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**Anaesthesia, surgery and life threatening allergic reactions.  
Epidemiology and clinical features of perioperative  
anaphylaxis: The 6th National Audit Project.**

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# Anaesthesia, surgery and life threatening allergic reactions. Epidemiology and clinical features of perioperative anaphylaxis: The 6<sup>th</sup> National Audit Project.

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36 **Running head:** NAP6: Epidemiology and clinical features  
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40 **Abstract 250**

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42 **Paper 5728**  
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**Abstract (250 words)**

The 6th National Audit Project on perioperative anaphylaxis collected and reviewed 266 reports of grade 3-5 anaphylaxis over one year from all National Health Service hospitals. Estimated incidence is  $\approx 1:10,000$  anaesthetics. Case exclusion due to reporting delays or incomplete data means true incidence may be 70% higher. The distribution of 199 identified culprit agents was antibiotics 47%, neuromuscular blocking agents (NMBA) 33%, chlorhexidine 9% and Patent Blue dye (PBD) 4.5%. Teicoplanin comprised 12% of antibiotic exposures but caused 38% of antibiotic-induced anaphylaxis. Suxamethonium-induced anaphylaxis, mainly presenting with bronchospasm, was two-fold more likely than other NMBAs. Atracurium-anaphylaxis mainly presented with hypotension. Non-depolarizing NMBAs had similar incidences to each other. There were no reports of latex-induced anaphylaxis.

Commonest presenting features were hypotension, (46%), bronchospasm (particularly in patients with morbidly obesity and asthma) (18%), tachycardia (9.8%), oxygen desaturation (4.7%), bradycardia (3%) and reduced/absent capnography trace (2.3%). All patients were hypotensive during the episode. Onset was rapid for NMBAs and antibiotics but delayed with chlorhexidine and PBD. There were ten deaths and 40 cardiac arrests. The review panel judged that cardiac compressions should be started in adults with systolic blood pressure  $< 50$ mmHg. Pulseless electrical activity was the usual type of cardiac arrest, often with bradycardia. Poor outcomes were associated with increased ASA, obesity, beta blocker and or ACE-inhibitor medication.

Seventy percent of cases were reported to the hospital incident reporting system and only 24% to Medicines and Healthcare Regulatory Authority via the Yellow Card Scheme.

This paper describes summary findings from NAP6: the full report is at

<http://www.nationalauditprojects.org.uk/NAP6Report#pt> .

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

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3 Anaphylaxis is defined as a severe, life-threatening generalized or systemic hypersensitivity  
4 reaction.<sup>1</sup> Most anaphylactic reactions are allergic. Severity is commonly graded 1-5, though multiple  
5 grading systems exist. Mild reactions, grades 1 and 2, do not constitute anaphylaxis. NAP6  
6 investigated grades 3, 4 and 5 (fatal) reactions occurring in the perioperative period.  
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9  
10 Estimates of the incidence of perioperative anaphylaxis vary between 1:6,000 to 1:20,000  
11 anaesthetics.<sup>2</sup> In a large French study, the estimated incidence of IgE-mediated perioperative  
12 hypersensitivity (grades 1-4) was 1:10,000 anaesthetics.<sup>3</sup>  
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15  
16 Perioperative anaphylaxis may vary over time and between different patient populations. Most  
17 studies have identified neuromuscular blocking agents (NMBAs) as the commonest cause. In a  
18 French study, latex was the second-commonest cause of anaphylaxis: unlike in a more recent UK  
19 study.<sup>4</sup>  
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24 The majority of previous reports have included all grades of perioperative hypersensitivity and all  
25 report similar patterns of clinical features (Table 1). In a small number of cases, there may be single  
26 organ-system involvement<sup>3 4</sup> and cutaneous features predominate in mild, non-IgE mediated  
27 perioperative hypersensitivity<sup>3 4</sup>. Most studies agree that the clinical features of severe anaphylaxis  
28 are very similar regardless of whether allergic or non-allergic,  
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33 It is important to understand how severe anaphylaxis presents as there is a wide differential  
34 diagnosis, no bedside tests, and prompt, specific treatment is essential.<sup>5 6 7</sup>  
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39 There are few large prospective studies of perioperative anaphylaxis with most looking  
40 retrospectively at cases that have been referred to allergy clinics for investigation. In addition, few  
41 studies have focused solely on severe (Grade 3-5) perioperative anaphylaxis or investigated  
42 relationships between presenting features and co-morbidities/concomitant medication. Individual  
43 trigger agents may elicit disparate patterns of presentation, including onset time, cardiovascular or  
44 respiratory system preponderance and outcomes may also differ.  
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50 It is known that onset of anaphylaxis to chlorhexidine, latex and Patent Blue dye can be delayed<sup>6 8-10</sup>  
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## Methods

Methods are discussed in detail in an accompanying paper.<sup>11</sup> Denominator data were derived from the NAP6 Activity<sup>12</sup> and Allergen Exposure<sup>13</sup> studies.

## Results

We identified 266 cases of Grade 3-5 anaphylaxis meeting our inclusion criteria. A further 261 cases were excluded due to failure to provide information on allergy clinic investigation, lack of detail or being uninterpretable, as described in the Methods paper.<sup>11</sup>

The Activity survey<sup>12</sup> estimated that 3 126 067 anaesthetics are delivered in the UK each year, giving a calculated incidence of perioperative anaphylaxis of 1:11 752.

In 148 cases the culprit was identified as 'definite' and in 51 cases as 'probable' (including seven cases where two probable culprits were identified), giving a total of 199 identified culprit agents. In 15 cases the culprit was designated 'possible' and in 57 cases the culprit could not be identified. The most common cause of perioperative anaphylaxis was antibiotics, followed by NMBAs, chlorhexidine and Patent Blue dye (Table 1).

(Table 1 near here)

Fifty-eight percent of the anaphylactic events occurred in the operating theatre, of which 3% were before induction of anaesthesia, 81% after induction and before surgery, 13% during surgery and 3% after surgery.

### *Clinical features*

The first clinical feature was hypotension (46%), bronchospasm/high airway pressure (18%), tachycardia (9.8%), cyanosis/oxygen desaturation (4.7%), bradycardia (3%) and reduced or absent capnography trace (2.3%). Three patients presented with cardiac arrest (1.2%). Bronchospasm was the presenting feature more frequently in morbidly obese compared with other patients and in (mainly well-controlled) asthmatic patients: (34%) compared with non-asthmatic patients (15%).

(Figure 1 near here)



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3 Presentation was similar regardless of whether the mechanism was allergic or non-allergic. In  
4 approximately 1 in 20 cases an awake patient reporting feeling unwell was the harbinger of  
5 anaphylaxis (Fig, 1). Fifteen (5.6%) patients presented with isolated cardiovascular features and four  
6 (1.5%) with isolated respiratory features.  
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10 (Figure 2 near here)  
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14 Hypotension as the presenting feature was proportionately more common in men than women,  
15 perhaps related to coronary artery disease (23.7% vs 8.4%), beta blockers (26.7% vs 11.2% and ACE-I  
16 medication (21.2% vs 15.2%). Bronchospasm was more common in women: more women had  
17 asthma (25% vs 15.5%) (Supplementary figure 1).  
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21 There was a marked difference between NMBA: bronchospasm was the most common  
22 presentation when suxamethonium was the trigger and hypotension with atracurium (Figure 3).  
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26 (Figure 3 near here)  
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30 Considering clinical features present *at any time* during the anaphylactic episode, hypotension was  
31 universal. Rash, seldom a presenting feature, developed in 56.4% of cases, bronchospasm/high  
32 airway pressure in 48.5%, tachycardia in 46.2%, cyanosis/oxygen desaturation in 41.4% and a  
33 reduced/absent capnograph trace in 32.7%. Bronchospasm at any time was also seen in a higher  
34 proportion of patients with asthma (59%) than others (46%). Again, this clinical pattern was very  
35 similar in the subgroup of allergic anaphylaxis patients (Figure 4).  
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40 Two notable features were almost absent. Rash was an uncommon presenting feature and was  
41 notably rare at any time in the most serious of cases. Airway problems were also rarely seen. A  
42 single patient required a front of neck airway to manage laryngeal oedema but there were no other  
43 presentations or significant clinical features of airway difficulty.  
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48 (Figure 4 near here)  
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52 Considering all cases, onset time was < 5 min in 66.2%; < 10 min in 82.7%; < 15 min in 87.6% and <  
53 30 min in 94.7%. Onset times for individual agents are discussed below.  
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3 *Fatalities, cardiac arrests and profound hypotension*

4 Ten patients died directly (eight) or indirectly (two) due to anaphylaxis, equating to an incidence of  
5 perioperative death from anaphylaxis of 1 in 313 000 and a per case mortality rate of 1 in 26.6 cases.  
6 All fatalities were aged >46 yrs and half aged >66. Two were ASA 2, six ASA 3 and two ASA 4. In the  
7 Activity survey<sup>12</sup> 25% of patients were aged >66 yrs, 77% were ASA 1-2 and <2% ASA 4-5.  
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12 Only one patient was of normal weight; four were overweight, one obese and four morbidly obese.  
13 In the Activity Survey<sup>12</sup> 21% of all patients were obese or morbidly obese. None of the patients who  
14 died had a history of atopy or asthma. Five had coronary artery disease, most of whom were  
15 undergoing non-cardiac surgery; six were taking beta blockers and six ACE inhibitors. Three were  
16 taking both and one patient neither drug. Amongst the 266 reports of life-threatening anaphylaxis  
17 14.7% had evidence of coronary artery disease, 17.4% were taking beta-blockers and 17.1% were  
18 taking ACE inhibitors.  
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25 Three patients were undergoing cardiac surgery. The surgical procedure was abandoned in nine  
26 cases and proceeded in one. Cardiac arrest was PEA in all fatal cases, none preceded by significant  
27 arrhythmias, though there was bradycardia in two. The clinical features (presenting, and at any time  
28 during the episode) of the ten fatal cases are shown in Figure 5. Management of these cases is  
29 described in the accompanying paper<sup>14</sup>  
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34 (Figure 5 near here)  
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37 Forty (15%) patients, all of whom were adults, experienced cardiac arrest, including nine of the  
38 patients who died. Thirty-one (77.5%) survived. Most (81%) events occurred after induction of  
39 anaesthesia and before surgery. A consultant was involved in all resuscitations. No particular trigger-  
40 agents were associated with a higher risk of cardiac arrest. However, survivors of cardiac arrest were  
41 younger, fitter and less comorbid than patients who died (Table 3).  
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46 (Table 3 near here)  
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50 The presenting features are shown in Figure 6. Hypotension and bronchospasm/raised airway  
51 pressure were prominent, and rash notably uncommon. Reduced or absent capnogram trace was  
52 not recorded as a presenting feature in any cases. Bradycardia was more common than tachycardia.  
53 Cardiovascular presenting features occurred in 25, respiratory in 11 and others in four. Of all cardiac  
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3 arrests 34 were pulseless electrical activity (PEA), 4 VF/VT and 2 asystole. Only six patients  
4 developed an arrhythmia prior to cardiac arrest: four bradycardia and two ventricular tachycardia.  
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6 There were no reports of atrial fibrillation or supraventricular tachycardia.  
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9 (Figure 6 near here)  
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12 Harm, as a result of anaphylaxis was judged to occur in 10 (32%) of 31 survivors. Sequelae included  
13 new anxiety, a change in mood, impaired memory, impaired coordination, impaired mobility,  
14 symptoms of PTSD, myocardial damage, heart failure and new renal impairment were reported.  
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18 In adult patients the lowest BP recorded in the first hour after the event was 'unrecordable' in 56  
19 (21%) cases, <50 mmHg in 58 (22%) cases and 51-59mmHg in 53 (20%) cases.  
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### 22 23 *Antibiotics*

24  
25 Ninety-two cases of antibiotic-induced anaphylaxis were identified (including 94 definite or probably  
26 antibiotic culprits): 48% of all cases with identified culprits. The majority were caused by co-  
27 amoxiclav or teicoplanin, between them accounting for 89% of identified antibiotic culprits. The  
28 overall incidence of reported antibiotic-induced anaphylaxis was 4.0 per 100,000 exposures. The  
29 highest incidence was seen with teicoplanin (16.4 per 100 000 exposures) then co-amoxiclav (8.7 per  
30 100 000 exposures). The relative anaphylaxis rate using cefuroxime as an index was 17.4 for  
31 teicoplanin and 9.2 for co-amoxiclav (Table 4)  
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37 The onset of anaphylaxis was within 5 minutes in 74% of cases; 18% between 6-10 minutes; 5%  
38 between 11-15 minutes, 2% between 16-30 minutes. None were delayed >30 minutes.  
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42 Of the 36 patients who reacted to teicoplanin, 20 (56%) stated preoperatively they were allergic to  
43 penicillin. Of the 36 reactions 16 were grade 3, 18 grade 4 and two grade 5. Ten developed  
44 moderate and two severe harm (death). Amongst the 20 who likely received teicoplanin because of  
45 a history of allergy, two reactions were grade 4 and one grade 5, six developed moderate harm and  
46 one died. The NAP6 Allergen survey<sup>13</sup> demonstrated the choice of antibiotic was influenced by  
47 preoperative allergy history in a quarter of patients who received teicoplanin or vancomycin.  
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3 In less than 1% of cases, communication failure led to an antibiotic being administered despite a  
4 relevant positive allergy history. Two cases were judged preventable by better allergy history  
5 communication.  
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9 Eighteen antibiotic related reactions related to test doses: in ten cases the patient reacted to the  
10 test dose itself (52.6%), which ranged from 5 – 30% of the therapeutic dose, and the other eight  
11 patients reacted to the full dose, which was given within 1 minute of the test dose in all but one case  
12 (given within 10 minutes). There was no evidence that administration of a ‘test dose’ of antibiotic  
13 reduced the severity of an ensuing reaction. On the contrary, in cases of anaphylaxis caused by an  
14 antibiotic where a test dose had been given, a greater proportion of severe reactions (Grade 4 and  
15 5) was seen than if no test dose had been given (58% vs 51%). Of the ten deaths, four were judged  
16 to be due to an antibiotic.  
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#### 22 23 *Neuromuscular blocking agents and reversal agents*

24 Sixty-five cases of anaphylaxis were triggered by NMBA, 25% of all cases and 32% of cases leading  
25 to death or cardiac arrest. Ninety-five percent of NMBA-induced reactions presented within 5  
26 minutes.  
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31 The culprit NMBA were rocuronium (42% of cases), atracurium (35%), suxamethonium (22%) and  
32 mivacurium (1.5%). There were no cases of anaphylaxis due to vecuronium, pancuronium or  
33 cisatracurium, though these only account for 4.4% of all NMBA use.<sup>13</sup> The review panel identified  
34 non-allergic anaphylaxis to atracurium in three cases, and to mivacurium in a single case. Incidence  
35 per 100 000 exposures is a more meaningful metric than occurrence rate. The overall incidence of  
36 reported NMBA-induced anaphylaxis was 5.3 per 100 000 exposures. The highest incidence was seen  
37 with suxamethonium (11.1 per 100 000 exposures) while all others were similar to each other.  
38  
39 Suxamethonium was twice as likely to cause anaphylaxis than any other NMBA (Table 5)  
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45 In 71% of cases where the anaesthetist suspected an NMBA, the culprit was confirmed by the panel  
46 and in 14.3% an alternative culprit was identified. The ratio of suspected/confirmed cases was 1.4  
47 for atracurium, 1.3 for rocuronium and 1.1 for suxamethonium (Table 5).  
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51 (Table 5 near here)  
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3 Previous exposure to pholcodine was recorded in only two patients, both of whom had NMBA-  
4 induced anaphylaxis (rocuronium and suxamethonium) but no conclusions can be drawn due to very  
5 limited recording of pholcodine exposure. No episodes were due to neostigmine. The anaesthetist  
6 suspected that sugammadex was the suspected trigger agent in two cases, and one of these was  
7 confirmed by the review panel.  
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### 10 11 12 *Chlorhexidine*

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14 There were 18 cases of chlorhexidine-induced anaphylaxis, representing 9% of culprits. The Allergen  
15 survey<sup>13</sup> identified 2 298 567 exposures to chlorhexidine by at least one route annually (73.5% of all  
16 cases). Based on NAP6 data, the incidence of anaphylaxis to chlorhexidine is 0.78 per 100 000  
17 exposures, likely an over-estimate as almost all patients are exposed to chlorhexidine during  
18 anaesthesia and surgery.  
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22 Despite reporting chlorhexidine allergy prior to the event, one patient was exposed resulting in  
23 anaphylaxis. One patient reported a prior reaction during anaesthesia that was not investigated and  
24 reacted to chlorhexidine when exposed. One patient experienced a subsequent reaction to  
25 chlorhexidine despite confirmation of allergy to chlorhexidine following investigation of the index  
26 NAP 6 event. There was one fatal reaction. Eight reactions were grade 4 and nine were grade 3.  
27 Consistent with published data, most cases were in males (16/18). Ten were ASA grade 2 and eight  
28 ASA grade 3. Urology (6), cardiac (3) and orthopaedic (3) surgery accounted for the majority of cases.  
29

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31  
32 The anaesthetist suspected chlorhexidine in only five (28%) cases. Reactions to cutaneous  
33 chlorhexidine was mostly slower than other agents and of lower grade. There was quicker onset and  
34 greater severity in patients with exposure via a coated central venous catheter (mostly onset <5  
35 minutes of exposure and grade 4 events) than those with only topical surgical site exposure (mostly  
36 onset at 1 hour and grade 3 events).  
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41 Approximately two thirds of cases presented with hypotension and none presented with  
42 bronchospasm (Supplementary figure 2x)  
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### 44 45 46 *Patent Blue dye*

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48 We identified nine (3.4%) cases of Patent Blue dye-induced anaphylaxis, five grade 3 and four grade  
49 4. Based on an estimated 61,768 annual exposures,<sup>13</sup> the incidence of anaphylaxis to Patent Blue  
50 was 14.6/100,000 administrations (higher than suxamethonium). All patients were female: eight  
51 were scheduled for breast cancer surgery, which was abandoned in two cases.  
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3 Onset was slower than other trigger agents with only two cases <5 mins, four presented after >15  
4 mins including two after >60 mins. Hypotension was the commonest presentation: all patients  
5 became significantly hypotensive and in three cases systolic blood pressure fell below <50mmHg.  
6 Four patients desaturated to <90%. Cutaneous features were present in six patients.  
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10 All cases were resuscitated successfully and no long-term physical sequelae were reported.  
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### 12 *Miscellaneous trigger agents*

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15 We identified three cases of anaphylaxis to succinylated gelatin solutions and two to blood products.  
16 Ondansetron, propofol, aprotinin, protamine and ibuprofen were responsible for a very small  
17 number of cases. The Allergen survey estimated that 48 203 UK patients are exposed to gelatin-  
18 based IV fluids during anaesthesia each year,<sup>13</sup> giving an approximate incidence of 6.2 per 100 000  
19 administrations, a rate similar to rocuronium.  
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### 24 *Reporting*

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26 As reporting is a positive action; it was inferred that this did not take place where the information  
27 was not provided. Nine percent of cases were reported to Medicines and Healthcare products  
28 Regulatory Authority (MHRA) by the anaesthetist, 8.3% by the local co-ordinator, 3% by the allergy  
29 clinic and 2.6% by others, including critical care. Only three deaths and nine of 31 who survived  
30 cardiac arrest (29% combined) were reported to the MHRA.  
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36 Reporting to the Trust's critical reporting incident system was performed in 70.3% of cases (including  
37 eight of ten deaths and 24 (77%) of 31 cardiac arrest survivors). Of these 187 cases, 160 were  
38 reported by an anaesthetist, six by the nursing team and five by the surgical team.  
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### 42 **Discussion**

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44 The overall incidence of perioperative anaphylaxis was estimated to be 1 in 10 000 anaesthetics. This  
45 is likely an under-estimate: we received 541 reports over a one-year period; 412 had Part A and Part  
46 B completed and only 266 NHS cases met inclusion criteria, were interpretable and were  
47 grade 3-5 anaphylaxis. Inability to interpret reports was predominantly due to lack of  
48 information, usually as a result of uncertainty about the comprehensiveness of allergy clinic  
49 testing. Of the reviewed cases only 17 were not anaphylaxis or were Grade 2, suggesting  
50 that the true incidence could be up to 70% higher than our estimate. Previous estimates are  
51 similar but the majority included perioperative hypersensitivity of all grades: despite  
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3 including only Grades 3 to 5, our estimated incidence is at least as high. It is possible that  
4 the incidence of perioperative anaphylaxis is rising, perhaps as a result of increasing  
5 antibiotic sensitization in the population, and it is notable that antibiotics have overtaken  
6 NMBAs as the most frequent trigger agent. Irrespective of absolute incidences, because of  
7 our methodology we believe our results accurately represent the relative incidence with  
8 different trigger agents.  
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### 13 14 15 *Presenting features*

16 Perioperative anaphylaxis has several unusual if not unique elements. First the vast majority of  
17 triggers are administered IV, therefore having the potential for the most rapid and severe reactions.  
18 Second multiple drugs are administered almost concurrently. These routinely alter normal  
19 physiology such that hypotension, arrhythmia, bronchospasm and even rash may be more  
20 commonly due to causes other than anaphylaxis. Lastly the events occur in the immediate presence  
21 of a trained 'resuscitator' who may be able to identify and manage the event more promptly  
22 than in many other settings.  
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29 Variation in presenting clinical features between different patient groups, with different drugs and  
30 with different severity of reactions are all notable and add to the available literature. It is worth  
31 noting that hypotension was universal. Bronchospasm was less common but was more often seen in  
32 the obese and those with pre-existing asthma. Rash was rarely present, sometimes missed (the  
33 patient hidden under drapes) and was particularly uncommon in the most severe cases, often only  
34 occurring when blood pressure and presumably perfusion had been restored. Bradycardia was  
35 relatively common, again in the more severe events and arrhythmias were rare. Airway  
36 complications were almost absent.  
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### 43 *Fatalities*

44 Our data suggest that perioperative anaphylaxis was more likely to be fatal in patients who were  
45 older, of a higher ASA class and significantly obese. Unlike anaphylaxis in the community,<sup>15</sup> we found  
46 no evidence of asthma as a risk factor for fatal perioperative anaphylaxis, but coronary artery  
47 disease and administration of beta blockers and or ACE inhibitors were prominent. Patients died  
48 despite prolonged attempts at resuscitation, with most aspects of care being rated as good  
49 (described in detail in the accompanying paper<sup>14</sup>).  
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### 54 *Cardiac arrest and survivors.*

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3 Most patients who survived cardiac arrest were younger and fitter than those who died. Prescription  
4 of ACEI again was prominent in those who developed cardiac arrest. A considerable majority were  
5 PEA and the absence of tachyarrhythmias either as a primary event or secondary to adrenaline  
6 administration is notable.  
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#### 9 10 *Profound hypotension*

11 A group of patients who had profound hypotension, without being designated as 'in cardiac arrest',  
12 was identified during review as an apparently high risk cohort with some poor outcomes. There was  
13 discussion regarding the point at which cardiac compressions should be started and, after seeking  
14 wide expert advice, we decided this should be 50mmHg, so any patient with a lowest systolic blood  
15 pressure <50mmHg was designated as requiring CPR, and therefore grade 4, and where cardiac  
16 compressions were not started this was judged to have been an omission. This is a newly identified  
17 group and perhaps contentious. Their management and outcomes are discussed in the.<sup>14</sup>  
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#### 24 *Antibiotics*

25 In contrast to many published series<sup>3 16 17</sup> antibiotics, not NMBA's, were the most common cause of  
26 perioperative anaphylaxis. The high frequency of teicoplanin-induced anaphylaxis is noteworthy and  
27 likely presents an upward trend. Our findings demonstrate that administration of teicoplanin is  
28 closely related to patient-reported penicillin allergy, the most commonly reported drug allergy in the  
29 community with up to 10% of the population labelled as allergic. It is likely that the majority are  
30 mislabelled and that at least 90% could be de-labelled if an adequate description of the original  
31 reaction could be obtained or the patient investigated in an allergy clinic.<sup>18</sup>  
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39 Considerably more than half of all patients received an antibiotic and almost all were administered  
40 after induction of anaesthesia. In three quarters, signs of anaphylaxis were identified in <5 minutes,  
41 and almost all in <10 minutes. Anaphylaxis-induced hypotension is likely to be exacerbated by  
42 general or neuraxial anaesthesia. There is a strong argument for antibiotics to be administered  
43 several minutes before induction of anaesthesia. There are several potential benefits; first, lack of  
44 allergy can be confirmed with the patient immediately before administration, second, the severity of  
45 physiological derangement due to anaphylaxis may be lessened and third, investigation of  
46 anaphylaxis is considerably simplified if fewer drugs have been administered.  
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53 It is likely that some of the anaphylactic reactions to antibiotics could have been avoided. Perversely,  
54 this is particularly likely to be the case in patients reported to be allergic to penicillin who were then  
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3 given teicoplanin, which we have shown has a 17-fold higher risk of anaphylaxis than flucloxacillin  
4 (or cefuroxime). If it were possible to identify the >90% of patients who report penicillin allergy, but  
5 who are not, then avoidance of second line antibiotics would likely lessen overall risk of  
6 perioperative anaphylaxis significantly. Of note, second line antibiotics are more expensive and are  
7 associated with increased duration of treatment, hospital stay and antibiotic resistance.<sup>19-21</sup> It is  
8 currently impractical for all putative penicillin allergy to be investigated in allergy clinics  
9 preoperatively, and the process is significantly complex. However, with the ever increasing  
10 importance of antibiotic stewardship, avoidance of a spurious label of 'penicillin- allergic' is an area  
11 ripe for research.  
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19 Thirteen patients with anaphylaxis due to co-amoxiclav and four of those with anaphylaxis to  
20 teicoplanin had received an IV 'test dose' of between 5%-30% of the therapeutic dose. It cannot  
21 reasonably be expected that a single test dose will eliminate the risk of anaphylaxis. In the allergy  
22 clinic the starting dose for drug challenge (which starts only after negative skin testing) will vary  
23 depending on: the severity of the index reaction, the dose that is believed to have caused it, the  
24 patient's concurrent comorbidities, whether the challenge is oral or intravenous and the drug itself.  
25 With some high-risk drug challenges this can be as low as  $10^{-9}$  of the therapeutic dose increasing in  
26 2-10 fold increments. Indeed, NAP6 provides evidence that anaphylaxis occurring after a test dose is  
27 at least as severe as after a full dose. A third of UK anaesthetists routinely administer a test dose  
28 when administering an IV antibiotic,<sup>22</sup> despite guidelines from the Association of Anaesthetists of  
29 Great Britain and Ireland (AAGBI) advising against their use<sup>6</sup> and we find no evidence to support the  
30 practice.  
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### 39 *NMBA and reversal agents*

40 In previous studies NMBAs were responsible for 40-66% of all cases of perioperative anaphylaxis<sup>17 23</sup>.

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43 Sensitization to NMBAs may occur during anaesthesia but the majority of patients do not give a  
44 history of previous exposure,<sup>24</sup> and environmental exposure to the quaternary ammonium (QA)  
45 epitope has been implicated in generating NMBA allergy.<sup>25</sup> In addition, pholcodine-containing cough  
46 medicines may cause sensitization to NMBAs<sup>26</sup> and NMBA-sensitization has declined in Norway since  
47 withdrawal of pholcodine cough medicine.<sup>27</sup>  
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3 Non-allergic anaphylaxis may occur with atracurium and mivacurium. Recent evidence implicates  
4 specific receptors on the surface of mast cells.<sup>28</sup> Variation in receptor expression may explain why  
5 these drugs cause dramatic non-IgE mediated mediator release in some individuals.  
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9 No previous study has undertaken parallel investigation of incidence and NMBA exposure. Studies  
10 relying on sales of drug ampoules to estimate the number of patient-exposures may not estimate  
11 the denominator accurately. Ampoule sales of suxamethonium likely overestimate usage as a result  
12 of waste. To avoid these pitfalls, NAP6 surveyed the number of patients receiving NMBAs during the  
13 same year as the case-reporting phase.  
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18 NMBAs accounted for approximately one third fewer cases of anaphylaxis than antibiotics, but carry  
19 at least as high a risk as antibiotics per administration, with the exception of teicoplanin. The lower  
20 occurrence rate of NMBA-induced anaphylaxis observed is due to  $\approx 2.5$  million administrations of  
21 antibiotics to surgical patients per year compared to  $\approx 1.2$  million administrations of NMBAs.  
22 Suxamethonium is well known to carry a greater risk of anaphylaxis than other NMBAs. Our data  
23 confirm this. The risk of suxamethonium-induced anaphylaxis was approximately twice that of all  
24 other NMBAs.  
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31 Sadleir and colleagues have suggested that rocuronium is associated with a relatively higher risk of  
32 anaphylaxis than vecuronium (Sadleir *et al.*, 2013). In that study the incidence of suxamethonium-  
33 anaphylaxis could not be accurately estimated, through lack of denominator data. Vecuronium is  
34 used only rarely in the UK.<sup>13</sup> Although our data cannot be definitive regarding the relative incidence  
35 of atracurium and rocuronium-induced anaphylaxis: we identified no major difference in their  
36 observed incidences. The difficulties inherent in interpreting the reported incidences of uncommon  
37 anaphylactic events are described by Laake and colleagues<sup>30</sup>. In particular, marginal under-reporting  
38 has a disproportionately-large effect on calculated incidence. Anaesthetists tended to overestimate  
39 the number of cases caused by NMBAs, perhaps as a result of their well-known allergenic potential.  
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47 We are unable to comment on the possible influence of pholcodine consumption on the incidence of  
48 NMBA-anaphylaxis. This information was not recorded in two thirds of reports: only 18% of allergy  
49 clinics routinely seek this information.<sup>31</sup>  
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53 A single case of sugammadex-induced anaphylaxis was reported. Onset was delayed, and  
54 anaphylaxis should be considered among other differential diagnoses if a patient deteriorates in the  
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3 recovery room. Sugammadex was used as treatment for anaphylaxis and this is discussed in the  
4 accompanying paper.<sup>14</sup>  
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### 6 7 *Chlorhexidine*

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9 Perioperative chlorhexidine exposure may occur via topical skin disinfection, chlorhexidine-coated  
10 central venous catheters (CVC) and the use of chlorhexidine containing lubricating gels.<sup>8</sup> It may not  
11 be immediately obvious that these products contain chlorhexidine, which has been called "the  
12 hidden allergen."<sup>32</sup>  
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16 There are geographical differences in the incidence of chlorhexidine-induced perioperative  
17 anaphylaxis. 7.7% in the United Kingdom<sup>33</sup> and 9.3% in Denmark,<sup>34</sup> but it is a rare allergen in  
18 France.<sup>35</sup> The cause for the variation is not clear but may be related to under-recognition and  
19 differences in practice (e.g. more use of povidone-iodine and lower use of chlorhexidine coated  
20 catheters). As exposure to chlorhexidine is highly likely in any surgical setting several centres  
21 routinely test all patients referred with perioperative anaphylaxis for chlorhexidine allergy. In  
22 countries adopting this practice chlorhexidine allergy is commonly identified.<sup>33 34</sup>  
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27 Sensitisation to chlorhexidine can occur in health care or the community as chlorhexidine-containing  
28 products are found in both environments.<sup>36 37</sup> The true prevalence of chlorhexidine allergy remains  
29 unknown. During a ten year period up to 2004 only 50 cases of IgE-mediated reactions were  
30 reported in the medical literature. More recently, 104 cases were reported, from four UK specialist  
31 centres covering only 2009-2013.<sup>9</sup>  
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37 Chlorhexidine is not yet considered among the 'mainstream' causes of perioperative anaphylaxis,  
38 despite evidence to the contrary. This is reflected by lost opportunities during perioperative history  
39 taking, and the low suspicion rate we observed. In previous studies up to 80% of patients diagnosed  
40 with chlorhexidine allergy reported possible chlorhexidine allergy that could have been identified  
41 prior to their adverse reaction.<sup>38 39</sup>  
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47 Despite an alert relating to chlorhexidine-containing medical products and devices being issued  
48 nationally by MHRA in 2012,<sup>40</sup> it appears that many clinical staff are unaware of which products  
49 contain this antiseptic and the risks of anaphylaxis.  
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52 It is unsurprising that reactions are more rapid and severe when a CVC is the source of the  
53 chlorhexidine and the allergen is delivered directly to the circulation. Removing the CVC is central to  
54 treating the reaction under these circumstances.  
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### *Patent blue*

Patent Blue dye is found as a food dye (E131), approved for use in the UK but not in the USA, Australasia, Japan, and several other countries. It structurally resembles other triarylmethane dyes widely-used in manufacturing. During surgery it may be injected into the tissues and taken up by the lymphatic system enabling sentinel lymph nodes to be seen directly. Sensitization is likely due to environmental exposure to the dye or a cross-reacting epitope.

The reported estimated incidence of allergic reactions, which are commonly mild, varies between 150 to 1000 per 100 000 administrations.<sup>10 41-43</sup> Reactions are frequently delayed, at 30-60 mins, possibly due to slow absorption from subcutaneous tissues and lymphatics.<sup>42</sup>

As Patent Blue dye interferes with pulse oximetry (causing spuriously-low readings) this has the potential to delay recognition of the onset of anaphylaxis. While two studies examining this effect reported mean reductions in digital oxygen saturation (SpO<sub>2</sub>) of <2%,<sup>10 44</sup> in some individuals considerably greater falls in oximetry values may be observed.<sup>45 46</sup>

In NAP6 reactions to Patent Blue dye were relatively common, were severe and required significant resuscitation. Cutaneous signs were absent in a third of patients and absence of rash should not dominate the differential diagnosis. As hypoxaemia is common after perioperative anaphylaxis, any fall in oxygen saturation should be assumed to be real until blood gas analysis has ruled this out.

### *Miscellaneous agents*

The very small number of cases of reactions to blood products (and none to red blood cells) is notable. The activity survey estimated approximately 84 000 perioperative administrations of blood products. The relative infrequency of these is perhaps attributable to the success of the serious hazards of transfusion (SHOT) haemovigilance scheme <https://www.shotuk.org/>.

Ondansetron is administered during an estimated 77% of general anaesthetics and 66% of all cases involving anaesthetist delivered care.<sup>13</sup> A single report of ondansetron-induced anaphylaxis indicates its extreme rarity. However, these reactions may be severe: two cases of fatal anaphylaxis attributed to ondansetron have been reported<sup>47</sup>.

We observed a single case of propofol allergy. Propofol is an extremely-uncommon cause of anaphylaxis. Our survey data indicate that well over two-million patients in the UK are exposed to

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2  
3 this induction agent perioperatively each year.<sup>13</sup> Twenty-four IgE-mediated cases were reported in a  
4 French eight-year study<sup>48</sup> and two cases were recorded in a UK seven-year single-clinic study.<sup>4</sup>  
5  
6 Asserhøj and colleagues suggested that propofol-induced anaphylaxis may occur in some patients  
7 via a non-IgE-mediated mechanism.<sup>49</sup> Skin testing is negative in this situation, and controlled  
8 provocation testing with IV propofol would be necessary to confirm the diagnosis: a procedure that  
9 is not generally available. The same publication dispelled the notion that propofol is contra-indicated  
10 in adults who are allergic to egg, soya or peanut, but some uncertainty still exists in egg-allergic  
11 children.<sup>50</sup> A diagnosis of hypersensitivity to propofol has serious implications for the patient, given  
12 the ubiquity of this induction agent and therefore merits full investigation.  
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18 We recorded one case of anaphylaxis to protamine in a patient with diabetes. It has been suggested  
19 that patients who have been exposed to Neutral Protamine Hagedorn insulin, which contains  
20 protamine, are more likely to experience protamine-induced anaphylaxis.<sup>51</sup> Fish allergy has been  
21 implicated as a risk factor for protamine-anaphylaxis as protamine is traditionally extracted from the  
22 sperm of fish. It is possible that the drug will be increasingly synthesised by recombinant  
23 biotechnology. Sensitization to the fish-derived product may be unlikely to result in anaphylaxis  
24 when a patient is exposed to the recombinant formulation.  
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31 Anaphylaxis due to non-steroidal anti-inflammatory drugs (NSAIDs) has been comprehensively  
32 reviewed by Kowalski and colleagues.<sup>52</sup> There is a wide spectrum of severity and pathogenesis.  
33 Reactions are commonly non-immunologically mediated and there may be cross-reactivity to drugs  
34 sharing COX-1 enzyme inhibition. An eight-year national study in France identified only three  
35 immunologically-mediated perioperative hypersensitivity reactions to NSAIDs.<sup>48</sup>  
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#### 41 *Reporting*

42 Reporting rates are disappointingly-low. All NAP6 cases were at least Grade 3, representing a life-  
43 threatening incident, yet almost a third were not reported to the hospital's critical incident reporting  
44 system, reducing the likelihood of lessons being learned where applicable. Only a quarter of cases  
45 were reported to the MHRA, despite AAGBI guidance, irrespective of severity of the outcome. Local  
46 Co-ordinators were responsible for many of the reports to MHRA, and it is unlikely that these would  
47 have been reported either by the index anaesthetist or the allergy clinic. Our data imply that  
48 pharmacovigilance is not being supported adequately and further mean that data reported back to  
49 anaesthetists and allergy clinics by the MHRA is likely to be unreliable. Factors contributing to poor  
50 reporting-rates have been discussed by Mahajan.<sup>53</sup>  
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## Conclusions

We believe this is the largest study of life-threatening perioperative anaphylaxis incorporating contemporaneous real-life data on exposure to potential allergens, permitting calculation of accurate relative-incidence rates. We highlight antibiotic allergy as an increasing problem, particularly teicoplanin and suggest that optimizing pre-operative allergy history could reduce the number of perioperative anaphylactic reactions. We hope our data have finally dispelled any notion that test doses might prevent or ameliorate anaphylaxis. An awake patient is able to report early symptoms of evolving anaphylaxis and our data support administering antibiotics before induction of anaesthesia if practicable. Early recognition is key to successful treatment and our results show that initial presentation can be varied, likely to be bronchospasm if suxamethonium is the trigger agent, and may be delayed, particularly with Patent Blue dye and some exposures to chlorhexidine, the 'hidden allergen'. We point to the ways in which patient factors e.g. ASA grade, obesity, beta blockers and ACEI influence clinical features of perioperative anaphylaxis, a dimension previously under-reported. We do not believe that the risk of anaphylaxis should be a determining factor in the choice of non-depolarizing NMBAs. We urge anaesthetists to report cases through the MHRA Yellow Card Scheme so that pharmacovigilance can be better supported in the future. This is the first of two companion papers describing the main findings of NAP6; in the second<sup>14</sup> we describe clinical management and outcomes and make recommendations for organizational and individual practice.

## Declaration of interest

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

SM, HK, NH LF, SF, DNL, TG, KFI, HT, MT, AW JH, KFe, WE, SN, SK, K-LK, NMCG and MB all declare they have no conflicts of interest.

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15 Campaign (Anaphylaxis Campaign).  
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#### 23 **Authors' contributions and authorship**

24 NJNH – Co-designed methodology of the study. Analysed results. Collated draft sections, wrote all  
25 drafts of the paper and the final draft.  
26

27 TMC – Co-designed the methodology of the study. Analysed results. Reviewed and revised drafts of  
28 the paper and the final draft.  
29

30 TG, SF, NL, MT, K-L K, SK, SM, JH, KF, MB, HT Co-designed methodology of the study. Analysed  
31 results and wrote draft sections of the paper.  
32

33 All other panel members contributed to the design and methodology of the study, reviewed the  
34 results and took part in review of draft manuscripts leading to finalisation.  
35

36 LF - Contributed to design and methodology of the study. Administered study. Took part in review of  
37 draft manuscript leading to finalisation.  
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**Table 1. Cases attributable to the four most common trigger-agents**

	Total number of cases	Antibiotic	NMBA	Chlorhexidine	Patent Blue Dye
Definite	148	67	49	14	8
Probable	51	27	16	4	1
Total identified	199	94 (47.2%)	65 (32.7%)	18 (9.1%)	9 (4.5%)

**Table 2. Comparison of patients who survived or died after perioperative anaphylaxis.**

	Died after anaphylaxis n=10	Survived anaphylaxis N = 256
Aged >66 yrs	40%	31%
Obese or morbidly obese	50%	36%
Coronary artery disease	50%	13%
Taking beta blocker	60%	15%
Taking antiotensin converting enzyme inhibitor	60%	21%
Asthma	0%	21%

**Table 3. Characteristics of patients who died, compared to those who survived cardiac arrest, or experienced profound hypotension or did not experience profound hypotension.**

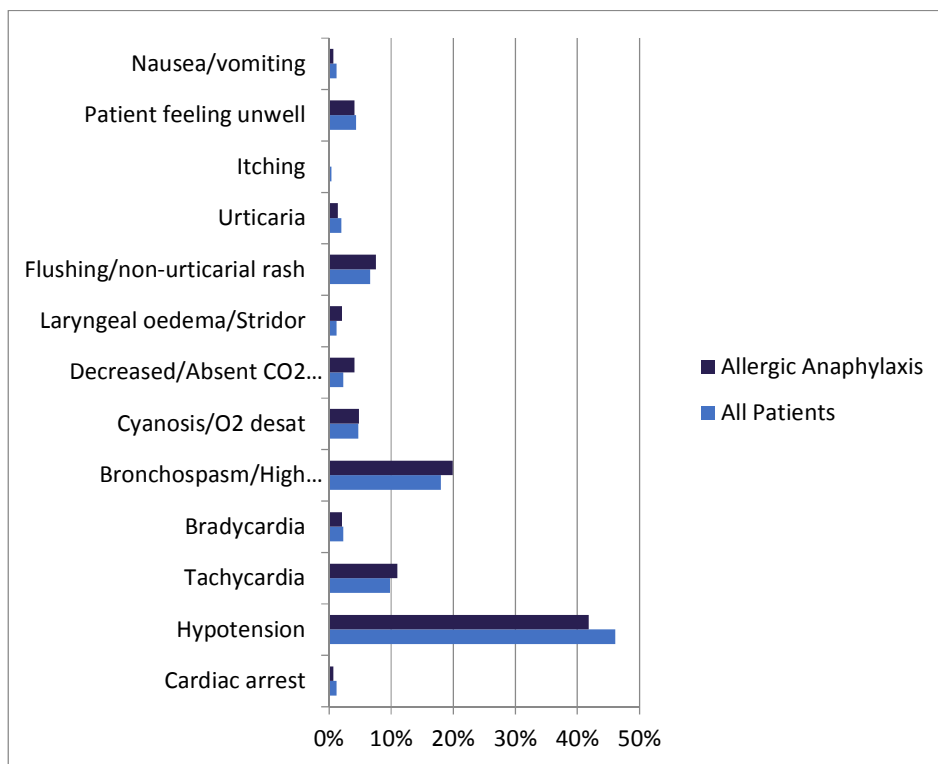
	Deaths (n=10)	Non-fatal cardiac arrest (n=31)	BP <50mmHG without cardiac arrest or death (n=79)	All others (n=135)
Patient characteristics				
Age >66	50%	35%	33%	34%
ASA≥3	80%	13%	33%	27%
Obesity	50%	31%	34%	43%
CAD	55%	8%	15%	14%
Beta blocker	60%	7%	14%	19%
ACEI	60%	32%	9%	17%
Asthma	0%	14%		

**Table 4. Estimated incidences for antibiotic-induced anaphylaxis with definite or probable attribution in NAP6. \*annual usage identified from Allergen survey<sup>13</sup>**

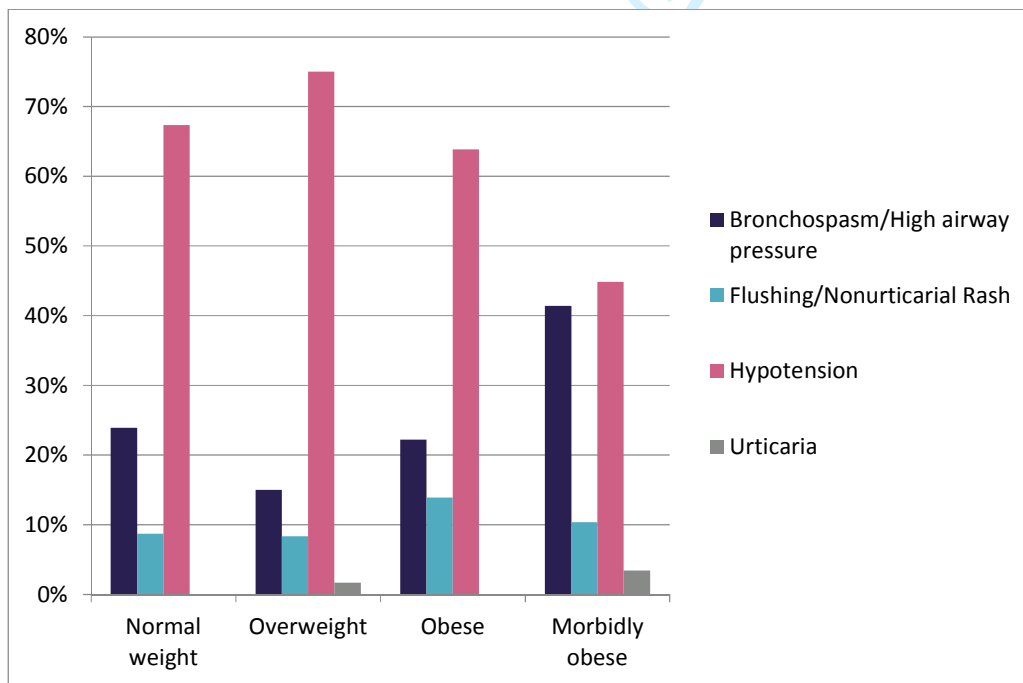
	Culprits identified by the review panel	Proportion of antibiotic usage*	Patients receiving the drug per annum*	Anaphylaxis rate /100,000 administrations	Relative rates (cefuroxime = 1)
Co-amoxiclav	46	29.8%	532,580	8.7	9.2
Teicoplanin	36	12.3%	219,621	16.4	17.4
Cefuroxime	4	23.7%	424,143	0.94	1.0
Gentamicin	3	34.5%	616,899	0.49	0.5
Flucloxacillin	2	11.9%	211,973	0.94	1.0
Piperacillin-tazobactam	1	1.6%	28,237	3.5	3.7
Vancomycin	1	1.0%	17,648	5.7	6.1
Metronidazole	1	15.2%	272,173	0.37	0.4
Total (all antibiotic administrations)	94 culprits (92 cases)	100%	2,323,274	4.0	4.2

**Table 5. NMBA confirmed as causative agents by the panel, absolute and relative risk. \*Data from the NAP6 Allergen survey<sup>13</sup>**

	Cases suspected by anaesthetist	Cases confirmed by review panel	Proportion of UK NMBA usage*	Patients receiving the drug per annum*	Anaphylaxis rate/100,000 administrations	Relative risk of anaphylaxis (atracurium = 1)
Atracurium	32	23	49.1%	554,543	4.15	1
Rocuronium	34	27	40.6%	459,047	5.88	1.42
Suxamethonium	16	14	11.2%	126,086	11.1	2.67
Mivacurium	0	1	2.7%	30,786	3.25	0.78
Vecuronium	0	0	2.2%	24,315	-	
Cisatracurium	0	0	1.6%	18,629	-	
Pancuronium	0	0	0.6%	7,059	-	



**Figure 1. First clinical feature (%) in allergic anaphylaxis and all patients with grade 3-5 perioperative anaphylaxis.**



**Figure 2. Presenting feature and body habitus in grade 3-5 perioperative anaphylaxis.**

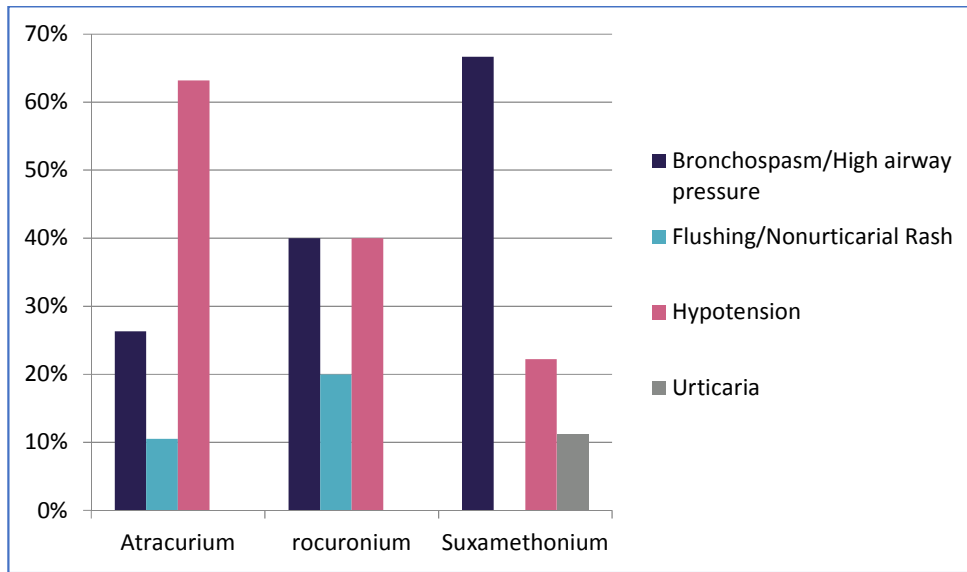


Figure 3. Initial features of Grade 3-5 Neuromuscular blocking agent-induced anaphylaxis

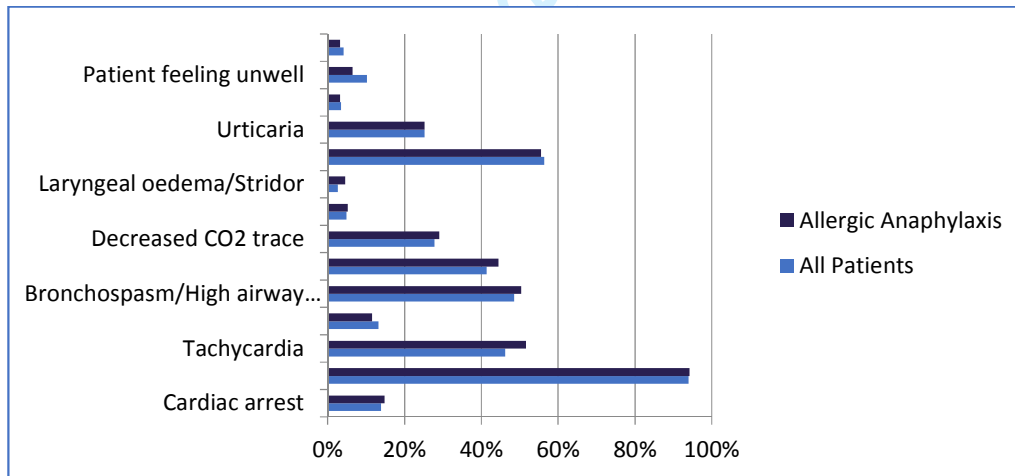
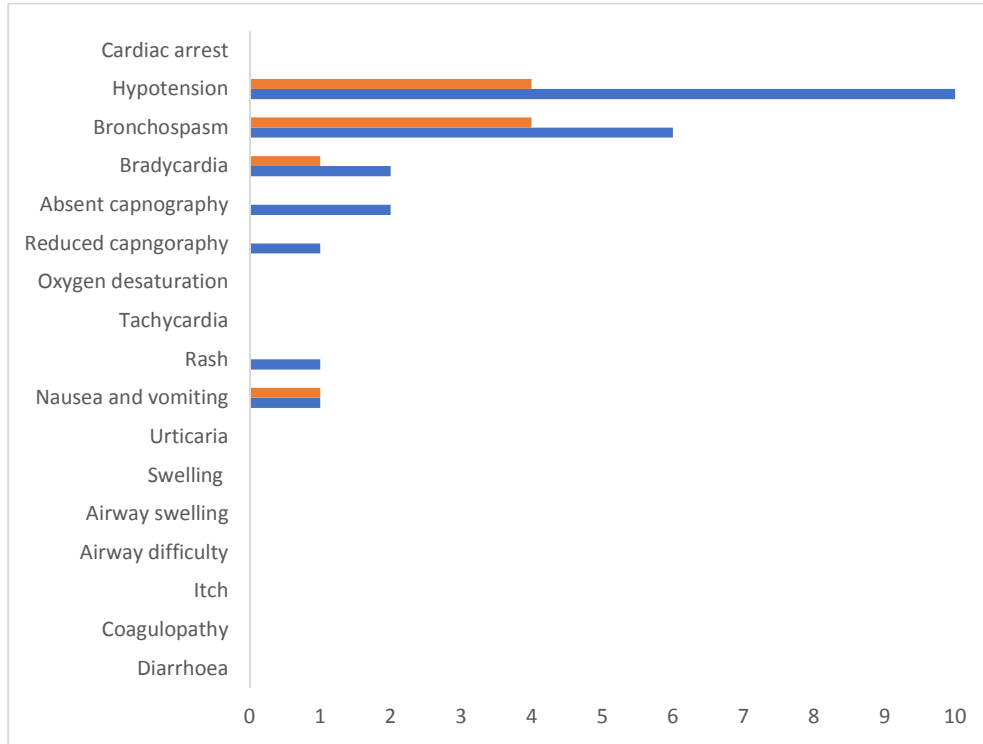
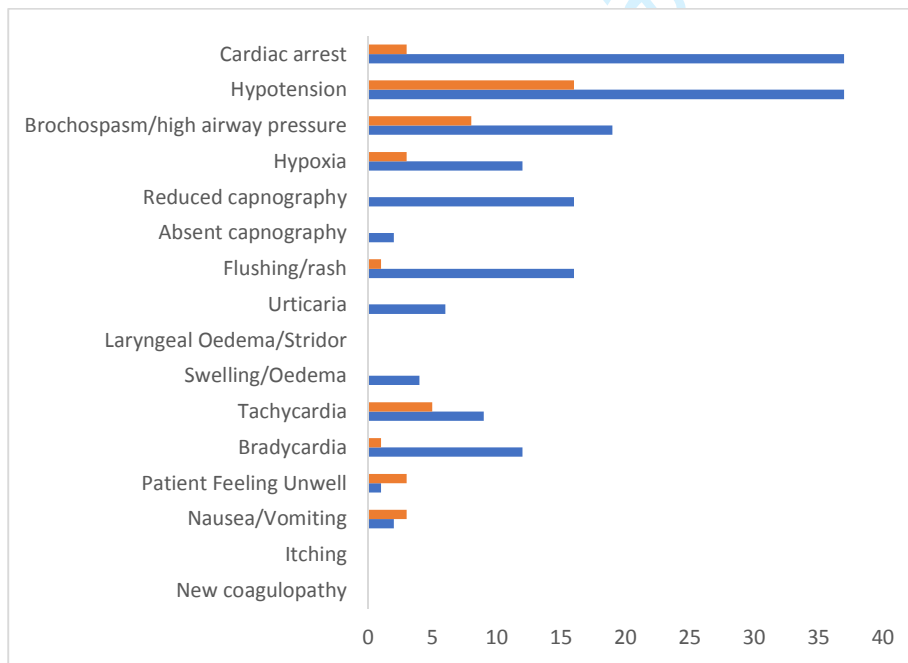


Figure 4. Clinical feature (%) present at any time during grade 3-5 perioperative anaphylaxis: allergic anaphylaxis and all patients



**Figure 5. Clinical features of ten fatal cases of perioperative anaphylaxis (presenting, and at any time during the episode). Orange, presenting feature, blue, during event.**



**Figure 6. Clinical features of 37 non-fatal cardiac arrests from perioperative anaphylaxis (presenting, and at any time). Orange, presenting feature, blue, during event.**