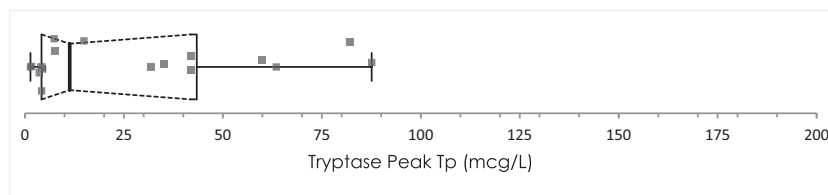
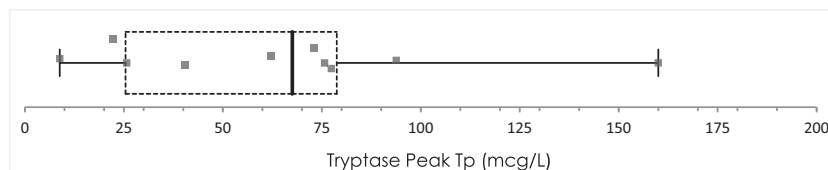
(A)**Antibiotics, antiseptics and dyes****Chlorhexidine****Teicoplanin****Co-amoxiclav****Patent Blue****3.3 | Tryptase levels**

Basal tryptase (Tb) were not significantly different in reaction Grade 3 (4.0 $\mu\text{g/L}$) vs 4 (5.0 $\mu\text{g/L}$, Material S1). 10% had raised basal tryptase (24 samples 15.4-54.2 $\mu\text{g/L}$, plus one at 153). Peak tryptase (Tp) results, defined as the highest result in the available series of samples, were mostly in the first sample. T1 includes all cases with single samples (Figure 1B and Material S1). 23 cases had single tryptase and most (65%) were positive ≥ 14 $\mu\text{g/L}$ (median 31, 95% CI 11-63, range 0.1-200). Nine fatalities had tryptase above 19.6 $\mu\text{g/L}$ (Table 2).

3.3.1 | Tryptase and triggers

The median Tp/T1 appeared lowest for chlorhexidine and highest for suxamethonium (Figure 2, Material S2). There were statistically significant differences ($P = .002-.4$) for both T1 and Tp for both distributions and medians using Mann-Whitney U test and Kruskal-Wallis ANOVA on SPSS for chlorhexidine against all other triggers.

FIGURE 2 Peak Tryptase in different panel-defined triggers, very high tryptases are rare in chlorhexidine and patent blue. The scattergram represents all individual results. The black bar represents the median value, and the dotted indents represent the 95th confidence interval of the median. The solid line box represents the 25th and 75th centiles of the distribution, and the whiskers represent the maximum and minimum values. Where no confidence interval indent is shown, it is too large to plot

(B) Muscle Relaxants**All Muscle Relaxant reactions.****Rocuronium****Atracurium****Suxamethonium****FIGURE 2** Continued

None of the muscle relaxants were significantly different from each other although atracurium vs Suxamethonium was almost significant at $P = .053$.

3.3.2 | Tryptase and severity

Statistically significant differences in distribution and medians were seen between Grade 3 and 4 reactions ($P = .001$, Figure 3, Material S3). There was no correlation between T1 and nadir oxygen saturation, lowest blood pressure recorded or the total dose of adrenaline given (Material S4).

3.3.3 | Tryptase and reaction speed

Reactions were slowest for chlorhexidine and fastest for suxamethonium, muscle relaxants and the antibiotics teicoplanin and co-amoxiclav (Material S5). NMBA reactions were faster, with only a few atracurium reactions occurring at >15 minutes. There was no statistically significant correlation between T1/Tp and reaction speed of onset ($P > .2$), although this will be confounded

by the obvious association of T1 with early sampling and variability of sample timing in individuals. 165 T1 were taken within 5 minutes of drug administration (Figure 4A). Earlier samples gave higher Tp results which rapidly fell within 30 minutes (Figure 4B).

3.3.4 | Tryptase levels in allergic and non-allergic groups

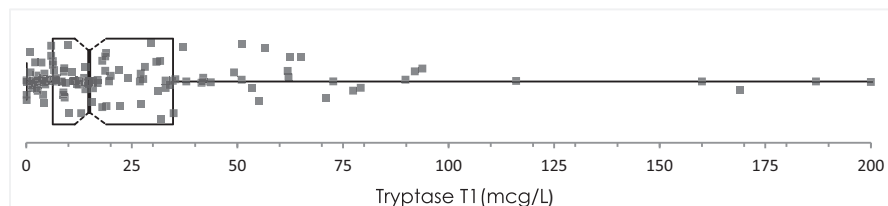
Median T1 levels were not significantly higher in allergic anaphylaxis ($P > .05$, Figure 5) vs non-allergic anaphylaxis (where specific IgE sensitization could not be demonstrated). Overall distributions and ranges were similar. Furthermore, the allergic and non-allergic cases had indistinguishable clinic phenotypes, tryptases, triggers and outcomes. The only difference was the inability to reliably detect sIgE.

Eight per cent of cases determined to be allergic anaphylaxis did not have tryptase rises; 20% had $Tp < 14 \mu\text{g/L}$ and 19 of these would only be detected by dynamic tryptase calculations.

Reaction Grade vs T1 tryptase

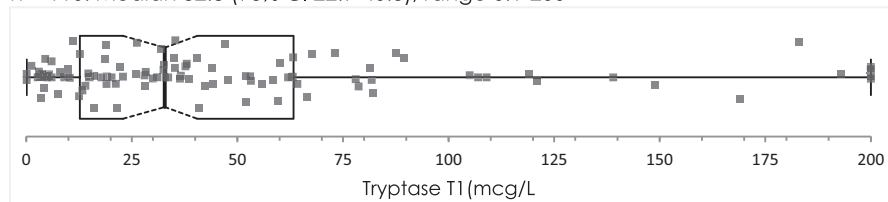
All Grade 3 reactions

n = 125. Median 14.9 (95% CI 11.5-18.9), range 0.1-576)



All Grade 4 reactions. P=0.001 for difference with Grade 3.

n = 110. Median 32.8 (95% CI 22.9-40.5), range 0.1-200



All Grade 5 reactions

n = 10. Median 134 (95%CI 19.8-200), range 11.6-300

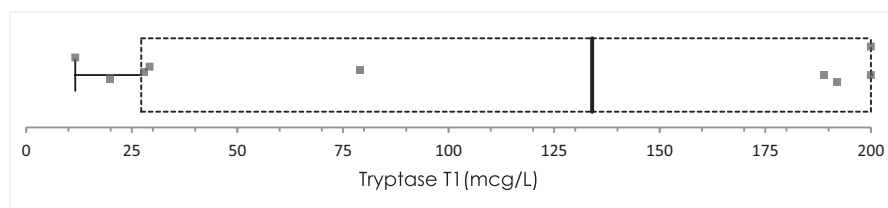


FIGURE 3 Tryptase results in Reactions Grade 3-5. Reaction Grade vs T1 tryptase. The scattergram represents all individual results. The black bar represents the median value, and the dotted indents represent the 95th confidence interval of the median. The solid line box represents the 25th and 75th centiles of the distribution, and the whiskers represent the maximum and minimum values. Where no confidence interval indent is shown, it is too large to plot

3.4 | Dynamic tryptase (DT)

Dynamic tryptase refers to the calculation of serial rises and falls in tryptase suggesting acute release within the reference range. 229 cases with ≥ 2 tryptase results enabled examination of the Dynamic Tryptase algorithm. DT postulates definitive acute tryptase release if the Tp exceeds ($T_b \times 1.2 + 2$) $\mu\text{g/L}$, even within reference ranges. DT detected an additional 37 (16%) cases where Tp $< 14 \mu\text{g/L}$ (99th centile reference limit; Table 3). DT was also useful at an 11.4 $\mu\text{g/L}$ (95th centile) threshold.

3.5 | Referrals to allergy clinics

A total of 190 (71%) of referrals were by the index anaesthetist, 45 by another anaesthetist (total 88% adherent), 17 by surgeons, 2 by GPs, 6 by others and 14 not specified. Panel graded 60% of referrals good, 19% good and poor, 9.5% poor and 11.6% unassessable. Use of referral proforma (AAGBI or other) was infrequent, many referrals failing to provide guideline-recommended information (Figure 6A-D).

Further information was needed from the anaesthetist on 22 (8%) occasions before clinic assessment and on 14 (5%) afterwards: this was provided in 21 and 9 cases.

4 | PERIOPERATIVE SPECIALIST ALLERGY CLINIC ASSESSMENT

4.1 | Quality of assessment in NCEPOD (National Confidential Enquiry into Patient Outcome and Death) urgent and expedited cases

4.1.1 | Delays in urgent treatment

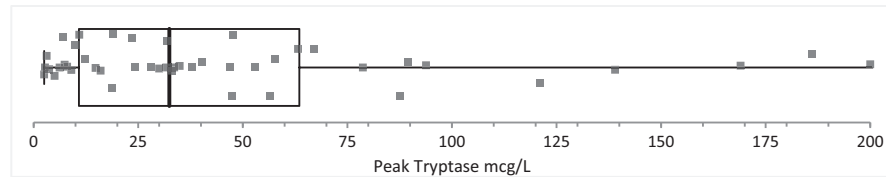
A total of 163 (61%) had delayed, modified or abandoned care overall. Delays were detrimental in 29 requiring urgent and 30 expedited surgery. This included 8 patients requiring urgent cancer surgery and 7 requiring non-urgent cancer surgery.

4.1.2 | Timeliness of assessment of urgent cases

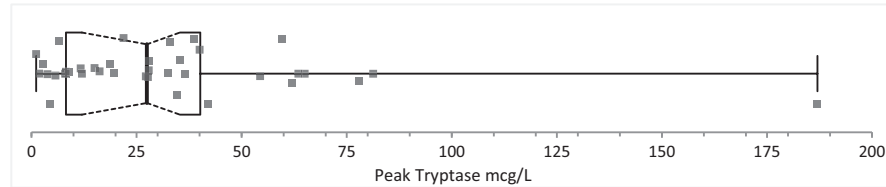
Urgent cases were not seen quickly. Eleven of 29 (38%) waited > 18 weeks. Allergy clinic conclusions were not received quickly. Median wait from referral to conclusions was 14 weeks (range 3-60 weeks) compared to 12.5 for non-urgent cases (Figure 7).

(A) Peak Tryptases (Tp)**Peak tryptase in samples taken at 0-5mins.**

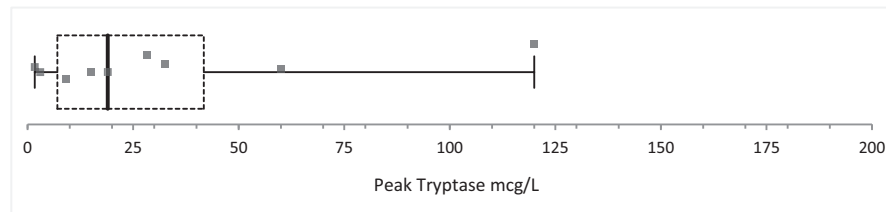
N = 46. Median 32.5 (95% CI 18.7-47.7), range 2.5-576.

**Peak tryptase in samples taken at 6-10 mins.**

N = 38. Median 27.5 (95% CI 12-35.3), range 1.1-187.

**Peak tryptase in samples taken at 11-15 mins.**

N = 9. Median 19 (95% CI 3-60), range 1.7-41.7.

**Peak tryptase in samples taken at 16-30 mins.**

N = 15. Median 34.1 (95% CI 10.1-64.2), range 7-81.8.

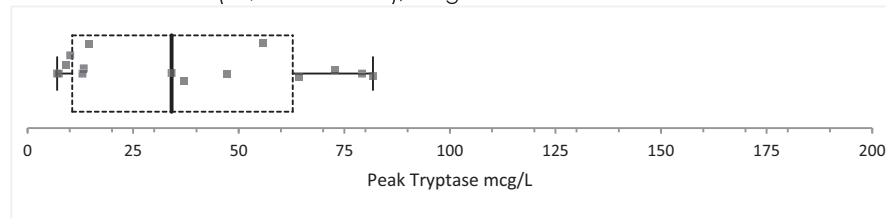


FIGURE 4 A, Immediate sampling is best to estimate the peak tryptase. B, Early-onset reactions tend to have higher tryptases. The scattergram represents all individual results. The black bar represents the median value, and the dotted indents represent the 95th confidence interval of the median. The solid line box represents the 25th and 75th centiles of the distribution, and the whiskers represent the maximum and minimum values. Where no confidence interval indent is shown, it is too large to plot

4.1.3 | Quality of urgent investigation (n = 29)

Even urgent cases had deficiencies in investigations, with missing culprits and incomplete investigation. Of 20 assessments reviewed, 2 were good, 12 good and poor and 6 poor. In 11 cases, the anaesthetist did not identify a suspect. The allergy clinic and panel-identified culprits in 25 (86%).

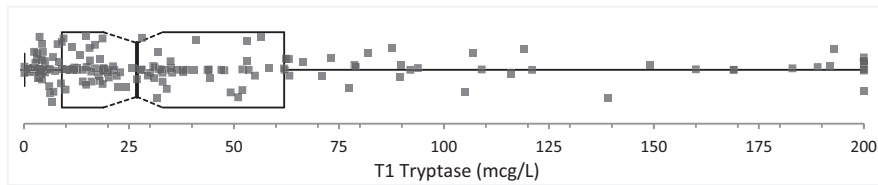
NMBA panels were inadequate in 55%, skin prick testing in 69% and intradermal testing in 76%. Forty-one had appropriate avoidance

advice and 66%-76% had appropriate letters to GP, patient and anaesthetist. Hazard warning advice was issued to 41%. 10 patients were still at potential risk after investigation: 7 from defective avoidance advice and 4 due to poor communication. Two anaesthetists received insufficient information to plan safe future anaesthetics.

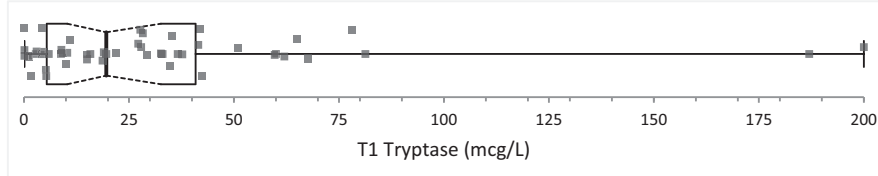
Few had investigated all potential culprits. Latex, opioids, chlorhexidine, gentamicin, ketamine, propofol, dexamethasone, midazolam, rocuronium and metronidazole were all omitted, and in 8, challenge testing was appropriate but not undertaken.

(B) First Tryptase (T1)**Rapidity of Onset <5 mins***

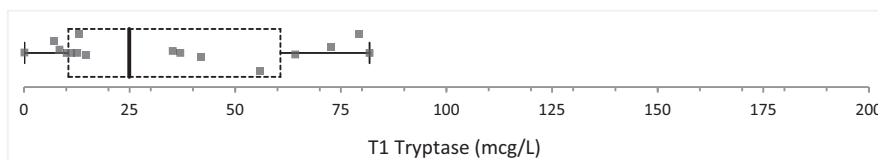
n = 165. Median 26.9, (95% CI 18.9-33)

**Rapidity of onset 5-15 minutes.**

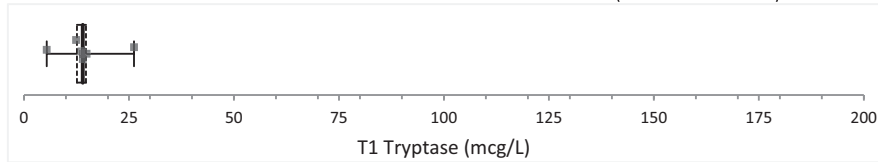
n = 51. Median 19.6, (95% CI 10.3-32.6)

**Rapidity of onset 15-30 minutes.**

n = 16. Median 24.9, (95% CI 10.1-64.2)

**Onset 30-60 minutes**

n = 7. Median 14, (95% CI 5.4-26.2)

**Onset 61-120 minutes**

n = 3 cases with T1 5.9, 11.5 and 6.3

Onset >120 minutes

n = 2 cases with T1 of 1.0 and 7.1

FIGURE 4 Continued**4.1.4 | Diagnostic concordance between clinic and panel for urgent cases**

In 12/29 (41%), the allergy clinic and the panel agreed the trigger. As a result of extended avoidance advice, the clinic safely advised avoidance of the panel-identified culprit in 20/29 (69%). The anaesthetist predicted the likely trigger in 15/20 (75%).

4.2 | Quality of assessment in NCEPOD non-urgent cases**4.2.1 | Timeliness of first clinic assessment**

About 23% breached the national UK 18-week target for first appointments (Figure 7). Only 39 (16%) were seen within the ideal 6 weeks. 7% waited longer than 6 months. Final clinic appointments occurred at a median of 24 weeks, range 3-54.

Eleven surviving patients were not referred to allergy clinics. Eighty-six of 266 (32%) had delays to non-urgent treatment. 22 (8%) had further surgery before clinic assessment. There was no

difference in further surgery or delay between the different diagnostic categories. Time from referral to receipt of allergy clinic conclusions was similar to urgent cases at a median wait 12.5 weeks (range 6-62; Figure 7).

4.3 | Quality: adherence to standards**4.3.1 | Overall guidance adherence**

Adherence was generally poor, in contrast to high self-reported adherence in the NAP6 Baseline Survey (Figure 6).¹ For AAGBI guidance 32% and BSACI guidance 17% were fully adherent; most non-adherence occurred through failing to test for potential culprits, deficiencies in communication with patients or healthcare staff. Twenty-six of 184 (14%) had minor omissions only.

4.3.2 | Written communication

Adherence to communication standards was much worse than the NAP6 baseline survey (Figure 6B). Provision of written information

to patients before clinic was rare, and information on patient support groups was only 25%. Written safe alternatives were identified in only 28% (74/266) and avoidance was provided to 63% (167/266).

4.3.3 | Hazard alert provision

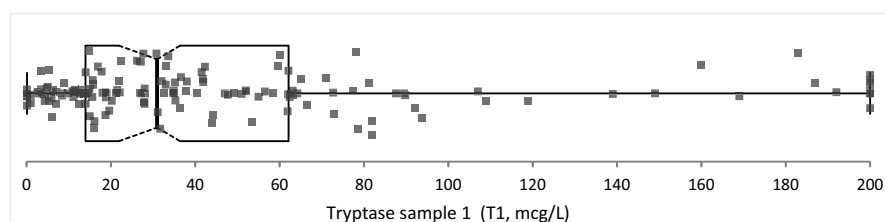
The NAP6 baseline survey suggested 95% of patients were issued alert information but only 21% were issued allergy alerts in NAP6; 14% by an anaesthetist and 7% by the clinic (Figure 6B).

4.4 | Testing strategies

Use of SPT and IDT were similar to the NAP6 baseline. Use of the NAP6 NMBA panel and latex was less than the baseline survey (Figure 6C). The appropriateness of the tests used was assessed (Figure 6D). Generally, the panels were not comprehensive and often missed potential culprits. Use of single tests (or tests to a single set of closely related agents only) was most common for suspected dye reaction and antibiotics. Forty potential drug culprits were omitted in the 184 reviewed cases (Material S6). Ondansetron, latex, chlorhexidine and fentanyl were the most frequently omitted.

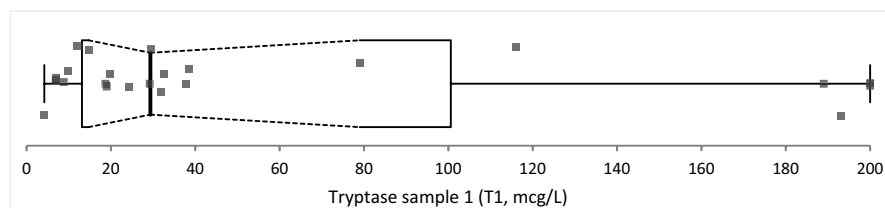
T1 in Panel-defined Allergic Anaphylaxis (positive IgE test confirming trigger or very high probability of allergic anaphylaxis where tests not possible/not positive)*

N = 138 Median 34.3, 95% CI 18.8-60.0



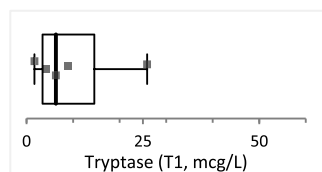
T1 panel-defined Non-Allergic Anaphylaxis (no confirmatory positive sIgE tests to the trigger)

n = 24 Median 29.4, 95% CI 14.7-79.0.



T1 in Panel-defined Non-Allergic Anaphylaxis (panel determined anaphylaxis was probably non-IgE mediated)

n = 6 cases, Range 1.7-24.9.



Panel-defined diagnosis uncertain (unable to determine)

n = 16 Median 6.6, 95% CI 1.4-30

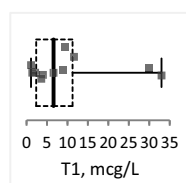


FIGURE 5 Tryptase results in panel-defined anaphylaxis with and without evidence of sensitisation to the trigger are not significantly different ($P > .05$). The scattergram represents all individual results. The black bar represents the median value, and the dotted indents represent the 95th confidence interval of the median. The solid line box represents the 25th and 75th centiles of the distribution, and the whiskers represent the maximum and minimum values. Where no confidence interval indent is shown, it is too large to plot

TABLE 3 The benefit of dynamic tryptase where Tp is within the reference range

Tp (peak tryptase) N = 229 with 2 or more tryptases	A: Number of Tp above or below	B: Cases without dynamic tryptase pattern	C: Cases detected by dynamic tryptase	Total positive cases (% of 229)
Tp $\geq$ 11.4	162	6 ^a	12	174 (76)
Tp $\geq$ 14	150	5 ^a	1	151 (66)
Tp <11.4	67	41	26	26 (11)
Tp <14	79	42	37	37 (16)

Lesson: best detection strategy is to use dynamic tryptase for any case where tryptase release is not obvious and the peak tryptase is below the upper limit of the reference range.

^aDynamic tryptase is most sensitive where Tp is in the reference range and can be false-negative when tryptases are high. Total cases detected: 200 (87%) using 95th centile vs 188 (82%) using a 99th centile reference range.

4.4.1 | NMBA

Where the NAP6 NMBA panel was not used, the most common combination was atracurium and rocuronium testing. Suxamethonium was the most common omission.

4.4.2 | Chlorhexidine

Routine use of chlorhexidine testing is less common than reported in the NAP6 baseline, only two-thirds of patients having even single modality testing.

4.4.3 | Latex

Only 31% were tested, mostly by sIgE blood tests. Only 1 weak latex IgE positive was seen, and only 1 of 12 SPT was positive.

4.4.4 | Multiple positivity to other agents

This was common (Material S7). No distinction is made between pre-event potential cross-reactive sensitization or primary occurrence of a second sensitization as we have no means of evidencing that supposition.

4.4.5 | Skin test concentrations

Ninety of 266 (34%) had IDT results reported; 135 (51%) SPT and 188 (71%) sIgE (Material S7). Little data on use of non-irritant concentrations were reported.

4.4.6 | Specific IgE (sIgE) blood tests

A limited range of the available sIgE tests was used including chlorhexidine, penicillins and latex. Few centres reported use of thiocholine (suxamethonium) or morphine/pholcodine testing. Local anaesthetic and latex sIgE were occasionally performed. Chlorhexidine and penicillin sIgE were frequently positive. Many potentially relevant sIgE tests were not used at all in NAP6 (Material S6).

Pholcodine exposure is rarely queried or recorded in UK practice in line with the baseline survey. Eighty-seven 266 (33%) reported no exposure. Pholcodine or morphine (quaternary ammonium groups) was only tested in 4.

4.4.7 | Challenge testing

Twenty-four cases reported the results of challenges (Material S8). In 10 of these, the panel thought the challenges were incomplete (missing relevant drugs) or inappropriate (in at least one case potentially exposing a patient to an unnecessary risk).

4.4.8 | Future risk estimates

Many patients were thought to remain at potential risk after clinic investigation for various reasons, most often because potential culprits had been omitted or not excluded satisfactorily. Some had ambiguous or absent avoidance advice and there was evidence of many defects in patient and clinic correspondence, particularly with regard to details of investigations. Four percent were still at risk from inadequate allergy referral, 38% were still at risk from inadequate clinic investigation and 76% were still at risk from inappropriate clinic advice. In addition, 17% were still at risk from inadequate communication with the patient and 23% were still at risk from inadequate communication with the healthcare team.

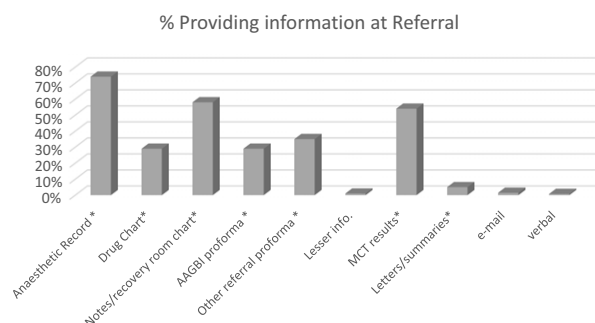
4.4.9 | Accuracy of diagnosis

There was good concordance between the clinic and the panel diagnoses. Most lack of concordance between clinic and panel was for ondansetron, teicoplanin, atracurium. Seven cases had 2 culprits that were equally probable. 88% of cases identified the same trigger in the clinic and the panel. 74% were correctly predicted by the anaesthetist; Clinic, panel and anaesthetist agreed in 65.5%, Clinic and panel agreed in 22.5%, anaesthetist and panel *but not clinic* agreed in 8.5%, anaesthetist and clinic *but not panel* agreed in 3.5%.

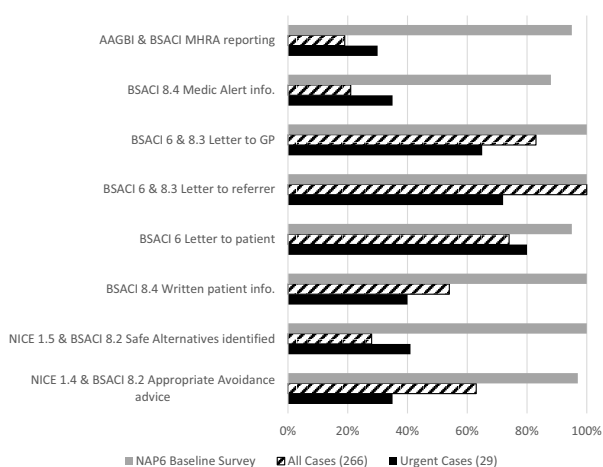
4.5 | Overall quality of allergy clinic assessment

The panel noted that all potential culprits had been adequately investigated in only 27%. Fifty-four per cent of assessments were good (9.5%) or good and poor (45%); 37% were judged poor. Most deficiencies were failing to test for all potential culprits, failure to MHRA report or poor communication with the patient or healthcare staff. Harm to the patient was rare.

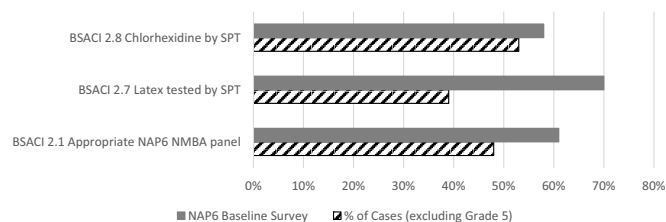
Twenty-five (9%) anaesthetists did not feel that the clinic provided enough information to plan future anaesthesia. Twelve (4.5%) had low confidence in the diagnosis. Four specifically noted no trigger was identified, 5 did not get clear alternative drugs to use, 5 noted poor communication of results or avoidance advice. Four had delayed investigation or challenge testing, one waiting over a year.

(A) Information provided at referral**(B) Adherence to Guideline Communication Standards**

Adherence to Guideline communication standards

**(C) Adherence to Guideline Test Standards**

Guideline Adherence to standards for Tests



Guidelines are referenced according to the numbering of the NAP6 baseline paper – see Supplementary material

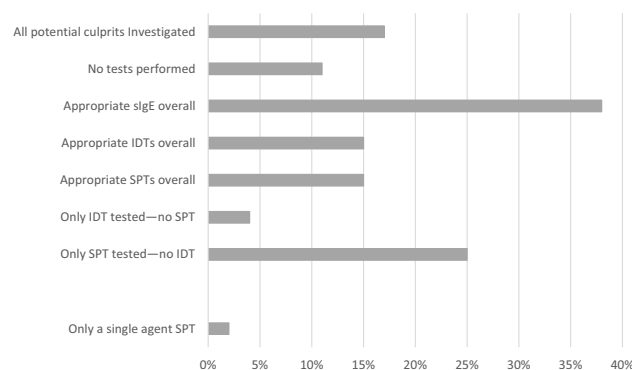
(D) Tests used in Allergy Clinic Assessment (BSACI 4.1 & 4.2)

FIGURE 6 Guideline adherence. A, Information provided at referral. B, Adherence to guideline communication standards. C, Adherence to guideline test standards. Guidelines are referenced according to the numbering of the NAP6 baseline paper—see Supporting Information Material. D, Tests used in allergy clinic assessment (BSACI 4.1 & 4.2)

4.5.1 | Avoidable causal factors were identified in a few cases

Only 3 events were judged avoidable. There were few incidences of failed risk factor identification in preoperative history taking (3), recording or ignoring of relevant information in pre-intervention allergy history (6), previous reaction (3) or possible cross-reactivity (3). These included administration of diclofenac to a NSAID-sensitive individual, chlorhexidine or penicillin to an allergic patient and likely unnecessary coadministration of both co-amoxiclav and teicoplanin.

4.6 | MHRA

Only 21% of 266 cases were reported to the MHRA, in contrast to 80% who reported to the local incident system (Material S9).

5 | DISCUSSION

Eighty-five per cent of those with an identified trigger had evidence of an IgE-mediated reaction on skin or blood testing. Most referrals were

by anaesthetists and were consistent with BSACI²⁴ and AAGBI²² guidelines, but provision of information to the clinic was suboptimal.

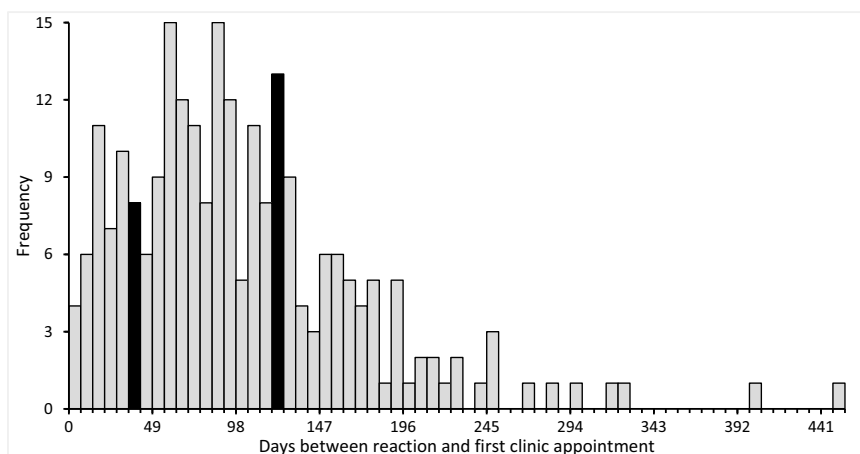
Clinics were unable to make timely assessments for most cases. Patients were rarely seen at 6 weeks and the excessive waiting times noted in the baseline clinic survey were confirmed. Delay in treatment was common for both urgent and non-urgent cases and underlined the need for better service provision and rapid referral protocols. No reliable distinction between allergic and non-allergic aetiologies can be made on the basis of skin or blood testing in delayed assessments, as skin testing and sIgE can become negative with time. There were no obvious differences between the clinical phenotypes, the triggers, the tryptase results or the outcomes for the patient labelled allergic or non-allergic anaphylaxis.

Approximately 400-600 Grade 3-5 cases are expected annually in the UK, similar to previously reported estimates³⁻⁶ and the NAP6 baseline survey.¹ NAP6 received 266 completed and interpretable 2-part reports from the UK. This suggests some under-reporting.^{3,25}

Tryptase sample timing was often suboptimal, sometimes too late to estimate peak tryptase. NAP6 data shows rapid falls within 30 minutes and support BSACI and AAGBI Guidelines (1st sample immediately post-reaction, 2nd at 1-2 hours, plus a 24-hour

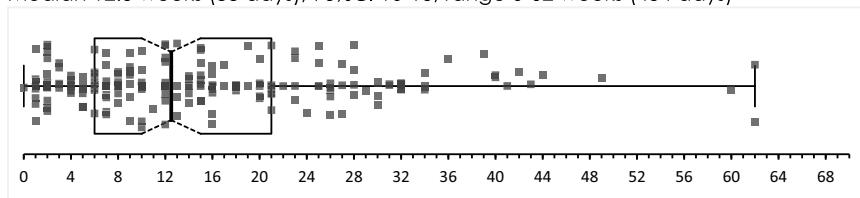
(A) Weeks from referral to first clinic visit (6 week ideal interval and 18 week NHS target in black)

Median 90(12.5 weeks), minimum 1 to max 450 days



(B) Days from referral to receipt of allergy clinic diagnosis by anaesthetist

Median 12.5 weeks (88 days), 95%CI 10-15, range 0-62 weeks (434 days)



(C) Time from referral to first clinic visit for NCEPOD Urgent cases

Median 14 weeks, minimum 42 to max 460 days

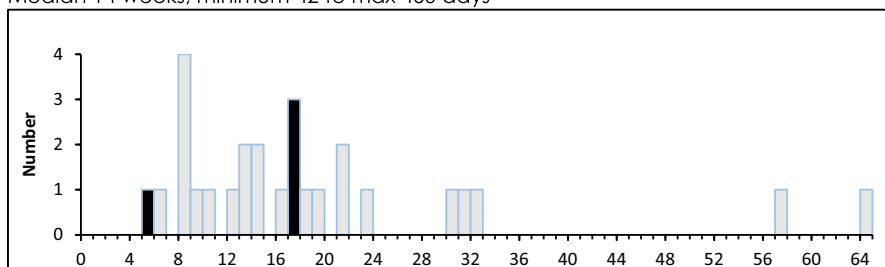


FIGURE 7 Time to first allergy clinic assessment for all cases. A, Weeks from referral to first clinic visit (6 wk ideal interval and 18 wk NHS target in black). B, Days from referral to receipt of allergy clinic diagnosis by anaesthetist. C, Time from referral to first clinic visit for NCEPOD Urgent cases. Black column represent 6 wk (the optimum interval to assessment in the allergy clinic) and 18 wk (the maximum wait until first appointment target in the UK health service). The scattergram represents all individual results. The black bar represents the median value, and the dotted indents represent the 95th confidence interval of the median. The solid line box represents the 25th and 75th centiles of the distribution, and the whiskers represent the maximum and minimum values. Where no confidence interval indent is shown, it is too large to plot

baseline.^{20,24} Second samples within 6 hours can still be informative (ANZAAG guidelines suggest 1-, 4- and 24-hour samples).^{2,14}

Ten per cent had elevated baseline tryptase suggesting mastocytosis or raised alpha tryptase due to gene duplication now sometimes referred to as hyper-alpha tryptasaemia syndrome (HATS).²⁶ It is impossible to verify that these are truly raised, due to the variation in baseline sampling and lack of follow-up samples. No patient was reported to have had known mastocytosis, and the significance of the single patient with an apparent baseline tryptase of 159 mg/L is unknown. Sample mislabelling is known to be common and an equally likely explanation.

Basal tryptase levels did not correlate with severity or grade of reactions, unlike the weak correlation in venom anaphylaxis.¹³ Where resuscitation interferes with timely sampling, prompt liaison with the laboratory to retrieve acute biochemistry or

haematology samples may be a practical alternative: serum or plasma is satisfactory. Tests can be performed on very low volumes. Pre-procedure samples also provide effective baseline levels.

Median Tp/T1 results by reaction grade were similar to those previously reported.³ Higher values appeared to be more strongly linked to rapidity of onset than trigger. Anaesthetists often overlooked chlorhexidine as a cause in NAP6. Anaesthetists predicted the culprit correctly in 3 of 4 cases. The closest temporal administration is a good guide to causation, except for chlorhexidine, latex, atracurium and patent blue where later reactions occur.

Case series have demonstrated that the Dynamic Tryptase algorithm can detect possible release more sensitively than thresholds.^{3,10} In NAP6, DT assessments increased detection of acute release and should be used when the Tp is within the reference range.

Guideline adherence regarding investigation was generally poor and lower than the NAP6 Baseline survey with 32% fully adherent to AAGBI but only 17% to BSACI guidance. Use of skin, blood and challenge testing appears suboptimal even when available. Use of extended NMBA panels is effective in selecting safe alternative agents.^{27,28} Few centres are using an extended panel despite high adherence reported in the baseline survey.

Revised guidelines should specify minimum and clear test sets that all services can use in screening for sensitization and cross-reactivity, including specific concentrations and modalities. SPT and IDT do not give the same results for all triggers. The clinic must identify safe alternatives where multiple NMBA test positive. It is difficult to know what to do with multiple positive IDT, particularly as false positives do occur.^{27–30}

Pan-reactivity across related drugs occurs but is not always clinically relevant, there are reports of patients tolerating drugs with positive tests. Risk assessment is difficult and the presumption to avoid is sensible, but necessitates the provision of a clear alternative plan—either for method of anaesthesia or specific safe drugs. The NAP6 panel recommends that involvement of an anaesthetist in all clinic assessments is essential for this.

Few reporters (42%) were able to provide interpretable details of the skin test concentrations used. Specialist centres should use consensus or locally derived threshold non-irritant doses as provided in guidelines.²⁴ Maximum non-irritant concentrations (NIC) need to be identified for novel drugs with increasing usage. This survey was unable to determine whether non-irritant concentrations were being used in all clinics as the concentrations used for every test were reported only in a minority of cases.

Importantly, multiple positivity is common in the UK cohort in both skin testing and sIgE tests implies at least a possibility that multiple triggers are involved in some cases, including those where a single culprit could not be identified. Future research and guidance are needed. Some appear to be the well-recognized cross-reactivity within NMBA, but others represent true multiple sensitization that can only be revealed and considered by extended panel testing to all potential triggers.

Multiple positivity to other agents was common in IDT, SPT and less so for sIgE testing (Material S6). This confirms previous observations in UK cohort.¹⁸ The NAP6 data set extends this observation of multiple positivity to cases of teicoplanin, rocuronium and suxamethonium allergy. This has implications for order and modality of testing, the need to test for all potential culprits and critical appraisal of the imputability of each potential trigger.

Latex is not a cause of perioperative anaphylaxis in NAP6, unlike chlorhexidine. Latex allergy has been falling in France since the late 1990's.³¹ Latex-free theatres and hospitals are now common in the UK and new sensitizations unlikely.

Normal clinical diagnosis is a Bayesian process, the NAP6 panel diagnosis mimics and strengthens this approach by utilizing a methodology that ensures a consensus of multiple experts via independent structured reviews of the evidence. The NAP6 panel

diagnosis and the clinic diagnosis agreed more frequently than published for the best Bayesian methods in general drug allergy.^{20,32} The ability to recognize the culprit may be assisted by the rapid presentation of perioperative reactions.

Excessive avoidance advice may also be harmful. Failure to offer appropriate IDT and challenge testing resulted in inappropriate avoidance in some cases. Inappropriate avoidance advice because of a low probability of penicillin allergy (not confirmed on clinic evaluation) was a problem and resulted in reactions to teicoplanin.³³ Use of teicoplanin as a penicillin substitute is increasing; proper pre-procedure evaluation for true penicillin allergy may reduce this. If penicillin avoidance advice is given, specific advice should also be given on safe alternatives.

MHRA reporting was poorer than the baseline survey. Reporting through the index anaesthetist (AAGBI guideline) is problematic if identification of culprit may change. BSACI expects the allergy clinic to report, but risks duplicate reporting of differing conclusions. Ensuring MHRA report ID is provided in clinic letters, or nominating a departmental anaesthetist to report after final clinic assessment is potential solutions.

Comprehensive and safe future avoidance advice was often lacking, perhaps due to inadequate communication or detail in the correspondence or conclusions issued by the clinic.

Allergen challenge testing is the ultimate arbiter of tolerability, but is problematic in perioperative investigations. There were few challenges reported in NAP6, mostly to oral penicillins or intravenous teicoplanin. Three of four teicoplanin challenges were positive. NMBA challenges are rarely done in the UK, although are performed in Denmark (where NMBA allergy is rare, and the risks may be different).

Alternatively, challenge tolerance to alternative drugs can be established to facilitate other anaesthetic approaches. This was used by some centres. In conclusion, NAP6 shows that adherence to existing guidelines is poor and confirms deficiencies in service availability, capacity, harmonization of investigation and reporting.

The main areas for improvement are

- Improved access to services in a timely manner.
- Reduced waiting times to meet the ideal of 6–8 weeks post-reaction.
- No patient should have to undergo non-urgent surgery without a completed allergy clinic assessment.
- Harmonization of use of testing and imputability assessment.
- Improved communication of diagnosis and clear safe instructions for future safe anaesthesia, with involvement of anaesthetists in clinic activities to achieve this.
- All potential culprits should be tested by all relevant test modalities (SPT, IDT, sIgE and where appropriate challenge testing) as modalities are not always concordant.

- More data on the predictive values of different modes of testing using standardized methods are required for all triggers.
- Clarity and unambiguity of guideline recommendations are essential.
- Better standardized clinic reports should be developed to encourage reporting of all the relevant information to include, drugs identified, type of reaction, drugs to avoid, safe alternatives, tests used and results: to both anaesthetists, general practitioners and patients (Material S10).
- Outcomes of these urgent investigations should be clearly and reliably communicated to the anaesthetist.
- This study describes summary findings from NAP6 and the NAP6 recommendations (Material S11).

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CONFLICT OF INTEREST

TMC: is an associate editor of the British Journal of Anaesthesia. He is not aware of any financial conflicts. The remaining authors have no conflict of interests to declare.

AUTHORS CONTRIBUTIONS

WE contributed to design and methodology of the study, analysed the results and wrote all drafts of the manuscript and the final draft. TMC contributed to design and methodology of the study, analysed the results, and reviewed and revised early drafts of the manuscript and the final draft. TG contributed to design and methodology of the study, analysed the results, and reviewed and revised early drafts of the manuscript and the final draft. NH contributed to design and methodology of the study, analysed the results, and reviewed and revised early drafts of the manuscript and the final draft. LF contributed to design and methodology of the study, administered the study and took part in review of draft manuscript leading to

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

ETHICAL STATEMENT

"The NAP6 project was approved by Confidentiality Advisory Committee of the NHS Health Research Authority (HRA), National and Local Caldicott Scrutiny Process in Scotland and Privacy Advisory Committee for Northern Ireland. The Confidential Advisory Committee deals with approvals for the handling of patient-identifiable information across the NHS. If such information is required, then approvals are required under Section 251 of its governance procedures. As no patient-identifiable information was used, no section 251 application was necessary. The National Research Ethics Service (NRES) confirmed it to be a service evaluation, not requiring formal ethical approval. The project received the endorsement of all 4 Chief Medical Officers of the UK."

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 33. Marinho S, Kemp H, Cook TM, et al. A cross sectional study of Perioperative drug and allergen exposure in United Kingdom practice in 2016: the NAP6 Allergen Survey. *Br J Anaesth*. 2018. In press.

SUPPORTING INFORMATION

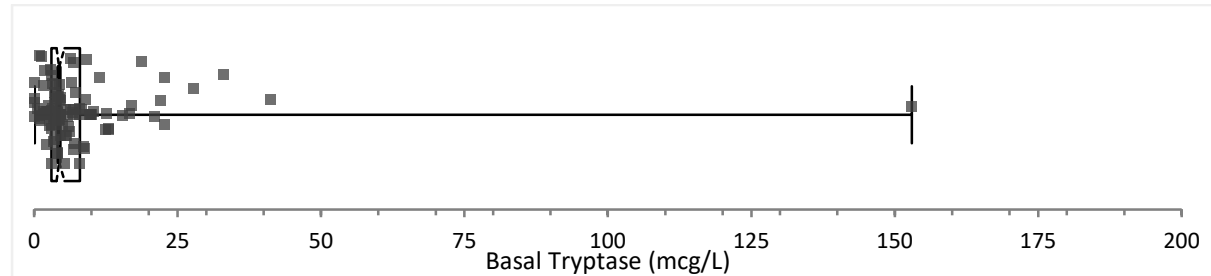
Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Egner W, Cook TM, Garcez T, et al. Specialist perioperative allergy clinic services in the UK 2018: Results from the Royal College of Anaesthetists Sixth National Audit Project (NAP6) investigation of perioperative anaphylaxis. *Clin Exp Allergy*. 2018;48:846–861. <https://doi.org/10.1111/cea.13180>

Supplementary Material A: Basal tryptase results by grade of reaction

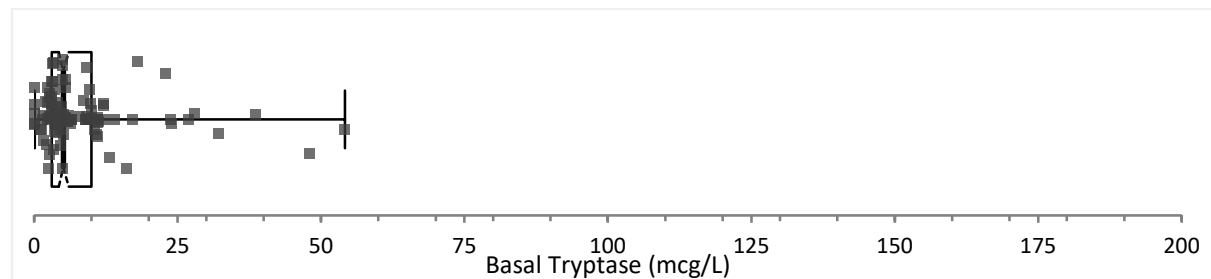
Grade 3 reactions: Basal Tryptase

Median 4, 95%CI 4.3-6 mcg/L



Grade 4 reactions: Basal Tryptase

Median 5, 95%CI 3.9-5.3 mcg/L



Key: Dots represent individual measurements. Black bar is the median and the box the 25th and 75th centiles. Dotted indents represent the 95% confidence intervals of median. Horizontal bar = max-minimum range.

Cases with one tryptase measurement only

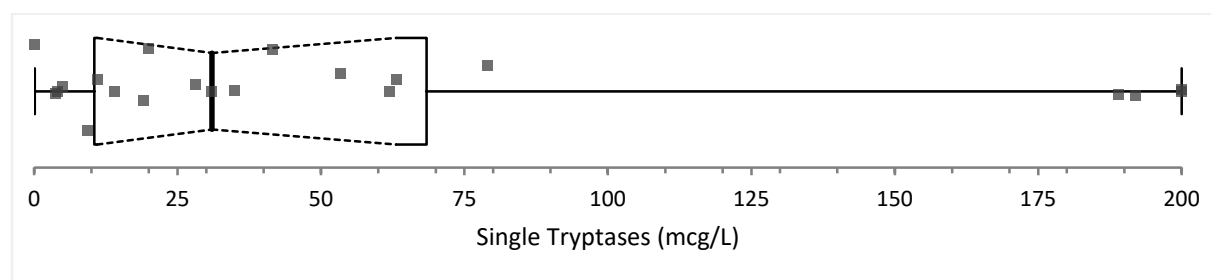


Figure legend

The scattergram represents all individual results. The black bar represents the median value and the dotted indents represent the 95th confidence interval of the median. The solid line box represents the 25th and 75th centiles of the distribution and the whiskers represent the maximum and minimum values. Where no confidence interval indent is shown, it is too large to plot.

Supplementary Material B: Correlation Between Panel Consensus Trigger And Tp Tryptase Levels

Consensus Trigger	N with Tp/total	Grades 3:4:5	Tp median (mcg/L)	95% CI (mcg/L)
Co-Amoxiclav	40/46	21:18:1	34.7	21.2-52.0
Teicoplanin	28/36	15:13:0	32.0	19-63.1
All muscle relaxants (Sux, Roc, Atrac, Miv)^	49/65	24:25:0	31.9	15.7-41.9
Suxamethonium	10/13	7:3:0	67.6	22.3-93.8
Rocuronium	23/27	16:4:3	36.4	15.7-56.5
Atracurium	18/23	9:10:0	11.5 ^{\$}	4.2-41.9
Patent Blue	8/10	5:3:0	24.2	5.9-40
Chlorhexidine	14/18	8:6:0	16.5 ^{\$}	13-26.2

Table B Legend

*Lower chlorhexidine and atracurium Tp, and higher Suxamethonium Tp are not due to differences in grade balance of cases.

\$ Statistics on differences are presented in the methods section.

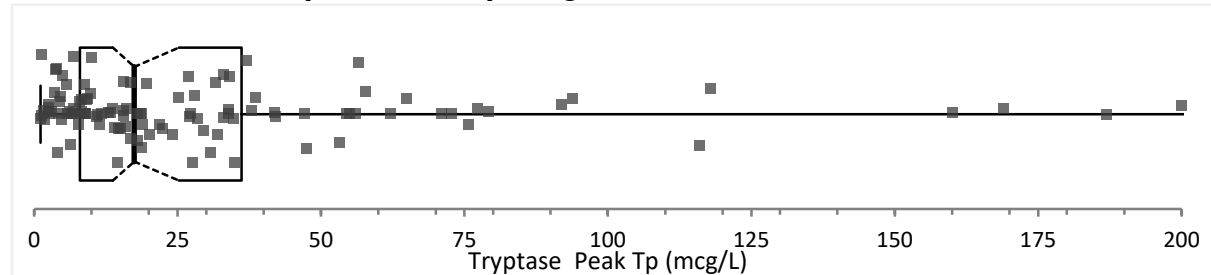
^1 sugammadex definite trigger had a Tp of 81 mcg/L (not included)

Supplementary Material C: Reaction grade Vs. Peak Tryptase

Reaction grade Vs. Peak Tryptase*

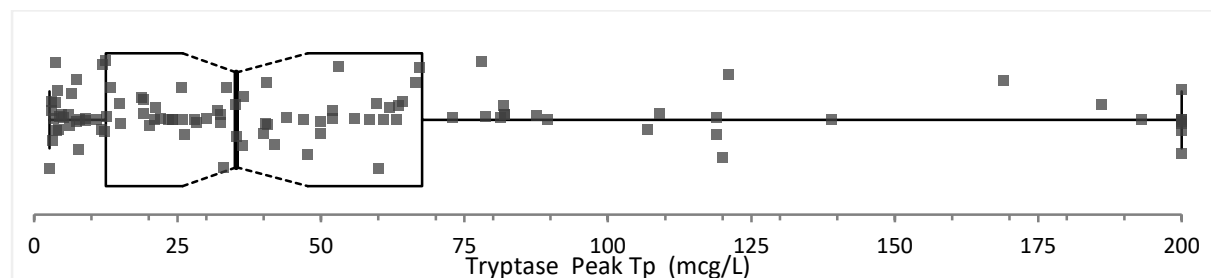
Grade 3 reactions

N=116. Median 17.5 (95%CI 14-25), range 1.1-576.



Reaction Grade 4

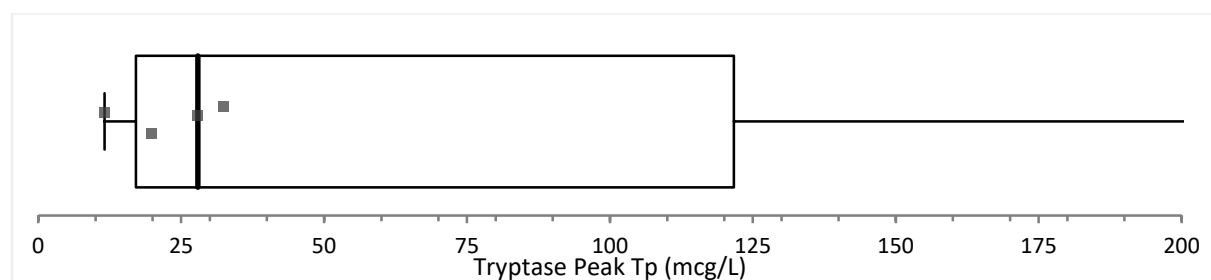
n=106. Median 35.3 (95%CI 26-48), Range 2.7-200.



Reaction Grade 5

N=5. Median 11.6 (95%CI n/a), range 11.6-300.

***Peak tryptase can only be estimated where 2 or more samples are available.**

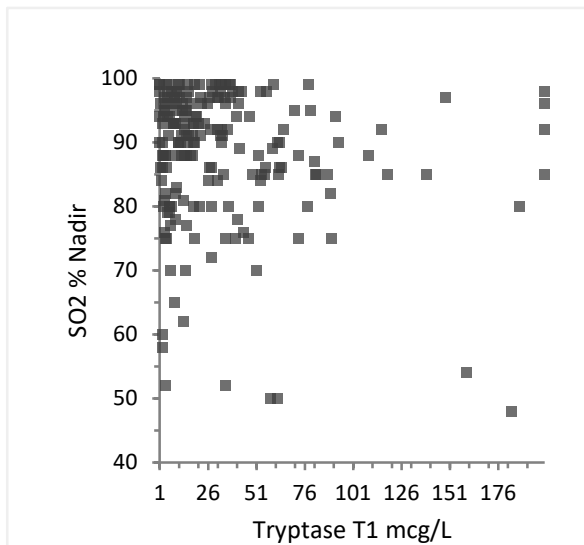


Legend

The scattergram represents all individual results. The black bar represents the median value and the dotted indents represent the 95th confidence interval of the median. The solid line box represents the 25th and 75th centiles of the distribution and the whiskers represent the maximum and minimum values. Where no confidence interval indent is shown, it is too large to plot.

Supplementary Material D Tryptase levels do not correlate with severity indices

Lowest SO2 Vs. T1



Lowest systolic Blood Pressure Vs. T1

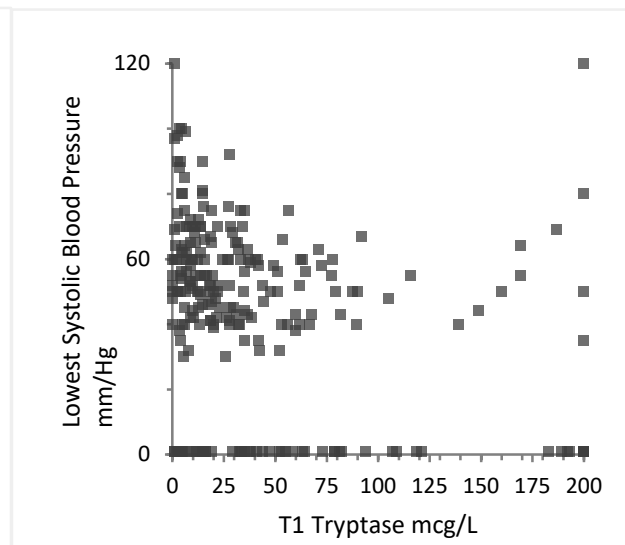
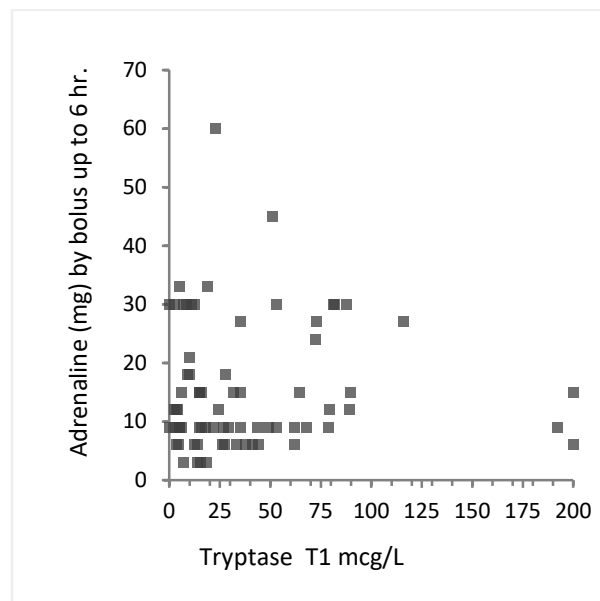


Fig 7cTotal dose (mg) IV adrenaline Vs. T1



Supplementary Material E

Time (mins) to onset for Panel Consensus Trigger: Later onset cases have lower median tryptases

Trigger	Median TpTryptase (mcg/L)	Onset 0-5 mins	6-10 mins	11-15 mins	16-30 mins	31-60 mins	61-120 mins	>120 mins
Chlorhexidine	16.5	7	3		3	4		1
Atracurium	11.5	15	2	3	2			1
Patent blue	24.2	2	2	1	1	1	2	
Co-amoxiclav	34.7	33	8	4	1			
Teicoplanin	32.0	23	7	2				
Rocuronium	36.4	26	1					
Suxamethonium	67.6	13	1					

Supplementary Material F

Potentially relevant sIgE tests not used in NAP6

There was no evidence that potentially relevant sIgE that are currently available were used for the following agents: polylysine, iodine, clindamycin, ciprofloxacin, cefuroxime, cephalosporin, cephalexin, cloxacillin, diazepam, atropine, metronidazole, lecithin, piroxicam, marcaine, rifampicin, diclofenac, indomethacin, naproxen, procaine, bupivacaine, ibuprofen, aminoglycosidase mix, streptomycin, chymopapain, doxycycline, acetyl salicylic acid, macrolide mix, sulfamethoxazole, lignocaine, mepivacaine, prilocaine, trimethoprim, thiopentone, prednisolone, pyrazolone, phenacetin, furosemide, tetracycline, erythromycin and methylene blue.

Forty other drugs were also identified as potential culprits whose investigations were not done or not completed.

Atropine, basilixumab, betadine, brufen, ceftriaxone, cefuroxime, Chloramphenicol, clonidine, cyclizine, diamorphine, dexamethasone, Enoxaparin, ergometrine, fentanyl, flucloxacillin, gabapentin, gentamicin, glycopyrrolate, hydrocortisone, lidocaine, Ketamine, latex, levobupivacaine, methylprednisolone, metronidazole, midazolam, mitomycin, neostigmine, non-steroidal anti-inflammatory drugs, ondansetron, paracetamol, parecoxib, povidone iodine, prochlorperazine, propofol, ranitidine, rocuronium, remifentanyl, teicoplanin, thiopental, tranexamic acid, vecuronium.

Supplementary Material G: Multiple Sensitisations Are Common In The UK Cohort, not all are NMBA cross-reactivity

Culprit	SPT pos to other agents/No. tested to other agents	IDT pos to other agents/No. tested to other agents	slgE pos to other agents/No. tested to other agents
Chlorhexidine	1equivocal to latex	1 positive to atracurium, vecuronium, rocuronium, tranexamic acid and fentanyl. Negative to suxamethonium	1 positive to penicillins (V,G, ampicilloyl, amoxicilloyl)
	1 equivocal to povidone iodine		
Teicoplanin	1 positive to tazocin & amoxicillin	1 equivocal to all agents but teicoplanin, 1 equivocal chlorhexidine, 1 equivocal to gentamycin	
	1 positive PPL and MDM penicillin determinants	1 positive to gentamycin	
	1 positive to atracurium	1 positive to ketamine	
	1 positive to atracurium		
Rocuronium	1 positive to vecuronium and pancuronium and suxamethonium	1 positive to atracurium, vecuronium, chlorhexidine, ondansetron but negative for suxamethonium	1 positive to chlorhexidine
	1 positive to pancuronium and suxamethonium	1positive to atracurium	
	1 positive to vecuronium	1 positive to suxamethonium, atracurium, Vecuronium	
	1 positive to suxamethonium	1 positive pancuronium, atracurium, mivacurium and negative to suxamethonium and vecuronium	
	1 equivocal to chlorhexidine	1 equivocal to alfentanyl	
	1 equivocal to vecuronium	1equivocal to gentamycin and propofol	
	1 equivocal to chlorhexidine	1 positive to pancuronium, Vecuronium and cisatracurium. Negative to suxamethonium and atracurium	
	1 equivocal to propofol and fentanyl	1 positive to atracurium, mivacurium and Vecuronium. Negative to suxamethonium and pancuronium	
	1 equivocal to cisatracurium and suxamethonium		
Suxameth-onium	1 positive to rocuronium and suxamethonium (no other NMBA done)	1 positive to rocuronium plus atracurium	1 positive to chlorhexidine and suxamethonium
	1 positive to vecuronium and suxamethonium only	1 positive to Rocuronium plus vecuronium	
	1 positive to All NMBA plus chlorhexidine		
	1 positive to cisatracurium, chlorhexidine, atracurium, Vecuronium but not pancuronium, mivacurium or rocuronium.		
	1 positive to atracurium and suxamethonium negative		

Supplementary Material H Challenge Test Results

	Drug - Final Dose	Units	Allergy clinic Challenge test results
Amoxicillin	500	mg	Negative
Amoxicillin			Negative
Amoxicillin	50	mg	Negative
Amoxicillin	500	mg	Negative
Amoxicillin	250	mg	Negative
Amoxicillin oral	250mg	mg	Negative
Bupivacaine			Negative
Bupivacaine	5	mg	Negative
Bupivacaine 0.25%	1.25	mg	Negative
Celecoxib oral	100mg	mg	Negative
Co-Amoxiclav oral			Negative
Fentanyl	5	mcg	Negative
Lignocaine	5		Negative
Lignocaine 1%			Negative
Lignocaine 1%			Negative
Methylprednisolone	30	mg	Negative
Metronidazole oral	400	mg	Negative
Ondansetron			Negative
Teicoplanin	4,40,80,280	mg	Negative
Vancomycin			Negative
Ibuprofen	300	mg	Positive
Teicoplanin	0.2	mg	Positive
Teicoplanin			Positive
Teicoplanin	20	mg	Positive

Supplementary Material I

Reporting of Events to MHRA and Local Incident Reports

Number	Index Anaesthetist	Another Anaesthetist	Allergy Clinic	Surgical team	Theatre Staff	Unknown	Pharmacist
MHRA (21% reported)	19	15	3	0	0	0	2
Local Datix (80% reported)	109	13	0	2	2	2	0

Supplementary Material J

Recommended Content of Standard Allergy Clinic Letter Following Assessment for Perioperative Anaphylaxis

TYPE OF EVENT	Allergic Anaphylaxis/Non-Allergic Anaphylaxis/not an allergic event Description of event detailing exposures	
CAUSE OF EVENT	Culprits identified	List definite culprits
	Culprits identified	List probable culprits
	Culprits identified	List possible culprits
	In non-allergic events	Describe cause, future risk and recommendations
	Drugs administered which are unlikely to be culprits	List
	Continued harm from event	e.g. new anxiety, a change in mood, impaired memory, impaired coordination, impaired mobility, symptoms of PTSD, myocardial damage, heart failure and new renal impairment
INVESTIGATIONS	Positive tests used skin prick	List with concentrations
	Negative tests used skin prick	List with concentrations
	Positive tests used Intradermal	List with concentrations
	Negative tests used Intradermal	List with concentrations
	Positive sIgE tests	List with results
	Negative sIgE tests	List
	Total IgE	Result
	Summary of tryptase results	Dated and timed results
	Challenge test results	List, total dose and route of administration
AVOIDANCE	Drugs/Substances to avoid: Definite	List
	Drugs/Substances to avoid: Probable	List
	Cross reactivity with other drugs requiring avoidance	List
SAFE ALTERNATIVES	Identified Safe alternatives for each culprit	List
	If no clear culprits identified	Clear statement on future risk and suitable drugs for future use based on a risk assessment
COMMUNICATION	Copy letter to patient, referring physician/surgeon and GP	Confirmed in letter
	Hazard warning	Advised/not advised
	Statement on MHRA reporting	Reported/ Not reported by clinic with MHRA reference number
	Additional written information issued	Yes/no and specify content/type/source

Supplementary Material K

NAP6 RECOMMENDATIONS 030218

DEPARTMENTAL ORGANISATION & IMMEDIATE MANAGEMENT

National

1. There is a pressing need for investment in and expansion of specialised perioperative allergy clinic services, to ensure prompt investigation of urgent cases and that no patient with suspected perioperative anaphylaxis has non-urgent surgery without a timely allergy clinic assessment. This applies to both adult and paediatric services.
2. 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.
3. 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

4. Procedures should be in place to ensure that an appropriate patient allergy history is sought and recorded before anaesthesia is administered.
5. 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.
6. 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.
7. 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.
8. Clinical Directors of anaesthetic departments should ensure their anaesthetists have been trained in the management of perioperative anaphylaxis.
9. Perioperative anaphylaxis guidelines and/or a management algorithm should be immediately available wherever anaesthesia is administered.

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

Individual

15. All anaesthetists responsible for perioperative care should be trained in recognition and management of perioperative anaphylaxis and relevant local arrangements.
16. Adrenaline is the primary treatment of anaphylaxis and should be administered immediately anaphylaxis is suspected. In the perioperative setting this will usually be IV.
17. Where a critical perioperative hypotensive event occurs, and perioperative anaphylaxis is one of several differential diagnoses, treatment for anaphylaxis should start promptly as there is little to be lost and much to be gained.
18. If IV access is not immediately available intramuscular or interosseous routes should be used promptly, until IV access is established.

19. A rapid IV crystalloid (not colloid) fluid challenge of 20ml/kg should be given immediately. This should be repeated several times if necessary.
20. 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.
21. If an IV colloid is being administered at the time of the anaphylactic event, it should be discontinued, and the IV administration set replaced.
22. Administration of IV vasopressin 2 Units, repeated as necessary, should be considered when hypotension due to perioperative anaphylaxis is refractory
23. During perioperative anaphylaxis in patients taking beta blockers early administration of IV glucagon 1 mg should be considered, repeated as necessary.
24. 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.
25. A corticosteroid should be administered as part of resuscitation of perioperative anaphylaxis.
26. 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.
27. 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
28. 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.
29. Where a trainee refers a patient to an allergy clinic the contact details of a consultant anaesthetist should be included in the referral.
30. If there is a need for urgent referral, the anaesthetist should phone the allergy clinic for advice, as well as making a written referral.

31. Where perioperative anaphylaxis has led to deferment of urgent surgery, alternative anaesthesia should be feasible by following simple rules

Research

32. There remains uncertainty about the benefits or potential harm of administering antihistamine drugs during resuscitation of perioperative anaphylaxis. Clinical trials would provide valuable evidence.
33. 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

34. 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.
35. Following a peri-operative anaphylactic event and before discharge from hospital the patient should be provided with a letter from their anaesthetist. The *NAP6 template patient letter content* is in Supplementary Material K. This letter should be in addition to the discharge summary and a copy should be sent directly to the patient's GP.
36. The practice of NHS drug allergy clinics should be standardised so that patients and commissioners can expect a consistent service. This would be best addressed as part of IQAS [Improving Quality in Allergy Services] accreditation.

Individual

37. Clinicians in allergy clinics could usefully reassure patients that allergic reactions happen unpredictably, and that the anaphylaxis was not the anaesthetists 'fault'.

Research

38. 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.

CLINICAL FEATURES

Institutional

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

Individual

40. 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.
41. 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.
42. 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
43. During perioperative anaphylaxis in patients taking beta blockers early administration of IV glucagon 1mg should be considered, repeated as necessary.

Research

44. 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.
45. 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.
46. Studies are indicated to establish the influence of mast cell activation disorders on the severity and clinical presentation of perioperative anaphylaxis.
47. 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).

48. In patients who experience perioperative anaphylaxis with a high risk of adverse outcome (elderly, obese, ASA≥3, patients taking beta blockers or ACEI, prolonged CPR), anaesthetists should be prepared to escalate treatment early.
49. 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.
50. During perioperative anaphylaxis in patients taking beta blockers early administration of IV glucagon 1mg should be considered, repeated as necessary.
51. Administration of IV vasopressin 2 Units, repeated as necessary, should be considered when hypotension due to perioperative anaphylaxis is refractory.
52. The need for a vasopressor infusion should be anticipated after severe perioperative anaphylaxis.
53. Non-essential surgery should not be started after severe perioperative anaphylaxis.
54. Where severe perioperative anaphylaxis occurs during non-essential surgery the operation should be curtailed unless there is an overriding reason to continue.
55. Patients with severe anaphylaxis should be admitted to critical care (HDU/ICU).
56. 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.
57. All cases of severe perioperative anaphylaxis, including fatalities, should be discussed with an allergy clinic at the first available opportunity.

REPORTING

Institutional

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

National

- 59. The departmental lead should ensure all cases have been reported to the Trust incident reporting system.
- 60. 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.
- 61. 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.

Individual

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

NMBA

Institutional

- 65. Allergy clinics should adhere to published guidelines on the investigation of suspected NMBA anaphylaxis. When NMBA allergy is diagnosed the clinic should identify a safe alternative, including for rapid sequence induction (i.e. establishing whether either succinylcholine (suxamethonium) or rocuronium is safe). The NAP6 minimum panel is suitable for this.

Individual

- 66. 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.

Research

67. 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.
68. 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.

ANTIBIOTICS

Institutional

69. 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*.
70. If antibiotic allergy is suspected despite negative skin tests, challenge testing should be performed.
71. Trust guidelines on antibiotic prophylaxis for surgery should be immediately available to anaesthetic and surgical teams in theatre.

Individual

72. Antibiotic administration should strictly follow national or local guidelines.
73. A test dose of antibiotic should not be used, as it will not prevent or reduce the severity of anaphylaxis.
74. 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.
75. The anaesthetist should consider Co- amoxiclav or teicoplanin amongst the likely culprits when anaphylaxis occurs after their administration.
76. 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

77. 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.

Institutional

78. Operating theatres should have an accessible list of chlorhexidine-containing items. Appropriate alternatives should be available for patients with suspected or confirmed chlorhexidine allergy.
79. Investigation of suspected perioperative anaphylaxis should include chlorhexidine.
80. More than one test for chlorhexidine is necessary to exclude allergy.
81. When allergy testing for chlorhexidine is positive during investigation of perioperative anaphylaxis, all other potential culprits should still be investigated, as there may be more than one sensitisation.

Individual

82. Chlorhexidine allergy should be included in the allergy history taken by anaesthetists, nurses and other healthcare professionals.
83. 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.
- 84.** 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

85. 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.

86. 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.
87. 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.

INVESTIGATION

National

88. There is a pressing need for investment in and expansion of specialised perioperative allergy clinic services, to ensure prompt investigation of urgent cases and that no patient with suspected perioperative anaphylaxis has non-urgent surgery without a timely allergy clinic assessment. This applies to both adult and paediatric services. [
89. Consideration should be given at a national level to reconfiguring paediatric services for investigation of perioperative anaphylaxis to address the current shortfall in provision. In view of the small number of cases involved collaboration with local hub services should be explored.

Institutional

90. Patients should be given appropriate information after investigation of perioperative anaphylaxis in an allergy clinic. This information should also be sent to the general practitioner and entered in the medical record. (Recommended content is shown in the *NAP6 template allergy clinic patient letter* Supplementary Material K)
91. 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.
92. 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.

93. Outcomes of urgent investigations by allergy clinics should be communicated urgently and directly to the referring anaesthetist, ideally by phone and in writing.
94. Allergy clinics should provide standardised clinic reports to encourage better communication to anaesthetists, general practitioners and patients.
- Recommended content is in the *NAP6 recommended allergy clinic letter content* (Supplementary Material K)

Individual

95. 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.
96. 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.
97. Blood samples for mast cell tryptase (MCT) should be taken in accordance with national guidelines.
- d. 1st sample as soon as the patient is stable.
 - e. 2nd sample as close to 1 -2 hours as possible after the event.
 - f. 3rd (baseline) at least 24 hours after the event
98. Where the baseline sample is not collected prior to attending the allergy clinic this should be collected at the clinic.
99. If the MCT is elevated >24 h after the event, a mast cell disorder should be considered.
100. A dynamic rise and fall in tryptase should be used to detect mediator release.
101. Where peak mast cell tryptase is less than the upper limit of the reference range (i.e. the 99th centile limit of 14 mcg/L) a dynamic rise and fall in tryptase level may still be useful to diagnose anaphylaxis.
102. When investigating suspected perioperative anaphylaxis, chlorhexidine and latex should be tested.
103. More than one test for chlorhexidine is necessary to exclude allergy
104. When allergy testing for chlorhexidine is positive during investigation of perioperative anaphylaxis, all other potential culprits should still be investigated, as there may be more than one sensitisation.

105. All potential culprits to which the patient has been exposed should be tested. The clinic should make a critical appraisal of the imputability of each potential trigger in making a diagnosis.
106. Avoidance advice should be specific and not excessive, as this may lead to harmful consequences. When no culprit is identified, further investigations should be carried out rather than giving 'blanket advice' on avoidance of multiple drugs.
107. All skin testing should be at concentrations validated to be below the non-specific histamine releasing/irritant concentrations (as published and verified locally).
108. Allergy clinics should adhere to published guidelines on the investigation of suspected NMBA anaphylaxis. When NMBA allergy is diagnosed the clinic should identify a safe alternative, including for rapid sequence induction (i.e. establishing whether either succinylcholine (suxamethonium) or rocuronium is safe). The NAP6 minimum panel is suitable for this.
109. The possibility of reaction to more than one agent should be considered.
110. Specific IgE bloods tests should be used to agents for which they are available as no modality is 100% sensitive or specific.
111. When allergy is suspected and allergy testing is negative, testing should be repeated after an interval to exclude a false negative test.
112. Where allergy testing has been performed less than four weeks after the event, retesting after an interval should be considered, to exclude false negatives and identify multiple sensitisations.
113. 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.
114. Allergy clinics should advise patients to keep a copy of their drug allergy clinic letter with them at all times and use this to inform clinicians of their allergy particularly when attending hospital appointments or before future surgery.

Research

115. As none of the test modalities is wholly reliable, there needs to be research to establish an appropriate form of challenge testing for chlorhexidine.

116. More data on the predictive values of different modes of testing using standardised methods are required for all triggers.
117. There is a need for further research and consensus on the logical interpretation of positive tests where mast cell tryptase is not raised, and negative tests where mast cell tryptase is raised, as current guidance is lacking.

OBSTETRIC

Institutional

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

Individual

119. An allergy history should be taken even when there is extreme urgency to deliver the baby.
120. Anaesthetists should be vigilant to non-obstetric causes of hypotension in obstetric patients.
121. 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.
122. Anaphylaxis should be actively considered where the cause of maternal hypotension or collapse is unclear, and mast cell tryptase levels should be measured.
123. Anaesthetists should be aware that hypotension due to anaphylaxis can be exacerbated by neuraxial blockade and or aortocaval compression.

PAEDIATRIC

National

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

Institutional

125. Protocols and anaesthetic anaphylaxis treatment and investigation packs appropriate for children should be immediately available wherever paediatric anaesthesia is administered
126. All anaesthetists administering anaesthesia to children should be trained in the management of paediatric anaphylaxis.
127. 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.

INDEPENDENT SECTOR

National

128. The results and recommendations of NAP6 are relevant to independent sector hospitals and should be disseminated to independent sector hospitals, their governance leads and anaesthetists working there.
129. For reasons of patient safety and quality assurance, commissioners of services in independent sector hospitals should ensure these hospitals, and the patients undergoing care in them, are included in national audits.

Institutional

130. Independent sector organisations should work to improve engagement with national audits focusing on quality and safety of patient care.
131. Independent sector hospitals should have the same levels of preparedness for managing life-threatening perioperative anaphylaxis as other sectors. This includes but is not limited to an anaphylaxis lead, a resuscitation team, anaesthetic anaphylaxis treatment and investigation packs in all theatres, appropriate training of all theatre staff, immediate availability of first line anaphylaxis drugs (adrenaline, corticosteroids), prompt availability of second line drugs (glucagon, vasopressin), standard operating procedures for management of anaphylaxis, escalation to provision of intensive care before transfer, on-going care and transfer to another hospital where necessary, and referral for specialist investigation.
132. Independent sector hospitals should have systems to ensure safety relevant matters can be discussed, disseminated and acted on by all anaesthetists who work there. Collaborative working between anaesthetists in independent sector

hospitals should be encouraged to increase governance and safety. An 'independent department of anaesthesia' is one solution to this and may have equivalent benefits to departments of anaesthesia in the NHS.

Individual

133. Anaesthetists working in independent sector organisations should be trained and prepared to manage life-threatening anaphylaxis.
134. Anaesthetists working in independent sector organisations should participate in national audits.
135. Anaesthetists working in independent sector organisations should be trained in and prepared to transfer a critically ill patient to another hospital for further care. Where they do not possess these skills, another clinician with these competences should be enrolled in the patient's care.