14 Investigation

William Egner

Key findings

- The average wait time before being seen in allergy clinic was 101 days (range 0–450 days). Only 39 (16%) were seen within the ideal six weeks. Twenty-three per cent breached the national UK 18-week target for first appointments and 7% waited longer than six months.
- Waiting times for urgent referrals were not shorter than for non-urgent referrals.
- Regarding mast cell tryptases (MCTs):
  - At least three MCT samples were available in 67% of cases, two in 19% and one in 8%
  - Forty-five per cent of early sampes met BSACI guidance for 'immediate' sampling, and 76% met ANZAAG guidelines
  - Earlier samples gave higher MCT levels which rapidly fell within 30 minutes
  - Median first MCT levels rose with reaction grade though this was less clear for peak levels
  - MCT level did not correlate with severity of clinical features
  - While median MCT values differed between trigger agents the differences were not statistically significant
  - The dynamic-tryptase algorithm [(baseline tryptase x1.2) +2 mcg/L] was found useful for detecting mediator release especially when peak tryptase was within the reference range and increased yield by 16%.
- Clinic investigations adhered fully to AAGBI guidance in 32% and to BSACI guidance in 17%; most non-adherence was through failing to test for all potential culprit agents and poor communication.
- All potential culprit agents had been adequately investigated in only 27% of cases.
- Ten per cent of assessments were judged as good, 49% good and poor, 41% poor.
- Despite limitations of testing in 88% of cases the same trigger was identified by the clinic and the panel.
- Seventy-four percent of triggers were correctly predicted by the anaesthetist.
- NAP6 shows that adherence to existing guidelines is poor and confirms deficiencies in service availability, capacity, harmonisation 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
  - Avoiding patients having to undergo non-urgent surgery without a completed allergy clinic assessment
  - Harmonisation 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 standardised methods are required for all triggers
  - Clarity and unambiguity of guideline recommendations is essential
  - Better standardised 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 communication of results: to anaesthetists, general practitioners and patients.

Introduction

The 2016 NAP6 allergy baseline survey showed that UK specialist perioperative allergy clinics are few and distributed unequally (Egner 2017a and Chapter 13). It also recorded self-reported clinical activity and perceived adherence to national guidance from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) (Harper 2009), the British Society for Allergy and Clinical Immunology (BSACI) guideline on investigation of anaphylaxis during general anaesthesia (Ewan 2010) and the National Institute for Health and Care Excellence CG183 'Drug allergy: diagnosis and management of drug allergy in adults, children and young people' (NICE 2014).

We examined all cases reported to NAP6 and performed either a full (184 cases) or short (82 cases) review of care (Chapter 5). This included classifying the nature of the reported reaction, identifying the trigger agent where possible and assessing the completeness and quality of allergy clinic investigation, judged both against prevailing standards and with the performance claimed in the NAP6 baseline survey.

What we already know

Tryptase release is seen in most but not all cases of perioperative anaphylaxis, most commonly in the higher grades of reaction (Grade 3–5) (Scolaro 2017, Egner 2016, Low 2016, Mertes 2003, Mertes 2011, Sprung 2015, Dybendal 2003).

There is a poor correlation between mast cell tryptase (MCT) levels and reaction grade individually but the median values are higher in more severe reactions (Egner 2016). Tryptase levels plateau between 30 and 90 minutes after the reaction (Sainte-Laudy 1998). Using the identification of a dynamic change in tryptase values may identify mediator release in more cases than using fixed thresholds of 11.4 or 14 mcg/L (ie, 95% and 99% upper limits of normal values) (Egner 2016, Baretto 2010).

Exposure to opioids like pholcodine may correlate with neuromuscular blocking agent (NMBA) anaphylaxis, because Denmark, where it is banned, rarely diagnose NMBA anaphylaxis, unlike Norway (until recently) and the UK (de Pater 2017, Brusch 2014) (See also Chapter 16, NMBAs)

Basal tryptase levels may correlate with severity of anaphylaxis in non-perioperative settings such as sting anaphylaxis (Rueff 2009).

The incidence of latex allergy is probably decreasing (Low 2016, Harper 2009, Kolawole 2017).

Rocuronium may now be a leading cause of NMBA reactions (Sadleir 2013).

Chlorhexidine and teicoplanin are increasingly identified as triggers (Low 2016, Harper 2009, Kemp 2017, Garvey 2016, Egner 2017b, Savic 2015). There is considerable variation in skin testing and no consensus on the best panel and sequence of testing.

Methods

Reports were assessed by the panel in a Bayesian-type expert consensus analysis of imputability (Agbabiaka 2008) as described in the NAP6 methods paper (Cook 2018 and Chapter 5).

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).

The non-parametric Kruskall-Wallis test was used to compare median MCT levels using the statistical package 'Analyse-IT and SPSS'. $P<0.05$ was used to indicate statistical significance.

Numerical analysis

Number of cases

Of 504 submitted reports, 266 met inclusion criteria.

Tryptase sampling

Peak tryptases (Tp) above 14 mcg/ml were seen in 71% of cases.

Number and timing of samples

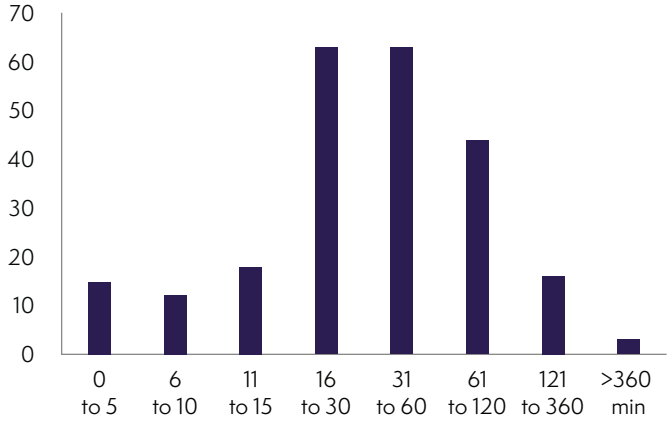
At least three MCT samples were available in 178/266 (67%) of cases, two in 51 (19%) and one in 22 (8%). In 8 (3%) samples were taken but not received/reported and 7 (3%) had no samples taken.

Eighty-one per cent of 184 reviewed cases had interpretable dynamic MCT samples (≥2 samples within 6 hours of the reaction) (Egner 2016, 2017c, Cook 2018).

First tryptase (T1)

Forty-five per cent of cases met BSACI guidance for 'immediate' sampling, 45 (17%) at <15 minutes post-reaction, 64 (28%) at 16–30 minutes. A total of 175 (76%) were taken within the hour, consistent with the ANZAAG guidelines (Figure 1). (Egner 2017a, 2017c, Kolawole 2017, Cook 2018, Ewan 2010).

Figure 1. Timing and levels of first tryptase (T1) (minutes) (number of cases)



Second tryptase (T2)

Twenty-three (10%) samples were taken within 60 minutes and 74 (32%) within 120 minutes, consistent with BSACI guidance, rising to 43% within 3 hours and 71% within 6 hours.

Third tryptase (T3)

One hundred and sixty eight (73%) patients had satisfactory >24 hour baseline samples, 12% were too early, taken less than 20 hours after the event.

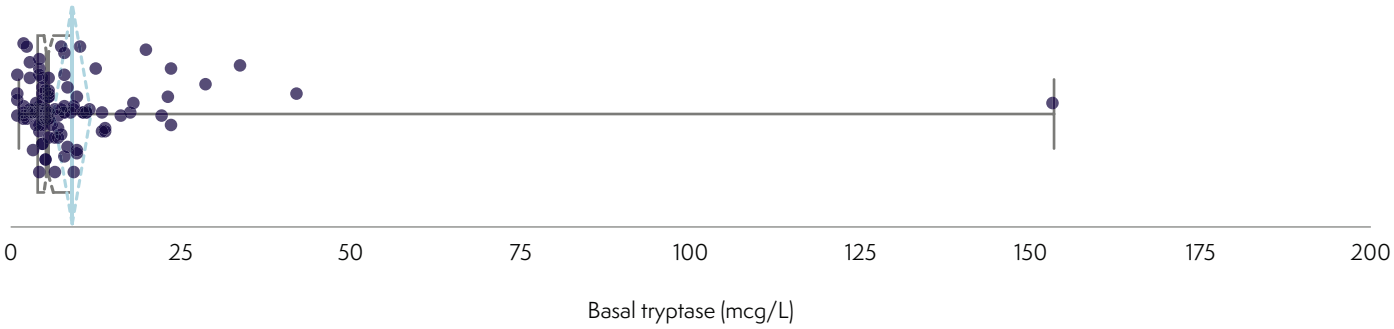
Tryptase levels

Basal tryptase (Tb)

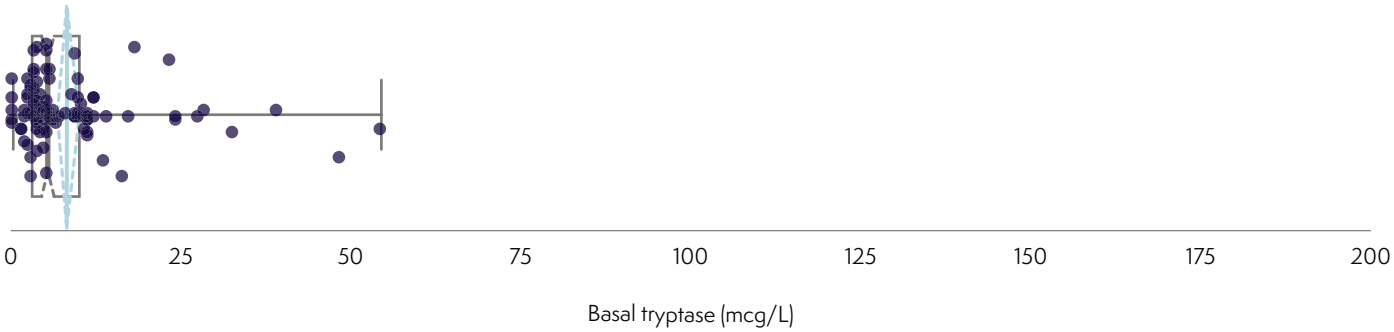
Basal Tb were not significantly different in reaction Grade 3 (4.0 mcg/L) and Grade 4 (5.0 mcg/L) (Figure 2). 10% had raised basal tryptase (24 samples 15.4–54.2 mcg/L, plus one at 153 mcg/L).

Figure 2. 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



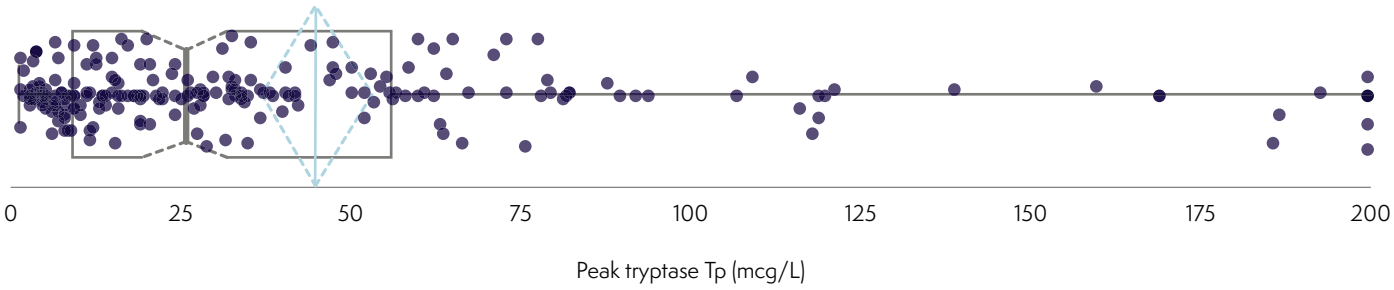
Key: Dots represent individual measurements. The black bar is the median and the box the 25th and 75th centiles. Dotted indents represent the 95% confidence intervals of mean and median. Horizontal bar = max–minimum range.

Peak tryptase (Tp)

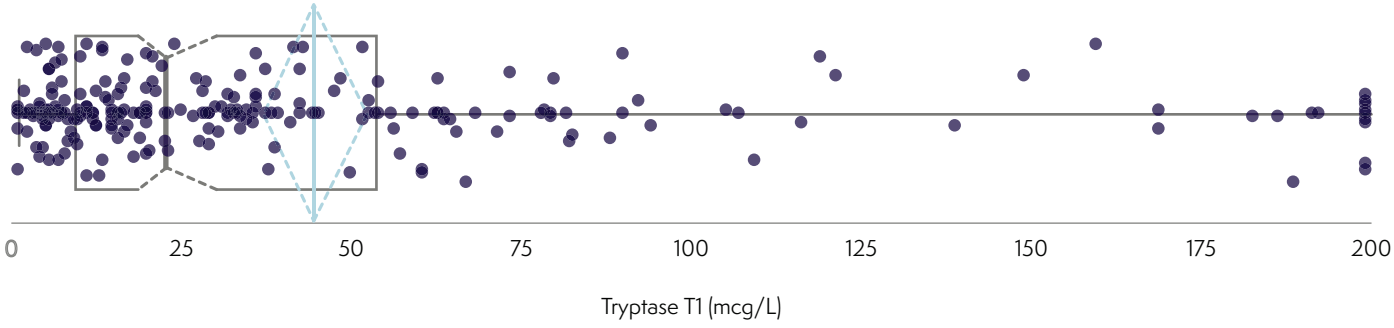
Tryptase values generally peaked at the first sample (T1):
T1 includes all single samples (Figure 3).

Figure 3. Timings of first (T1) and peak (Tp) tryptase samples

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



Tryptase and culprit agents

The median Tp/T1 appeared lowest for chlorhexidine and highest for suxamethonium (Figure 4, Supplementary material B). There were statistically significant differences for both T1 and Tp for both distributions and medians using Mann Whitney U test and Kruskall-Walis as follows:

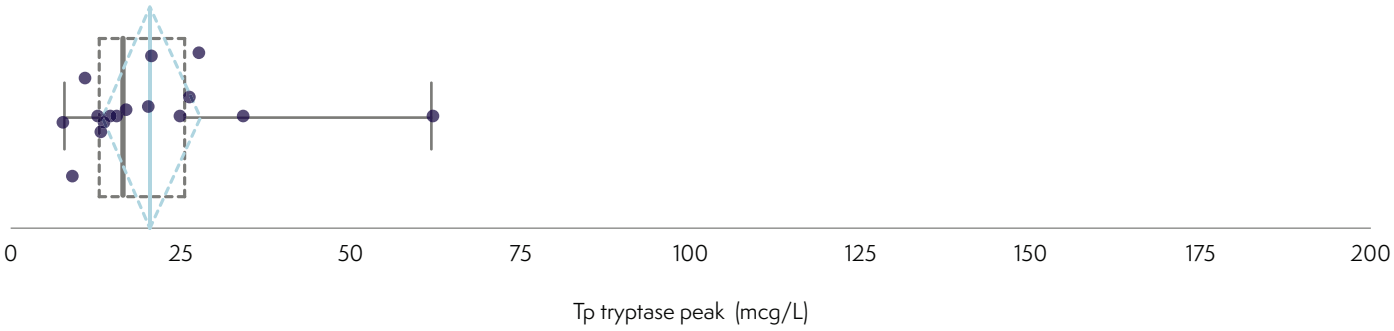
- Chlorhexidine vs teicoplanin p=0.002
- Chlorhexidine vs co-amoxiclav p=0.04
- Chlorhexidine vs rocuronium p=0.004
- Chlorhexidine vs suxamethonium p=0.002.

None of the muscle relaxants were significantly different from each other although atracurium vs suxamethonium was almost significant at p=0.053.

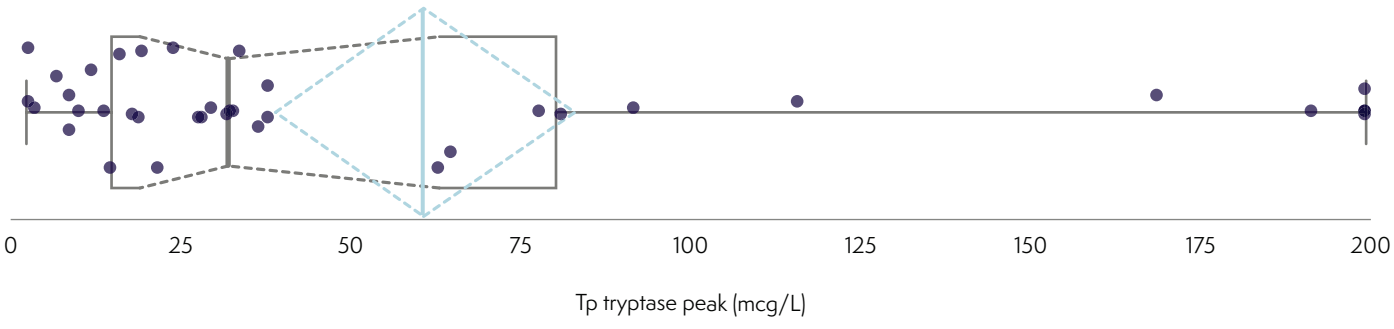
There was no significant difference between co-amoxiclav and teicoplanin p=0.51, nor chlorhexidine and Patent Blue p=0.31, nor chlorhexidine and atracurium p=0.56.

Figure 4. Peak tryptase in cases where a single culprit was identified

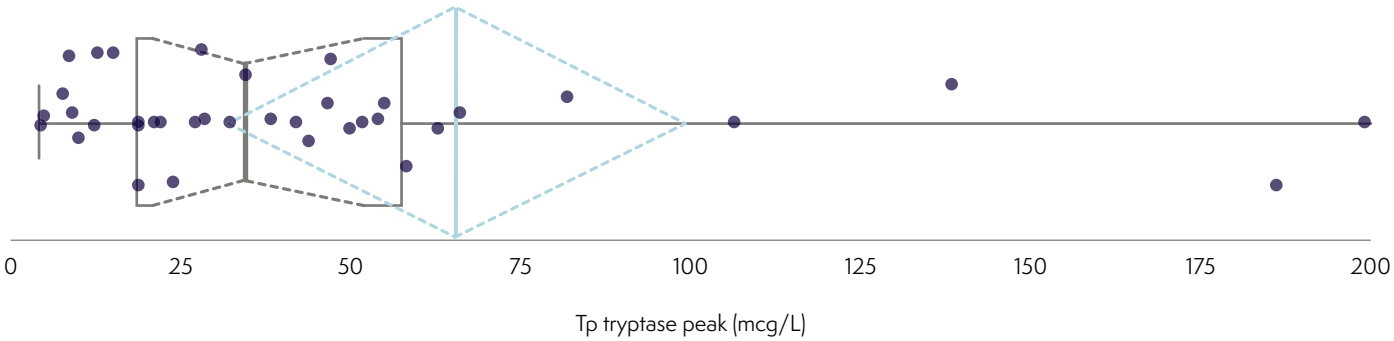
Chlorhexidine



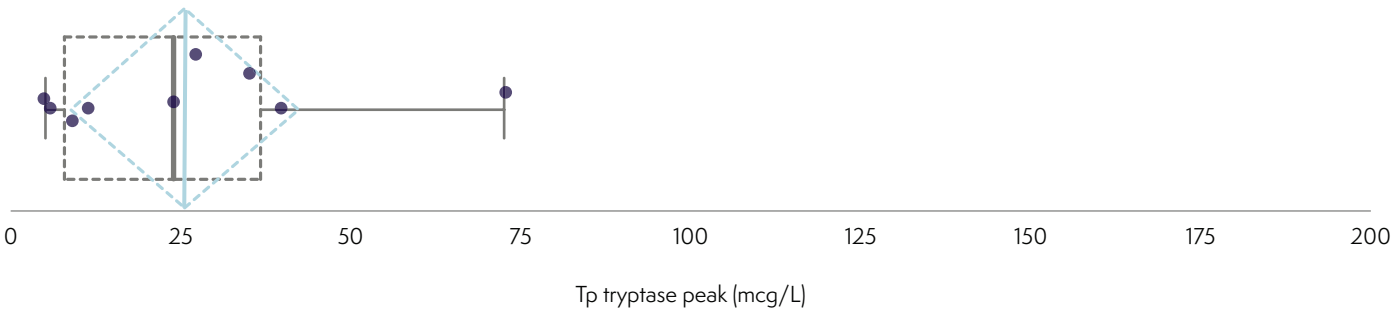
Teicoplanin



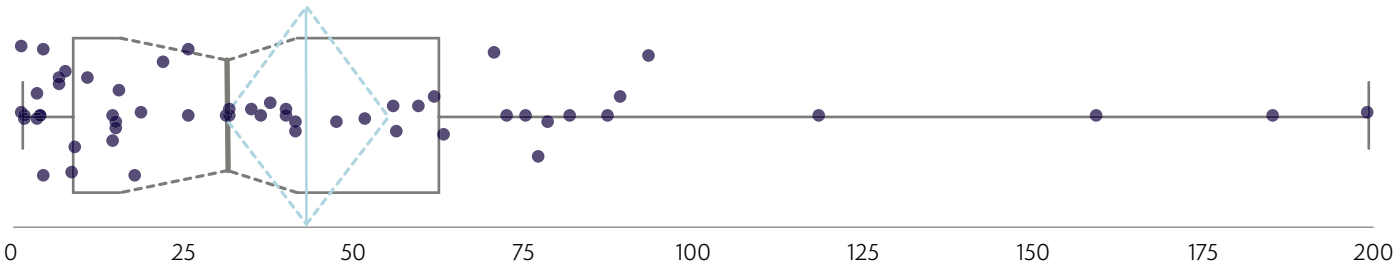
Co-amoxiclav



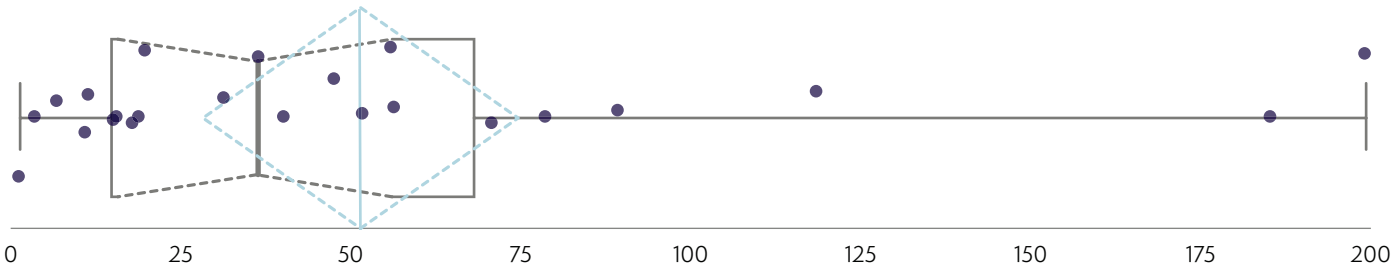
Patent Blue



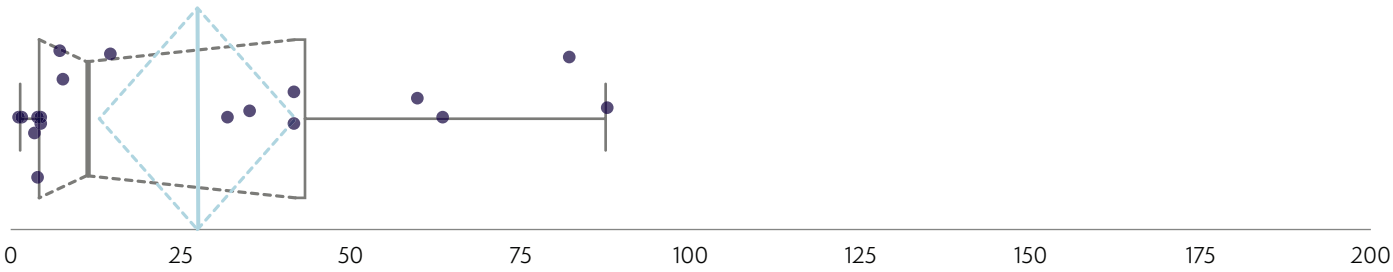
Muscle relaxants
All muscle relaxant reactions



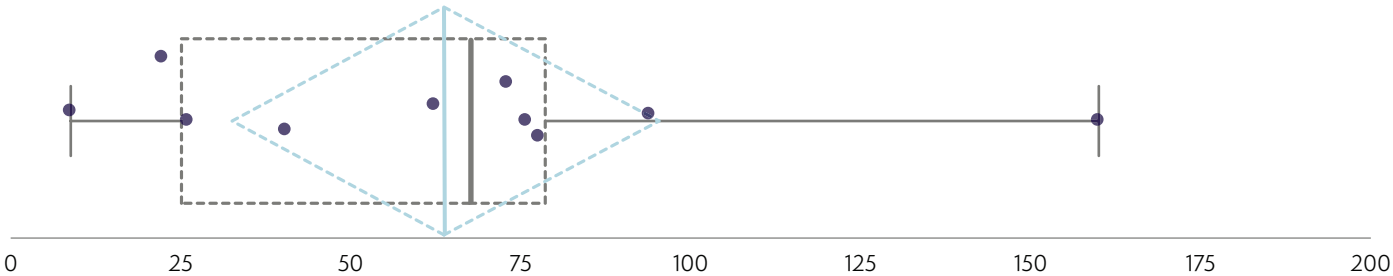
Rocuronium



Atracurium



Suxamethonium



Cases with single tryptases

Twenty-three cases had single tryptases, and most (65%) were positive >=14 mcg/L (median 31, 95%CI 11-63, range 0.1-200). Nine fatalities had tryptase above 19.6 mcg/L (Figure 5).

Tryptase and speed of onset of anaphylaxis

Anaphylaxis onset was fastest (time from drug administration to presenting feature) for muscle relaxants and the antibiotics teicoplanin and co-amoxiclav, and slowest for chlorhexidine (Table 2). For antibiotics and NMBAs, speed of onset was almost universally less than 30 minutes: see also Chapter 10, Clinical features.

Table 1. Correlation between panel-identified trigger and peak tryptase (Tp) levels

Trigger	Number 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	19/23	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

Figure 5. Tryptase levels in cases with one tryptase measurement only

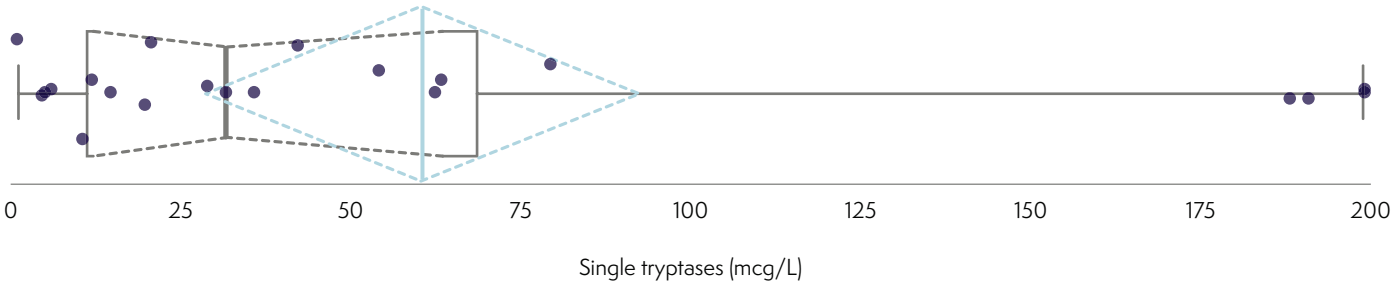


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Table 2. Interval between drug administration and first clinical feature

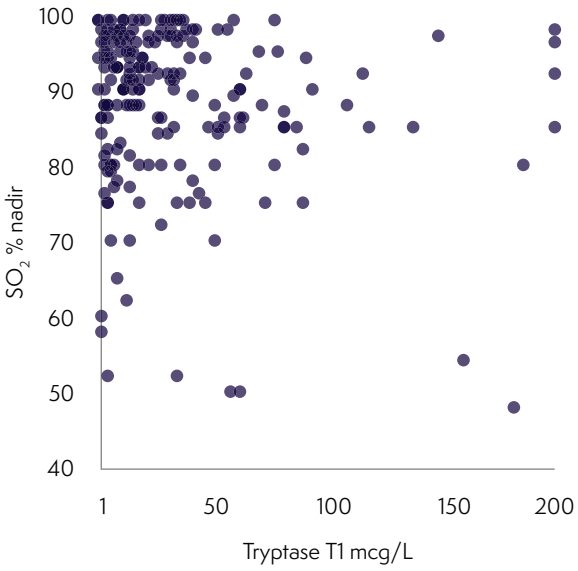
Time (mins) to onset for panel consensus trigger	Median peak tryptase (mcg/L)	0-5	6-10	11-15	16-30	31-60	61-120	>120
Co-amoxiclav	34.7	33	8	3	1	-	-	-
Teicoplanin	32.0	23	7	2	-	-	-	-
Rocuronium	36.4	25	1	-	-	-	-	-
Atracurium	11.5	14	2	3	2	-	-	1
Suxamethonium	67.6	12	1	-	-	-	-	-
Patent Blue	24.2	2	2	1	1	1	2	-
Chlorhexidine	16.5	5	3	-	3	4	-	1

Tryptase levels and severity of anaphylaxis

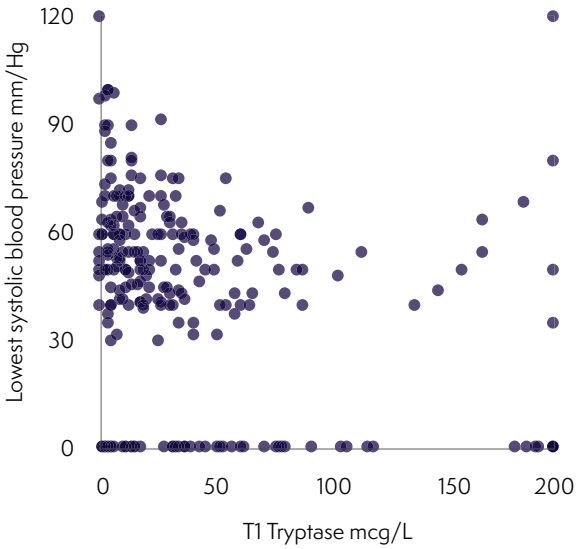
There was no correlation between T1 and nadir oxygen saturation, lowest recorded blood pressure, or the total dose of adrenaline given (Figure 6).

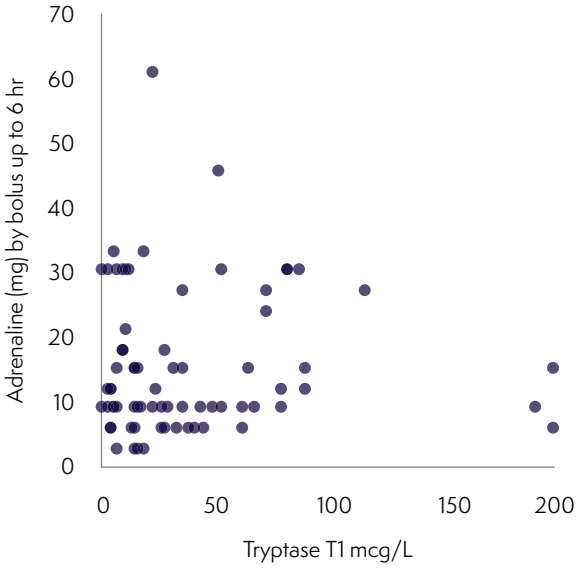
Figure 6. Tryptase levels do not correlate with severity indices

Lowest SpO_2 vs. T1



Lowest systolic blood pressure vs. T1

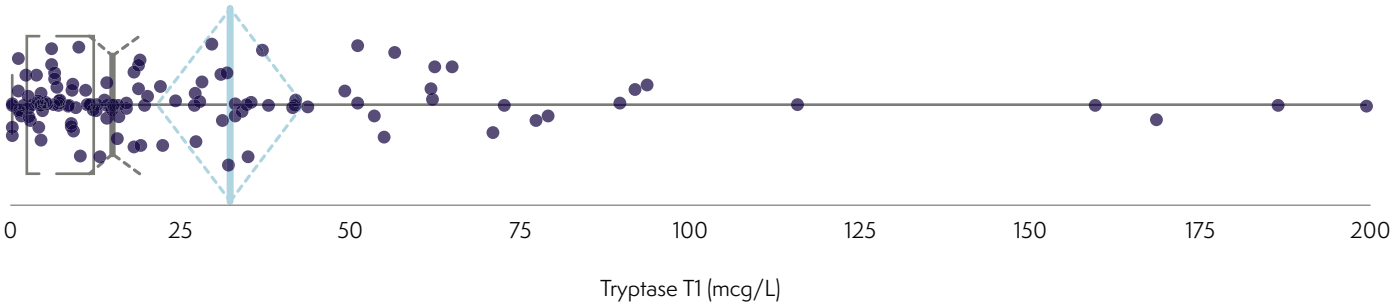




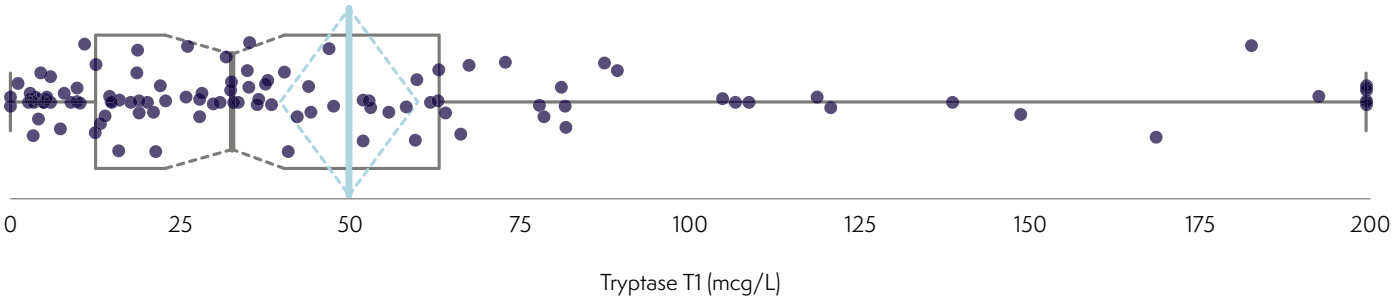
Median T1 tryptase levels rose with reaction grade (Figure 7 and Table 3), though this was less clear for peak levels (Figure 8 and Table 3) – the T1 level may be more relevant for Grade 5 cases, as only one sample is usually feasible.

Figure 7. First tryptase level (T1) and grade of anaphylaxis

All Grade 3 reactions n=125. Median 14.9 (95% CI 11.5-18.9), range 0.1-576)



All Grade 4 reactions 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

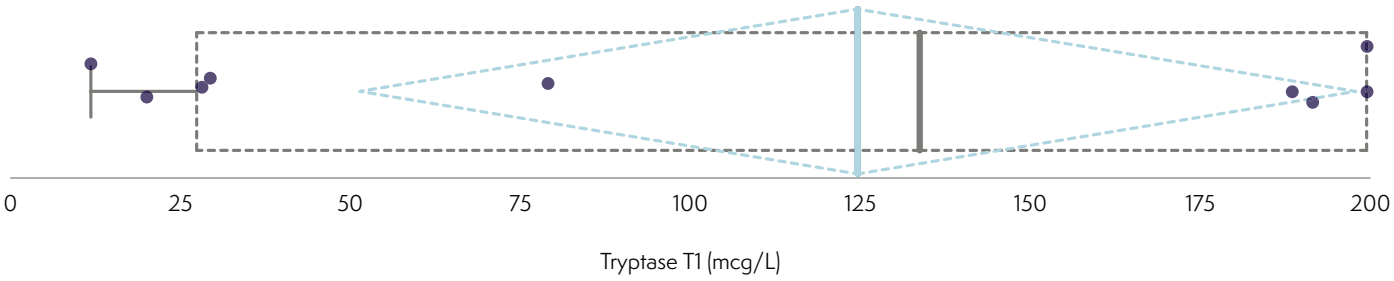
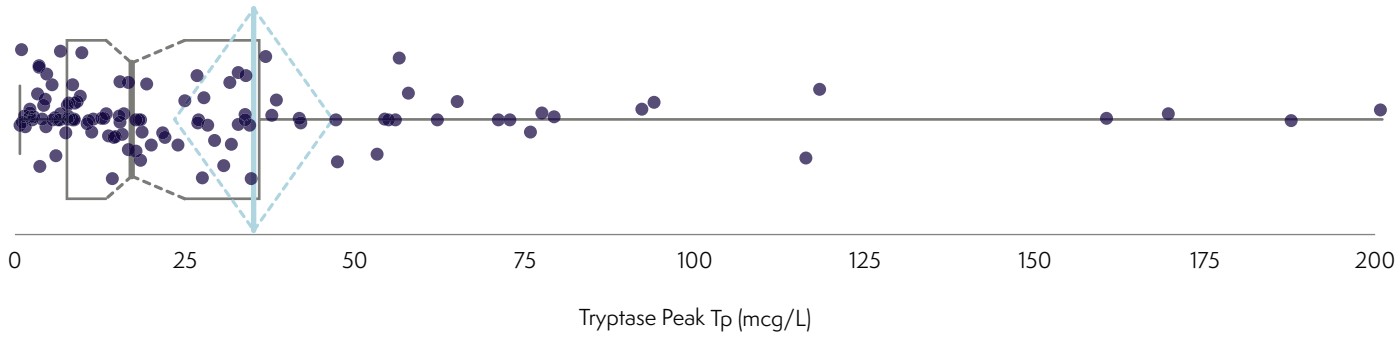
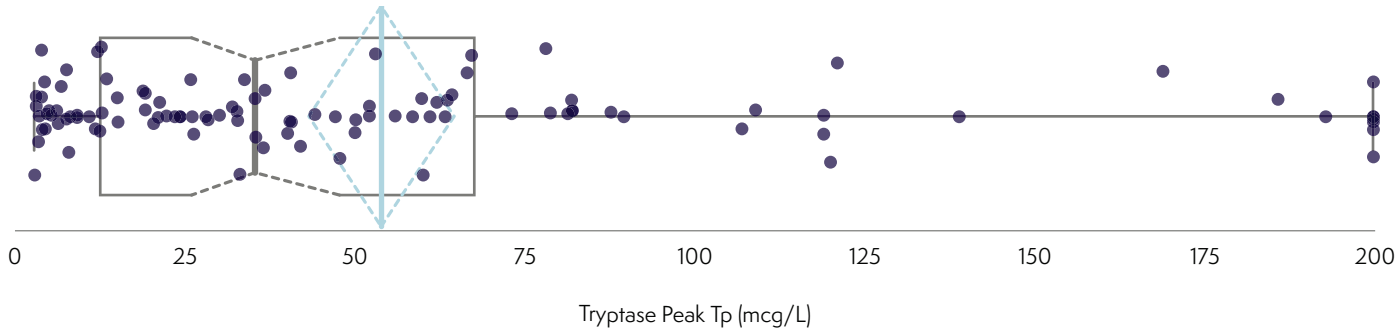


Figure 8. Peak tryptase level (Tp) and grade of anaphylaxis

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

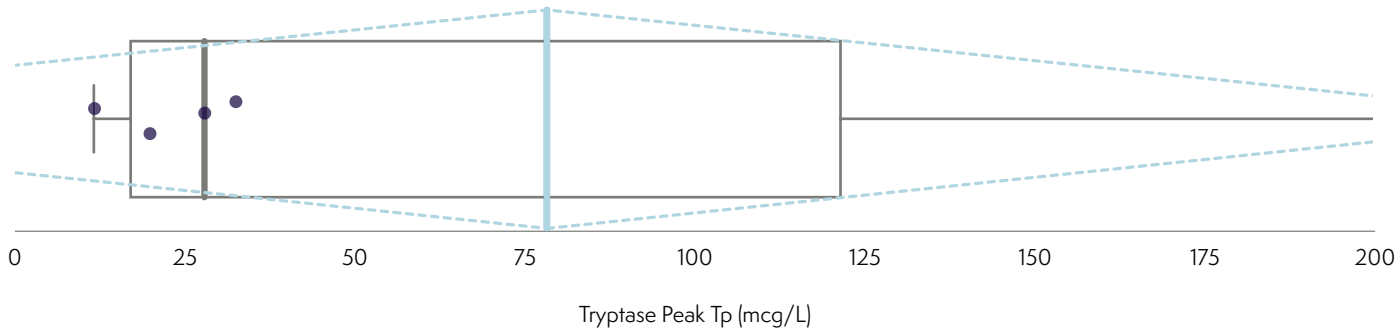


Table 3. Median tryptase values by reaction grade
*Peak tryptase can only be estimated where two or more samples are available, hence T1 is a more accurate reflection of levels in Grade 5

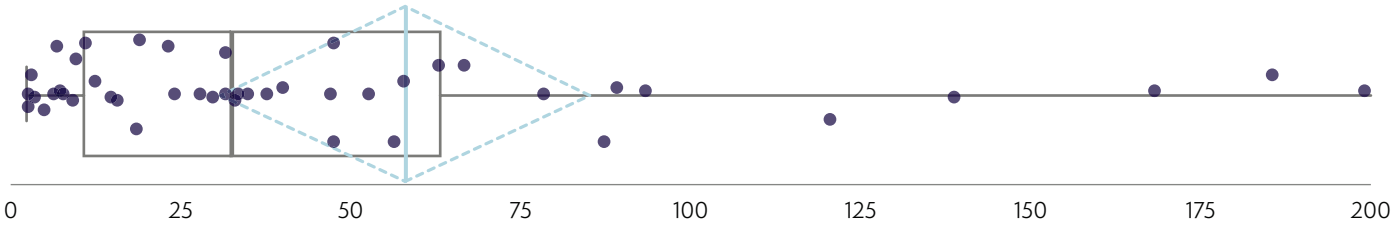
Reaction grade	Number (n)	T1 median (mcg/L)	95% CI (mcg/L)	Tp Median (mcg/L)	95% CI (mcg/L)
Grade 3	125	14.9	12-19	17.5	14-25
Grade 4	110	32.8	23-41	35.3	26-48
Grade 5	10	134*	10-200	11.6*	n/a

Speed of sampling and tryptase levels

The first tryptase sample was taken within 5 minutes of drug administration in 161 cases. Earlier samples gave higher T1 results which rapidly fell within 30 minutes and rapid onset events were associated with higher peak tryptase levels (Figure 9).

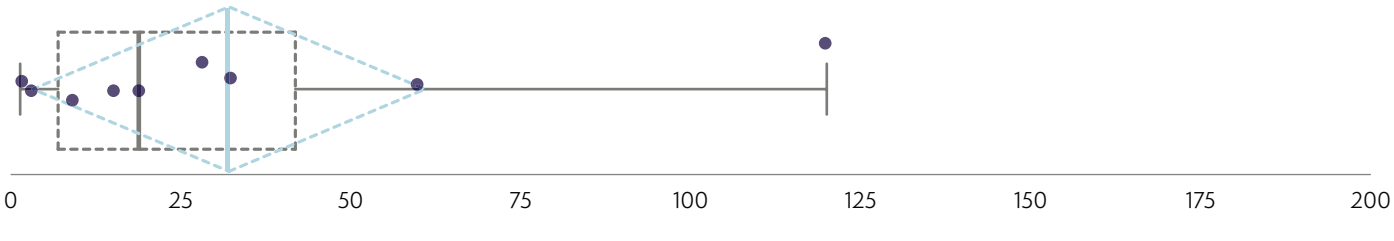
Figure 9. Timing of sampling and tryptase level

Peak tryptase in samples taken at 0–5 minutes n=46. Median 32.5 (95% CI 18.7-47.7), range 2.5-576



Peak tryptase in samples taken at 6–10 minutes n=38. Median 27.5 (95% CI 12-35.3), range 1.1-187

Peak tryptase in samples taken at 11–15 minutes n=9. Median 19 (95% CI 3-60), range 1.7-41.7



Peak tryptase in samples taken at 16–30 minutes n=15. Median 34.1 (95% CI 10.1-64.2), range 7-81.8.

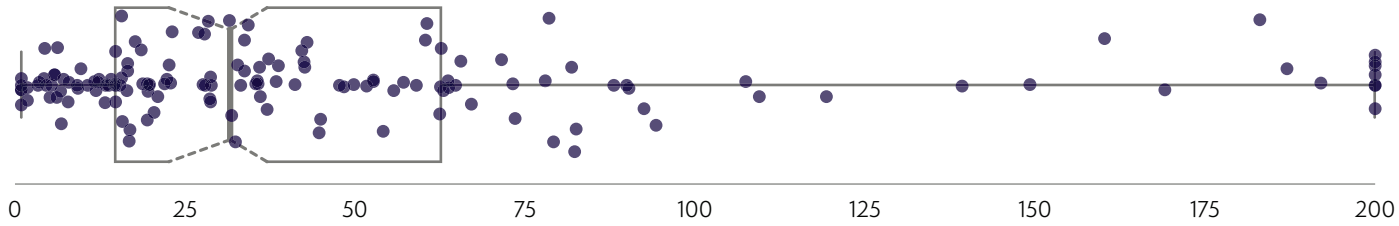
Tryptase levels in anaphylaxis

Median T1 levels were higher in allergic anaphylaxis (Figure 10).

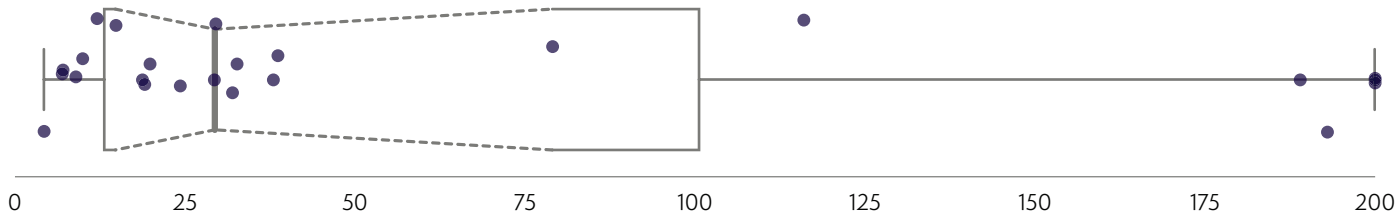
Eight per cent of allergic anaphylaxis reports showed no tryptase rise. Twenty per cent had a peak tryptase of <14 mcg/L though most of these showed a dynamic tryptase rise.

Figure 10. Tryptase results in panel-defined anaphylaxis with and without evidence of sensitisation to the trigger are not significantly different (p>0.05)

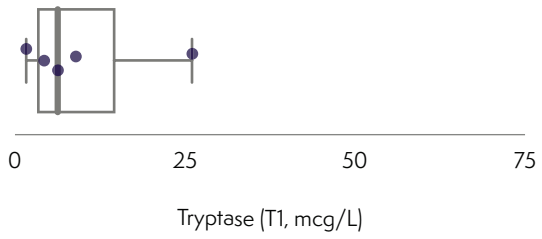
T1 in panel-defined Allergic Anaphylaxis (positive IgE test confirming trigger or very high probability of allergic anaphylaxis where tests not possible/not positive)* n=138 Median 34.3, 95% CI 18.8-60.0



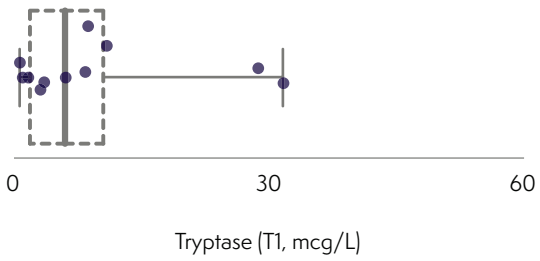
T1 in panel-defined Non-Allergic Anaphylaxis (no confirmatory positive sIgE tests to the trigger)
n=24 Median 29.4, 95% CI 14.7-79.0



T1 in panel-defined Non-Allergic Anaphylaxis (panel determined anaphylaxis was probably non-IgE mediated)
n=6 cases, Range 1.7-24.9



T1 in panel-defined diagnosis uncertain (unable to determine)
n=16 Median 6.6, 95% CI 1.4-30



*There was no significant difference between allergic anaphylaxis and non-allergic anaphylaxis (p>0.05).

Dynamic tryptase (DT)

Two hundred and twenty-nine cases with ≥2 tryptase results enabled examination of the dynamic-tryptase algorithm. This postulates definitive acute tryptase release if the peak tryptase exceeds (baseline tryptase x1.2) +2 mcg/L,even when the result lies within the reference ranges.

Dynamic tryptase detected an additional 37 (16%) cases where peak tryptase was <14 mcg/L. (99th centile reference limit) (Table 4). Dynamic tryptase was also useful at an 11.4 mcg/L (95th centile) threshold.

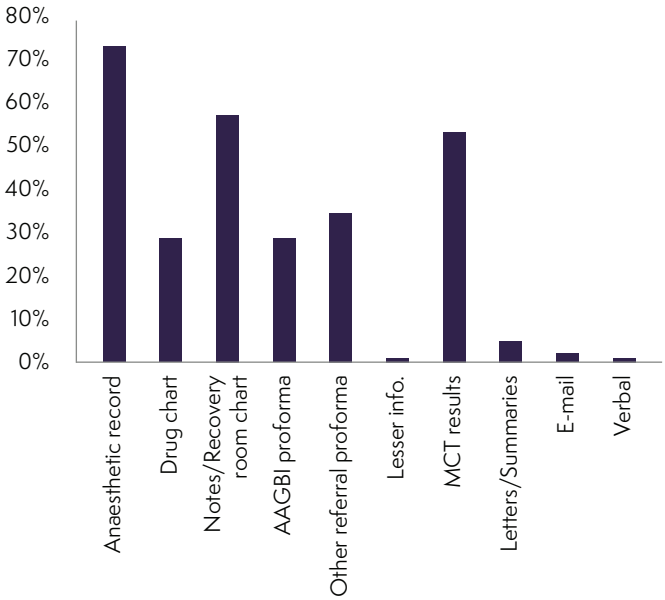
Table 4 illustrates that the best detection strategy is to use dynamic tryptase for any case where tryptase release is not obvious and the peak tryptase is below the upper limit of the reference range.

Table 4. Use of the dynamic tryptase algorithm to enhance diagnosis of mediator release where peak tryptase (Tp) is within the reference range. Results from 229 cases with ≥2 tryptases

Peak tryptase (Tp)	Number of Tp above or below	Cases without dynamic tryptase pattern	Cases detected by dynamic tryptase	Total positive cases (% of 229)
Tp >=11.4 mcg/L	162	9	12	174 (76%)
Tp >=14 mcg/L	150	5	1	151 (66%)
Tp <11.4 mcg/L	67	41	26	26 (11%)
Tp <14 mcg/L	79	42	37	37 (16%)

Dynamic tryptase is most sensitive where Tp is in the reference range, and can produce false-negative when tryptases are high. The total number of cases detected using the 95th centile of the reference range was 200 (87%) and using the 99th centile was 188 (82%).

Figure 11. Information provided at referral



Referrals to allergy clinics

Who referred?

Ninety-eight per cent of survivors were referred for investigation.

One hundred and ninety (71%) of referrals were by the index anaesthetist, 45 by another anaesthetist (total 88% adherent to AAGBI recommendations), 17 by surgeons, two by GPs, six by others, and 14 not specified.

Was referral information appropriate?

The panel graded 60% of referrals 'good', 19% 'good and poor', 9.5% 'poor' and 11.6% unassessable.

Use of referral pro-forma (AAGBI or other) was infrequent, many referrals failing to provide guideline-recommended information (Figure 11).

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.

Perioperative specialist allergy clinic assessment

Investigation of paediatric cases is discussed in Chapter 21, Paediatric anaesthesia. The following results describe investigation of the whole dataset except where specified.

Of the 252 patients referred to allergy clinics, the time taken to be seen was available for 233; the average wait time before they were seen was 101 days. The range was large – 0 days and 450 days.

As a result of the anaphylactic episode, 61% of all patients had a procedure delayed, modified or abandoned. Delays were detrimental in 29 (12%) patients requiring urgent and 30 (12%) requiring expedited surgery. This included eight patients requiring urgent cancer surgery and seven requiring non-urgent cancer surgery. Thirty-two per cent had delays to non-urgent treatment. Six per cent of patients had further surgery before clinic assessment.

Timeliness of clinic assessments

NCEPOD non-urgent cases

Only 39 (16%) were seen within the ideal six weeks. Twenty-three per cent breached the UK national 18-week target for first appointments, and 7% waited longer than 6 months (Figure 12a).

Final clinic appointments occurred at a median of 24 weeks, range 3–54.

The median time from allergy clinic referral to receipt of allergy clinic conclusions was 12.5 weeks (range 6–62) (Figure 12b).

NCEPOD urgent cases

Of 29 patients whose assessment was judged urgent, 11 (38%) waited more than 18 weeks.

Median wait from referral to conclusions was 14 weeks (range 3–60 weeks) compared with 12.5 weeks for non-urgent cases.

Overall waiting times varied little between urgent and non-urgent cases (Figure 12c).

Figure 12. Time to first allergy clinic assessment
Blue bar = 6 weeks (ideal wait), grey bar = 18 weeks (max wait before breach)

Figure 12a. Days from referral to first clinic weeks all patients
Median 90 (12.5 weeks), minimum 1 to max 450 days

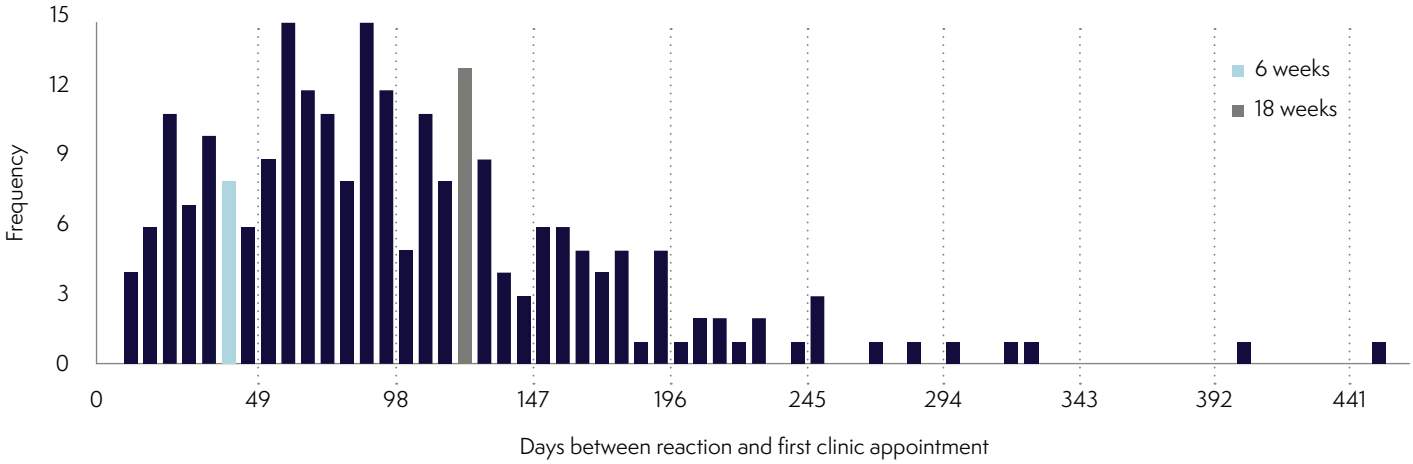


Figure 12b. Weeks from referral to receipt of allergy clinic diagnosis by anaesthetist
Median 12.5 weeks (88 days), 95% CI 10-15, range 0–62 weeks (434 days)

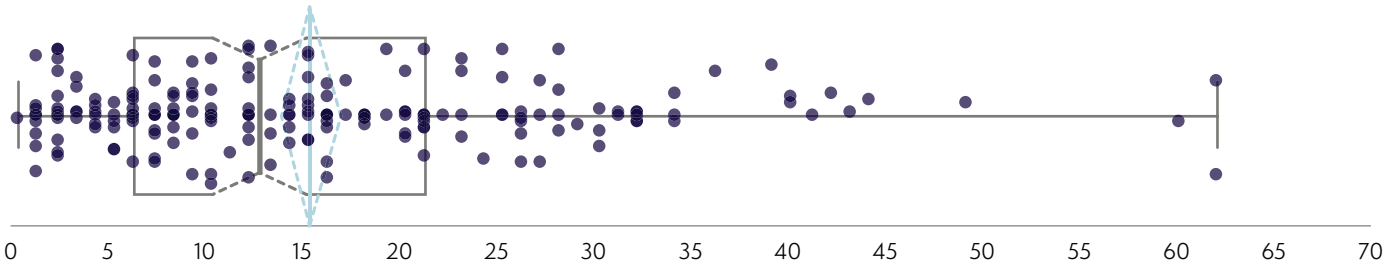
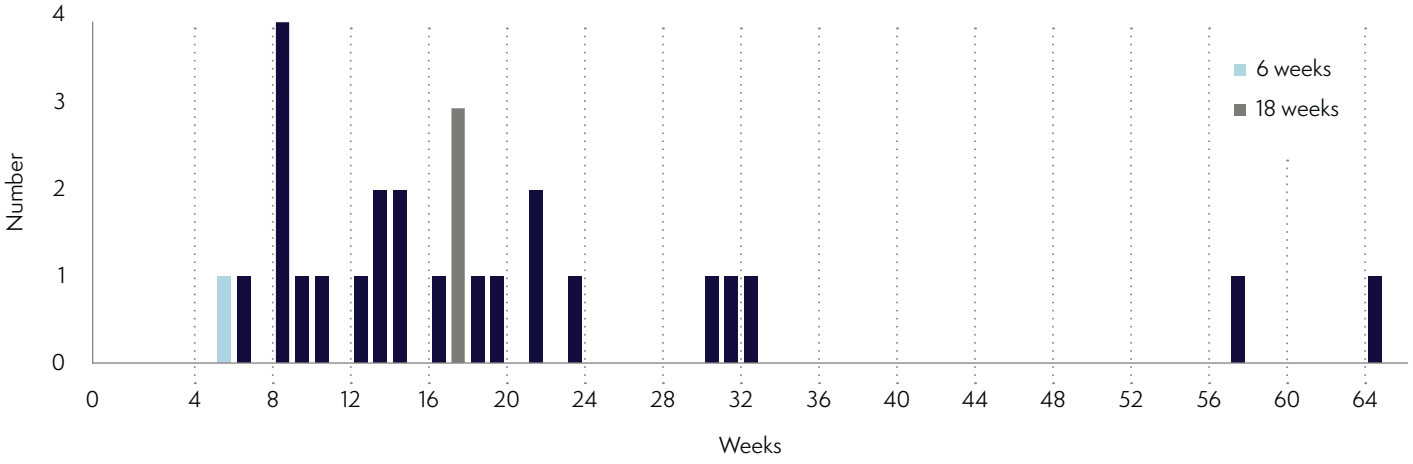


Figure 12c. Weeks from referral to first clinic visit for NCEPOD urgent cases
Median 14 weeks, minimum 42 to max 460 days



Quality of urgent investigation

Even urgent cases had deficiencies in investigations, with missing culprit agents and incomplete investigation. Of 20 assessments where a judgement was made, two were 'good', twelve 'good and poor', and six 'poor'. The allergy clinic and panel identified culprits in 25 (86%).

NMBA panels were inadequate in 55% of cases, skin prick testing in 69%, and intradermal testing in 76%.

Forty-one per cent had appropriate avoidance advice, and 66–76% had appropriate letters to GP, patient and anaesthetist. Hazard warning advice was issued to 41%.

Ten (34%) patients were still at potential risk after investigation: seven from defective avoidance advice and four due to poor communication. Two anaesthetists received insufficient information to plan safe future anaesthetics.

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

Diagnostic concordance between clinic and panel for urgent cases

Of 29 cases, the anaesthetist provided a suspect in 19 cases and the panel agreed with this in 15 (75%). Excluding multiple (>2) triggers the clinic identified a trigger in 18 cases and the panel agreed in 14. The panel identified a definite or probable trigger in 22 (76%) cases. In twelve (41%) cases the anesthetist, the allergy clinic and the panel all agreed the trigger, which was an antibiotic or NMBA in all but two cases.

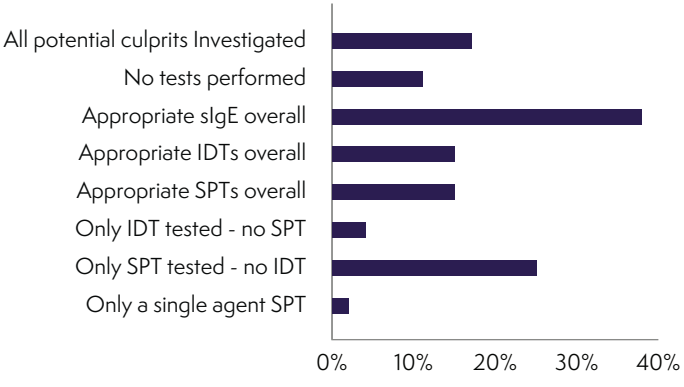
As a result of extended avoidance advice, the clinic safely advised avoidance of the panel-identified culprit agent in 20/29 (69%) cases.

Overall guidance adherence

Adherence to guidelines was generally poor, in contrast to high self-reported adherence in the NAP6 baseline survey (Figure 13).

There was full compliance with AAGBI guidance in 32% of cases, and with BSACI guidance in 17%. Most non-adherence was through failing to test for potential culprits, deficiencies in communication with patients or healthcare staff. Out of the 184 cases, 26 (14%) had only minor omissions.

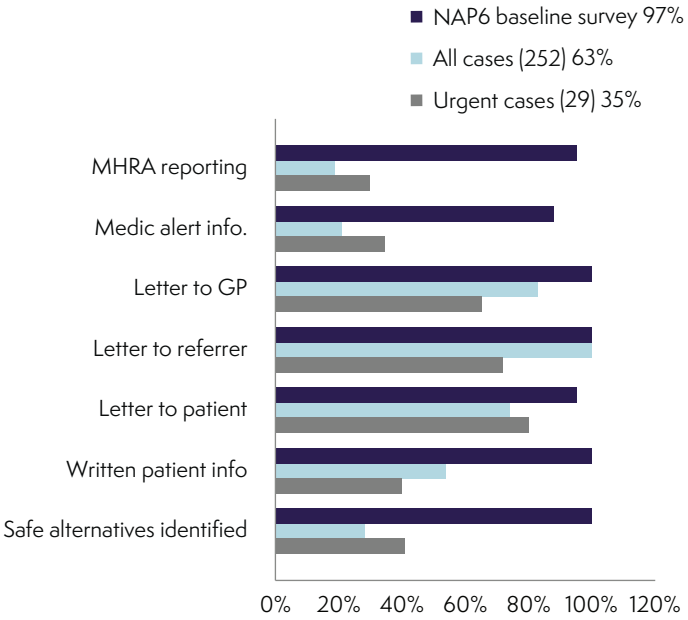
Figure 13. Tests used in allergy clinic assessment
SPT = skin prick testing, IDT = intradermal testing



Written communication

Adherence to communication standards was much worse than the NAP6 baseline survey (Figure 14). Provision of written information to patients before clinic was rare, and information on patient support groups was only provided in 25% of cases. Written advice was given on safe alternatives in only 28% of cases and avoidance advice in 63%.

Figure 14. Adherence to guideline communication standards by allergy clinics



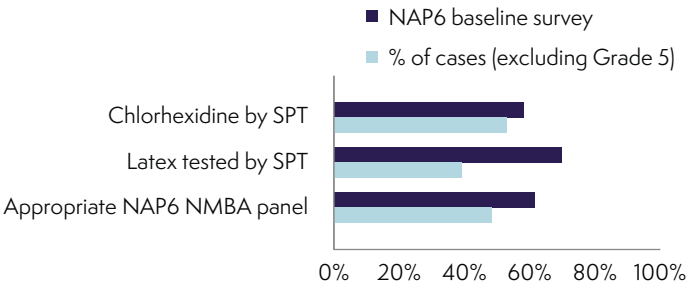
Hazard alert provision

The NAP6 baseline survey suggested that 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 14).

Testing strategies

Use of skin prick testing (SPT) and intradermal testing (IDT) were similar to that reported in the NAP6 Allergy clinic baseline survey (Chapter 13). Use of the NAP6 minimum NMBA panel and latex testing was less than in the baseline survey (Figure 15).

Figure 15. Adherence to guideline test standards by allergy clinics



The appropriateness of the tests used was assessed (Figure 13 above). 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 reactions and antibiotics.

Forty potential drug culprits were omitted in the 184 reviewed cases (see Supplementary 1). Ondansetron, latex, chlorhexidine and fentanyl were the most frequently omitted.

NMBA

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

Chlorhexidine

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

Latex

Only 31% of cases were tested, mostly by sIgE blood tests. Only one weak latex IgE positive was seen, and only one of twelve skin prick tests was positive.

Multiple positivity to other agents

This was especially notable in those with chlorhexidine positive tests, but occurred in all diagnoses (Table 5).

Table 5. Multiple sensitisations observed in the NAP6 cohort

Culprit	SPT positive to other agents/ No. tested to other agents	IDT positive to other agents/ No. tested to other agents	sIgE positive to other agents/ No. tested to other agents
Chlorhexidine	**2/14**	**1/7**	**1/8**
	1 equivocal 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	**4/26**	**4/25**	**0/8**
	1 positive to tazocin and amoxicillin	1 equivocal to all agents but teicoplanin, 1 equivocal to chlorhexidine, 1 equivocal to gentamicin	-
	1 positive PPL and MDM penicillin determinants	1 positive to gentamicin	-
	1 positive to atracurium	1 positive to ketamine	-
	1 positive to atracurium	-	-
Rocuronium	**9/20**	**8/14**	**1/9**
	1 positive to vecuronium and pancuronium and suxamethonium	1 positive to atracurium, vecuronium, chlorhexidine, ondansetron but negative to suxamethonium	1 positive to chlorhexidine
	1 positive to pancuronium and suxamethonium	1 positive 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 alfentanil	-
	1 equivocal to vecuronium	1 equivocal to gentamicin and propofol	-
	1 equivocal to chlorhexidine	1 positive to pancuronium, vecuronium and cisatracurium, and negative to suxamethonium and atracurium	-
	1 equivocal to propofol and fentanyl	1 positive to atracurium, mivacurium and vecuronium, and negative to suxamethonium and pancuronium	-
	1 equivocal to cisatracurium and suxamethonium	-	-
Suxamethonium	**5/10**	**2/6**	**1/6**
	1 positive to rocuronium and suxamethonium (no other NMBA done)	1 positive to rocuronium and atracurium	1 positive to chlorhexidine and suxamethonium
	1 positive to vecuronium and suxamethonium only	1 positive to rocuronium and vecuronium	-
	1 positive to all NMBAs plus chlorhexidine	-	-
	1 positive to cisatracurium, chlorhexidine, atracurium, vecuronium, but not to pancuronium, mivacurium or rocuronium	-	-
	1 positive to atracurium and negative to suxamethonium	-	-

Skin testing and concentrations used

In total, 51% had SPTs reported, 34% IDTs and 71% sIgE. Table 6 shows that the two skin tests to not provide equivalent results.

Few data were returned on use of non-irritant concentrations.

Table 6. Skin prick tests, intradermal tests and sIgE tests are not equivalent. All tests where >25% are positive are in bold

Test results reported	SPT done (% tested)	SPT +ve (%)	IDT done (% tested)	IDT +ve (%)	sIgE done (% tested)	sIgE +ve (%)
Penicillins	26 (15%)	**10 (38%)**	20 (12%)	**5 (25%)**	47 (28%)	**13 (28%)**
Teicoplanin	9 (5%)	2 (22%)	9 (5%)	**5 (55%)**	n/a	n/a
Rocuronium	15 (9%)	**7 (47%)**	18 (11%)	**6 (33%)**	n/a	n/a
Atracurium	31 (18%)	5 (17%)	23 (14%)	**7 (30%)**	n/a	n/a
Suxamethonium	9 (5%)	**6 (67%)**	3 (2%)	**1 (30%)**	27 (16%)	4 (15%)
Chlorhexidine	25 (15%)	**8 (32%)**	11 (7%)	**5 (45%)**	73 (43%)	15 (21%)
Patent Blue	4 (2%)	**4 (100%)**	1 (0.5%)	**1 (100%)**	n/a	n/a
Latex	12 (7%)	1 (8%)	0	0	41 (24%)	1 (2%)
Local anaesthetic	4 (2%)	0	5 (3%)	0	0 (0%)	0

Specific IgE (sIgE) blood tests

A limited range of the available sIgE tests was used, including chlorhexidine, penicillins and latex (Table 7).

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 (see Supplementary 2).

Table 7. Specific IgE blood test results in the NAP6 cohort

Name	No. Tested	No. Positive
Penicilloyl G (benzyl penicillin)	35	11
Penicilloyl V (phenoxymethylpenicillin)	34	10
Ampicilloyl	15	7
Amoxicilloyl (amoxycillin)	31	1
Clavulanic Acid	2	1
Cefaclor	4	0
Gentamicin	4	0
Suxamethonium	17	3
Pholcodine	4	0
Chlorhexidine	57	16
Latex	28	0
Morphine (quaternary ammonium compounds)	3	2
Diclofenac	1	0
Codeine	1	1
Gelatin Bovine	3	0

Pholcodine exposure

Pholcodine exposure is rarely queried or recorded in UK practice, in line with the baseline survey. Eighty-seven (33%) reported no exposure. Pholcodine was only tested in four cases.

Challenge testing

Twenty-four (16%) cases reported the results of challenges (Table 8). In ten of these the panel thought the challenges were incomplete or inappropriate.

Preparation for anaesthesia allergy testing

Table 8. 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	250	mg	Negative
Bupivacaine	-	-	Negative
Bupivacaine	5	mg	Negative
Bupivacaine 0.25%	1.25	mg	Negative
Celecoxib oral	100	mg	Negative
Co-Amoxiclav oral	-	-	Negative
Fentanyl	5	mcg	Negative
Lidocaine	5	-	Negative
Lidocaine 1%	-	-	Negative
Lidocaine 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

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 (Table 9).

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.

Table 9. Patient risks following allergy clinic investigation

At risk from inadequate allergy referral	At risk from inadequate clinic investigation	At risk from inappropriate clinic advice	At risk from inadequate communication with patient	At risk from inadequate communication with Team
4%	38%	76%	17%	23%

Accuracy of diagnosis and concordance

There was good concordance between the clinic and the panel diagnoses (Table 10). Most lack of concordance between clinic and panel was for ondansetron, teicoplanin and atracurium.

Seven cases had two culprits that were equally probable. Eighty-eight per cent of cases identified the same trigger in the clinic and the panel. 74% were correctly predicted by the anaesthetist.

Table 10. Diagnostic concordance between anaesthetist, clinic and NAP6 panel

Clinic, panel and anaesthetist	Clinic and panel	Anaesthetist and panel but not clinic	Anaesthetist and clinic but not panel
65.5%	22.5%	8.5%	3.5%

Reporting to local incident reporting systems and the Medicines and Healthcare products Regulatory Agency (MHRA)

Less that one quarter of cases were reported to the MHRA, in contrast to approximately three quarters that were reported to the local incident system. In children the frequency of reporting was even lower. This is discussed in Chapter 24, Reporting and learning.

Overall quality of allergy clinic assessment

The panel noted that all potential culprits had been adequately investigated in only 27%.

Of 165 assessable cases 10% of assessments were judged 'good', 49% 'good and poor', and 41% 'poor' (Table 10). The most common deficiencies were failing to test for all potential culprit agents, poor communication with the patient or healthcare staff, and failure to report to the MHRA report (Table 11).

Table 11. NAP6 panel review of quality of investigation

Quality of Clinic Assessment	Number	%
Good	17	10%
Good and Poor	81	49%
Poor	67	41%
Unassessable	15	–

Harm to the patient was rare

Overall, 9% of anaesthetists did not feel that the clinic provided enough information to safely plan future anaesthesia, 4.5% had low confidence in the allergy clinic diagnosis: 4 specifically noted that no trigger was identified, 5 reported a lack of clear alternative drugs to use, 5 noted poor communication of results or avoidance advice, and 4 cited delayed investigation or challenge testing.

Avoidable causal factors

Only three events were judged avoidable. There were few incidences of failed risk-factor identification in preoperative history taking, failed recording or ignoring of relevant information (Table 12). These included administration of diclofenac to a NSAID sensitive individual, penicillin to a penicillin-allergic individual (a recognised cause of litigation) (Cranshaw 2009), and probably the unnecessary co-administration of both co-amoxiclav and teicoplanin.

Table 12. Avoidable causal factors

Incomplete pre-intervention allergy history (n)	Pre-intervention allergy history not heeded (n)	Possibility of cross-sensitivity not heeded (n)	A previous reaction was not appropriately investigated (n)	Was the index event preventable? (n)
3	6	3	3	3 (1.5%)

Discussion

Most referrals were by anaesthetists and were consistent with BSACI (Ewan 2010) and AAGBI (Harper 2009) guidelines, but provision of information to the clinic was suboptimal.

Clinics were unable to make timely assessments for most cases. Patients were rarely seen within six 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.

Approximately 400–600 Grade 3–5 cases are expected annually in the UK, which is similar to previously reported estimates (Egner 2016, Low 2016, Mertes 2011) and the NAP6 baseline survey (Egner 2017a). NAP6 received 266 completed and admissible two-part reports from across the UK. This suggests some under-reporting (Egner 2016). Some cases were lost due to lack of Part B forms or insufficient detail to be interpretable.

Tryptase-sample timing was often suboptimal, and was sometimes too late to estimate peak tryptase. NAP6 data shows rapid reduction within 30 minutes and support BSACI and AAGBI Guidelines (first sample immediately post-reaction, second at 1–2 hours, plus a 24-hour baseline) (Harper 2009, Savic 2015). Second samples within 6 hours can still be informative (ANZCA guidelines suggest 1, 4 and 24 hour samples) (Kolawole 2017).

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.

Basal tryptase levels did not correlate with severity or grade of reactions – unlike the weak correlation in venom anaphylaxis. (Rueff 2009).

Few cases had elevated baseline tryptase suggesting mastocytosis or raised alpha tryptase due to gene duplication – now sometimes referred to as 'hyper-alpha trypsaemia syndrome' (HATS) (Lyons 2016).

Median peak tryptase and first tryptase results by grade were similar to those previously reported (Egner 2016). Higher values appeared to be more strongly linked to rapidity of onset than to trigger agent.

Anaesthetists predicted the culprit agent correctly in 75% of cases, but were prone to overlook chlorhexidine as a cause (see Chapter 17, Chorhexidine). The closest temporal administration is a good guide to causation, except for chlorhexidine, Patent Blue, latex and orally administered drugs for which later reactions are not uncommon. Late reactions may also occur with atracurium or co-amoxiclav.

Case series have demonstrated that the dynamic-tryptase algorithm can detect possible mediator release more sensitively than thresholds (Egner 2016, Baretto 2017). In NAP6 this algorithm increased detection of acute release, and it should be used when the peak tryptase level is within the reference range.

Compliance with guidelines for investigation was generally poor, and lower than self-reported compliance in the NAP6 baseline survey. Only 32% fully complied with AAGBI guidance, and only 17% with BSACI guidance. Non-compliance was mostly due to failure to test all potential culprits, or to deficiencies in communication with patients and healthcare staff.

Use of skin, blood and challenge testing appears suboptimal even when available. Use of extended NMBA panels is effective in selecting low risk of future reactions (Leysen 2014). 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 sensitisation and cross-reactivity, including specific concentrations and modalities. Skin prick tests and intradermal tests do not give the same results for all triggers.

The clinic must identify safe alternatives where multiple NMBAs test positive. It is difficult to know what to do with multiple positive IDTs, particularly as false positives do occur (Leysen 2014, Trautmannn 2016, Brockow 2013, Mertes 2007). Cross-sensitisation to NMBAs is discussed in Chapter 16, NMBAs.

Pan-reactivity across related drugs occurs, but is not always clinically relevant; there are reports of patients tolerating drugs which have given positive allergenic 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. In several cases excessive avoidance advice created problems for patients or anaesthetists after allergy clinic visits. The NAP6 panel recommends that direct involvement of an anaesthetist in all clinics is essential for the provision of reasonable advice on avoidance and on alternative safe drugs/plans.

Few reporters (42%) were able to provide details of the concentrations used, but there was considerable variation in those that did. Specialist centres should use consensus or locally-derived threshold non-irritant doses. Maximum non-irritant concentrations need to be identified for novel drugs with increasing usage.

Importantly, multiple positivity is common in the NAP6 cohort in both skin testing and sIgE tests. This creates at least a possibility that multiple triggers are involved in some cases, including those where a single culprit could not be identified. In this cohort seven of 192 cases with definite or probable triggers were judged to have two equally likely triggers. Further research and guidance is needed.

In the presence of chlorhexidine-positive tests, multiple positivity to other agents was common in intradermal and sIgE testing, but not in skin prick testing. This confirms previous observations in a UK cohort (Egner 2017b). The NAP6 dataset extends this observation of multiple positivity to cases of teicoplanin, rocuronium and suxamethonium allergy. This has implications for order and modality of testing, for the need to test for all potential culprits, and for critical appraisal of the imputability of each potential trigger.

Latex is not a cause of perioperative anaphylaxis in NAP6. Latex allergy has been falling in France since the late 1990s (Vandenplas 2007). Latex-free theatres and hospitals are now common in the UK and new sensitisations unlikely.

The NAP6 panel diagnosis and the clinic diagnosis agreed more frequently than published for the best Bayesian methods in general drug allergy (Agbabiaka 2008, Varallo 2017). This may be helped 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 caused serious reactions to teicoplanin. Use of teicoplanin as a penicillin substitute is increasing (see Chapter 6, Main findings; Chapter 15, Antibiotics); 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.

Communication to patients and anaesthetists fell short in this cohort. In Appendix A we provide a template of the information dataset that could usefully be included in a report from an allergy clinic to the referring anaesthetist and their GP. In Appendix B we provide a template letter to the patient for use after an allergy clinic visit.

MHRA reporting was poorer than the baseline survey. Reporting through the index anaesthetist (AAGBI guideline) is problematic if identification of the culprit agent may change on clinic investigation. BSACI expects the allergy clinic to report, but this risks duplicate reporting of differing conclusions. Ensuring the MHRA report identifier is provided in clinic letters, or nominating a departmental anaesthetic lead to report after final clinic assessment are potential solutions (see Chapter 11, Immediate management and departmental organisation and Chapter 24, Reporting and learning).

Evidence that future avoidance advice was comprehensive and safe 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, and those were mostly to oral penicillins or intravenous teicoplanin. Three out of four teicoplanin challenges were positive. NMBA challenges are rarely done in the UK, although common in Denmark (where NMBA allergy is rare, and the risks may be different). As an alternative, challenge tolerance to alternative drugs can be established to facilitate other anaesthetic approaches, and this was used by some centres.

In conclusion, NAP6 shows that adherence to existing guidelines is poor and confirms deficiencies in service availability, capacity, harmonisation 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
- Patients should not have to undergo non-urgent surgery without a completed allergy clinic assessment
- Harmonisation 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
- Including all potential culprits and all relevant test modalities (SPT, IDT, sIgE and, where appropriate, challenge testing), since different test modalities do not always yield consistent results
- More data on the predictive values of different modes of testing using standardised methods are required for all triggers
- Better standardised clinic reports should be developed to encourage reporting of all the relevant information, which should include, drugs identified, type of reaction, drugs to avoid, safe alternatives, tests used, and recording the communication of results to anaesthetists, GPs and patients
- Improved communication of the results of urgent investigations, clearly and reliably, to the anaesthetist.

Recommendations

National

- There is a pressing need for investment in and expansion of specialised perioperative allergy clinic services to ensure prompt investigation of urgent cases and to ensure 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
- 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

- Patients should be given appropriate information after investigation of perioperative anaphylaxis in an allergy clinic. This information should also be sent to their GP and entered in their medical record. Recommended content is shown in the NAP6 template allergy clinic patient letter (Chapter 11, Appendix B)
- Specialist perioperative allergy clinics should adopt a multidisciplinary-team 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

- 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 (eg. the NAP6 or AAGBI pro-forma) should accompany the referral
- Outcomes of urgent investigations by allergy clinics should be communicated urgently and directly to the referring anaesthetist, ideally by phone and in writing
- Allergy clinics should provide standardised clinic reports to encourage better communication to anaesthetists, GPs and patients. Recommended content is in the NAP6 recommended allergy clinic letter (Chapter 11).

Individual

- 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, ie. the consultant anaesthetising or supervising the case
- The anaesthetist referring the patient for investigation of perioperative anaphylaxis should explain the importance of attending the clinic, and allay any fears the patient may have to improve uptake of allergy clinic appointments
- Blood samples for mast cell tryptase (MCT) should be taken in accordance with national guidelines:
  - 1st sample as soon as the patient is stable
  - 2nd sample as close to 1–2 hours after the event as possible
  - 3rd (baseline) at least 24 hours after the event
- Where the baseline sample is not collected prior to attending the allergy clinic it should be collected at the clinic
- If the MCT is elevated more than 24 hours after the event, the possibility of a mast cell disorder should be considered
- A dynamic rise and fall in mast cell tryptase should be used to detect mediator release
- Where peak mast cell tryptase level is less than the upper limit of the reference range (ie, the 99th centile limit of 14 mcg/L) a dynamic rise and fall in tryptase level may still be useful to diagnose anaphylaxis
- When investigating suspected perioperative anaphylaxis, chlorhexidine and latex should be tested
- More than one test for chlorhexidine is necessary to exclude allergy
- 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
- All potential culprit agents 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
- Avoidance advice should be specific and not excessive, as this may lead to harmful consequences. When no culprit agent is identified, further investigations should be carried out rather than giving 'blanket advice' on avoidance of multiple drugs
- All skin testing should be at concentrations validated to be below the non-specific histamine-releasing/irritant concentrations (as published and verified locally)
- 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 (ie. establishing whether either succinylcholine (suxamethonium) or rocuronium is safe). The NAP6 minimum NMBA panel is suitable for this
- The possibility of reaction to more than one agent should be considered
- Specific IgE bloods tests should be used for agents for which they are available, as no modality is 100% sensitive or specific
- 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
- Broad advice to avoid beta-lactam should be discouraged, and patients should be further investigated to clarify the specific drug(s) to avoid and to identify safe alternatives
- Allergy clinics should advise patients to keep a copy of their drug allergy clinic letter with them at all times, and to use this to inform clinicians of their allergy, particularly when attending hospital appointments or before future surgery.

Research

- As none of the test modalities is wholly reliable, there needs to be research to establish an appropriate form of challenge testing for chlorhexidine
- More data on the predictive values of different modes of testing using standardised methods are required for all triggers
- There is a need for further research and consensus on the logical interpretation of positive tests where mast cell tryptase level is not raised, and negative tests where mast cell tryptase level is raised, as current guidance is lacking
- Studies are needed to establish the influence of mast cell activation disorders on the severity and clinical presentation of perioperative anaphylaxis.

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Supplementary 1. 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, NSAID, ondansetron, paracetamol, parecoxib, povidone iodine, prochlorperazine, propofol, ranitidine, rocuronium, remifentanil, teicoplanin, thiopental, tranexamic acid, vecuronium.

Supplementary 2. Potentially relevant sIgE tests not used in NAP6

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

Appendix A:

Recommended content of standard allergy clinic letter to the referring clinician following assessment of 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	eg. 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 sIg E tests	List with results
	Negative sIg E 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

Appendix B:

Letter to the patient following allergy clinic visit for investigation of perioperative anaphylaxis

[Hospital HEADER] Date ……..

Patient's name .....

Patient's address .....

Medical record number ……..

NHS Number ……..…....

Dear .....

Following your investigation at the ……..perioperative allergy clinic.
We have concluded the following –

You have had a reaction classified as:
Allergic anaphylaxis/Non-allergic anaphylaxis/Not an allergic event

The agent(s) identified as the cause of this are:

1) ……..

2) ……..

3) ……..

You should avoid all these drugs and agents in the future as exposure to them may lead to a serious or even fatal reaction.

The diagnosis was made based on the following tests:

1) ……..

2) ……..

3) ……..

We have established safe alternatives to these drugs as:

1) ……..

2) ……..

3) ……..

Your GP has been written a more detailed letter which you may wish to discuss with him/her.

You should consider:

A) Wearing a medic alert bracelet/necklace available from ……

B) Carrying this letter with you to all Medical or Dental appointments and discussing its contents prior to any procedure

C) Carrying an adrenaline auto-injector for emergency treatment yes/no

Yours sincerely,

Consultant Allergist/Clinical Immunologist

Contact phone number……