15 Antibiotics

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Key findings

- Antibiotics were the main cause of perioperative anaphylaxis in the UK, being responsible for 46% of cases with identified culprit agents (ahead of NMBAs, the second leading cause, responsible for 33% of all cases).
- The incidence of antibiotic anaphylaxis was 4.0 per 100,000 administrations.
- Teicoplanin (16.4 episodes per 100,000 administrations) and co-amoxiclav (8.7 per 100,000 administrations) had the highest incidences of reactions, and both were notably higher than all other antibiotics.
- Co-amoxiclav and teicoplanin accounted for 17.3% and 13.5% respectively of all cases of perioperative anaphylaxis, 23% and 18% of identified culprits, and together accounted for 89% of antibiotic-induced perioperative anaphylaxis.
- The most common first clinical feature was hypotension: in 42% of all antibiotic cases.
- The onset of anaphylaxis was within 5 minutes in 74% of cases, within 10 minutes in 92% and in all cases within 30 minutes.
- Administration of antibiotics several minutes before induction of anaesthesia would be likely to improve detection, may simplify treatment, and will help investigation when reactions occur.
- Several cases of anaphylaxis were related to antibiotic 'test doses'. Test doses were not administered in doses consistent with allergy-clinic challenge testing, and there was no evidence that a test dose reduced the severity of events when they occurred.
- Teicoplanin was frequently administered because of a history of penicillin allergy. With the knowledge that the attribution of penicillin allergy is unfounded in more than 90% of cases, effective de-labelling of penicillin allergy would decrease overall risk of anaphylaxis.
- Improvements in allergy-history taking and selective referral for investigation of antibiotic allergy may reduce antibiotic-induced perioperative anaphylaxis.
- Allergy clinics did not identify the antibiotic culprits in a quarter of all cases. This was mostly the result of incomplete investigations, including omission of appropriate skin tests and drug-provocation challenges. Allergy clinics may be underdiagnosing antibiotic allergy and potentially placing patients at risk of future reactions.
- In two thirds of cases, inappropriate advice on future avoidance was given by allergy clinics.

What we already know

Antibiotics are well-recognised, common causes of perioperative anaphylaxis, noted as being among the main causes in several reports from large international databases, from France, Australia, New Zealand, Norway and the United Kingdom. Nevertheless, there is substantial geographic variability regarding the different drugs or substances causing perioperative anaphylaxis (Mertes 2016), and the true incidence of anaphylactic reactions during the perioperative period and their causes remain poorly defined. These regional differences, likely to be a reflection of local drug preferences and geographical differences in bacterial resistance patterns, are a strong incentive for repeated epidemiological surveys in different countries.

Reactions involving neuromuscular blocking agents (NMBAs) are reported as the leading cause of perioperative anaphylaxis in several countries, including in many European studies (Harboe 2005, Mertes 2011, Dong 2012, Mertes 2012, Tacquard 2017), but are less frequently reported in the United States or Denmark (Garvey 2001, Gurrieri 2011).

Reactions involving antibiotics are reported with a high and sometimes increasing frequency in most series (Volcheck 2014, Mertes 2016). Antibiotics appear to be the most common cause of perioperative anaphylaxis in the United States (Gurrieri 2011) and Spain (Lobera 2008, Gurrieri 2011, Gonzalez-Estrada 2015), accounting for between 40–50% of the reported reactions. Penicillins and cephalosporins are the main antibiotic culprits reported.

A series of multicentre French surveys, which began in the mid-1990s and have continued to the present, reported NMBAs as the main culprit of perioperative anaphylaxis, responsible for as many as 60% of reactions, followed by antibiotics, responsible for ≈20% (of which more than 50% were cephalosporins) (Mertes 2011, Dong 2012, Mertes 2012, Tacquard 2017). These studies report a rapid increase in antibiotics as culprit agents, rising from 2% in the late 1980s to around 20% in recent reports. A German study of 107 cases reported 24 (45%) of the 53 identified culprit drugs to be antibiotics, of which 15 were cephalosporins and five penicillins (Trautmann 2016). In an American series, antibiotics accounted for 50% of IgE-mediated reactions (Gurrieri 2011, Kuhlen 2016).

In the UK, antibiotics have been noted to account for approximately 15% of anaesthesia-related anaphylactic episodes (Harper 2009), but this proportion may have increased in recent years. In a case series of 21 UK patients with identified culprits, antibiotics accounted for 11 (52%) of perioperative reactions (Meng 2017). The antibiotics identified as culprits were penicillins, teicoplanin, metronidazole and rifampicin. In a report of 316 UK cases over a seven-year period, antibiotics accounted for 31% of cases and were the second commonest cause of reactions after NMBAs (Low 2016). Penicillins were prominent causes (74% of antibiotic-induced reactions), but teicoplanin, 5.6%, was not.

The NAP6 Anaesthesia baseline survey of perceptions and experiences of anaesthetists in relation to perioperative anaphylaxis (Kemp 2017, Chapter 7), revealed that antibiotics were suspected by anaesthetists as causative agents in 38% of cases. Penicillins were both perceived to be the most likely causative antibiotics and were avoided most often. Teicoplanin, although prominent among suspected culprit agents, was not frequently avoided.

Penicillin and beta-lactam antibiotics

Penicillin allergy is the most commonly reported drug allergy, with up to 10% of the population and 20% of in patients so labelled (Kerr 1994, Lee 2000, Gomes 2004, Macy 2009, 2014a, 2015, Weiss 2010, Albin 2014). Importantly, 90–99% of patients who report penicillin allergy are mislabelled and could be de-labelled if documentation of the original reaction was adequate or the patient was investigated via skin and drug provocation tests (Borch 2006, Dworzynski 2014, Macy 2015).

Sensitisation to antibiotics requires previous exposure, although in some cases this occurs through exposure to a cross-reacting agent or drug. Individuals may be allergic to only one antibiotic, or have allergy to others containing a cross-reacting allergenic epitope. Allergy to beta-lactam antibiotics occurs through sensitisation to the beta-lactam ring or to a side-chain. Sensitivity to the beta-lactam ring leads to general allergy to penicillins and cephalosporins. Side-chain-specific allergy can lead to unexpected cross-reactivity, for example, between amoxicillin and cefadroxil, or ceftazidime and aztreonam. If allergy to one antibiotic is confirmed, it is important that related antibiotics, eg. other penicillins, are also be tested in order to identify potential cross-reactivity and safe alternatives.

Teicoplanin

Teicoplanin is often used as an alternative to a beta-lactam when there is a history of allergy. There is emerging evidence that teicoplanin is an important trigger of anaphylaxis events (Asero 2006, Savic 2015, Azamgarhi 2018), and in a recent survey it was reported as the suspected cause of 28% of antibiotic-related anaphylaxis (Kemp 2017, Chapter 7, Baseline survey).

A growing body of evidence has shown that use of second-line (often more expensive) antibiotics has significant public health implications and increased healthcare costs with increased duration of treatment and hospital stay and leads to higher rates of antibiotic resistance and infections, including methicillin-resistant Staphylococcus aureus (MRSA), Clostridium difficile (C. diff) and vancomycin-resistant enterococcus (VRE) (Sade 2003, Macy 2014b, Solensky 2014).

Numerical analysis

Ninety-two cases of antibiotic-induced anaphylaxis were identified. In two cases both tecicoplanin and gentamicin were judged equally probable as culprits, so there were 94 definite or probable antibiotic culprits in 92 cases – 46% of all cases with identified culprits. The majority were caused by co-amoxiclav or teicoplanin, which between them accounted for 89% of identified antibiotic culprits.

The overall incidence of reported antibiotic-induced anaphylaxis was 4.0 per 100,000 exposures. The incidences of the three most prevalent antibiotics were:

- *Co-amoxiclav:*
  46/532,580 = 1 in 11,578 (95% CI 1 in 8,680 – 1 in 15,814)
- *Teicoplanin:*
  36/219,62 = 1 in 6,101 (95% CI 1 in 4,407– 1 in 8,710)
- *Cefuroxime:*
  4/424,143 = 1 in 106,035 (95% CI 1 in 41,414 – 1 in >150,000).

The relative anaphylaxis rate using cefuroxime as an index was 17.4 for teicoplanin and 9.2 for co-amoxiclav (Table 1). Eighty-eight per cent occurred during general anaesthesia, 8% during moderate sedation, 1% during minimal sedation and 2% during managed anaesthesia care.

Table 1. Estimated incidences for antibiotic-induced anaphylaxis with definite or probable attribution in NAP6
*Annual usage identified from the Allergen Survey (Chapter 9)

	Culprits identified by the review panel	Proportion of antibiotic usage*	Patients receiving the drug per annum*	Anaphylaxis rate per 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

Patient characteristics

The gender ratio of affected patients (1.4:1) and ethnicity (89% white British) were both similar to the surgical population as shown in the NAP6 Activity Survey (Chapter 8). Obesity was over-represented in the cohort of anaphylaxis patients (37% of the anaphylaxis population and 21% of the surgical population – Chapter 8), but obesity and morbid obesity rates were similar in those with antibiotic-induced anaphylaxis (17% and 12%) and anaphylaxis induced by any trigger (21% and 14%) (Figure 1). There was only one paediatric case (Figure 2) and, while paediatric anaesthesia accounts for 13% of overall activity, antibiotic use is considerably less frequent (see Chapter 21, Paediatric anaesthesia). Overall, there was little evidence that any particular patient characteristics altered rates of antibiotic-induced anaphylaxis.

Figure 1. Body habitus distribution in cases of perioperative anaphylaxis due to antibiotics

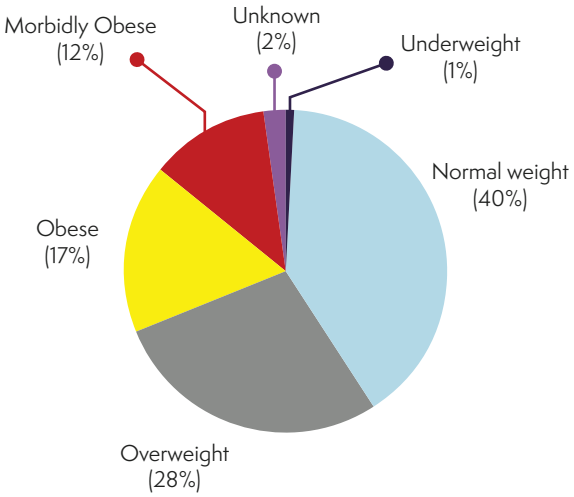
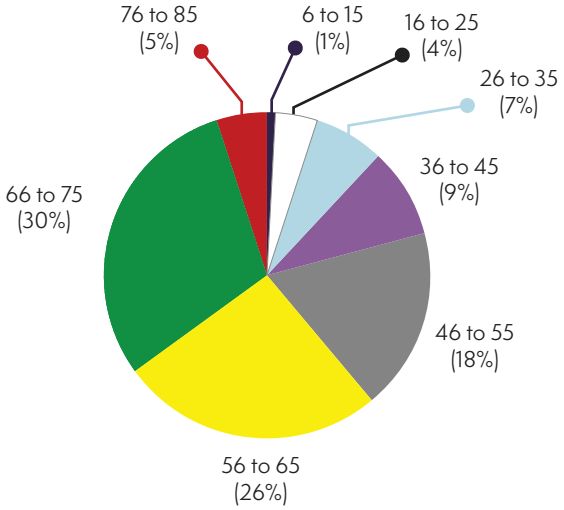


Figure 2. Age distribution (yrs) in cases of perioperative anaphylaxis due to antibiotics



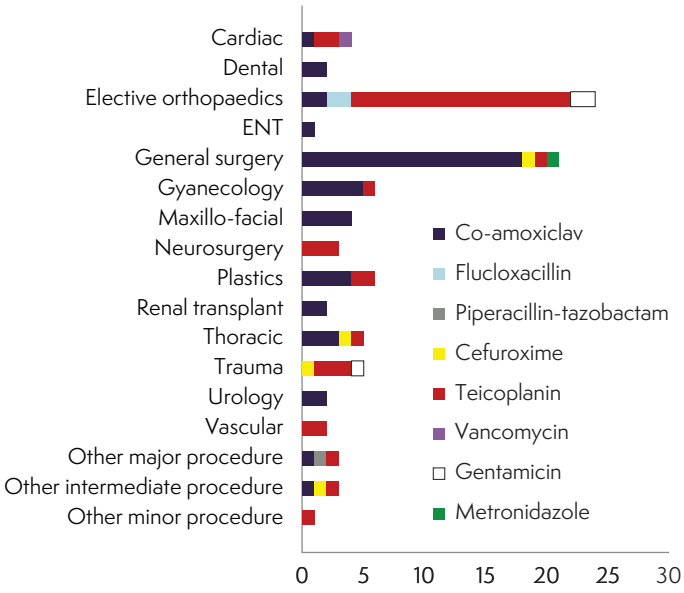
Risk and culprit agents

The NAP6 Allergen Survey (Chapter 9) reported that 1,787,360 (57.2%) patients received 2,469,754 antibiotic administrations annually. The main antibiotics used were gentamicin, co-amoxiclav, cefuroxime, and metronidazole, the first two each accounting for around half a million administrations per year. Distribution of antibiotic use is detailed in Table 1.

Of the 36 patients who reacted to teicoplanin, 20 (56%) stated preoperatively that they were allergic to penicillin. Half of all teicoplanin reactions were either Grade 4 or fatal.

Although the Allergen Survey (Marinho 2018, Chapter 9) demonstrated that teicoplanin was administered to 21% of orthopaedic/trauma patients, it was responsible for 75% of antibiotic anaphylaxis in this specialty (Figure 3). Gentamicin was administered to 33% of these patients, flucloxacillin to 18%, and cefuroxime to 18%, but they were responsible for very few cases of anaphylaxis. Similarly, co-amoxiclav is used in 33% of general surgical procedures, but caused 86% of antibiotic-induced anaphylaxis within that specialty. Metronidazole is used in 23% and gentamicin in 17%, but rarely caused anaphylaxis.

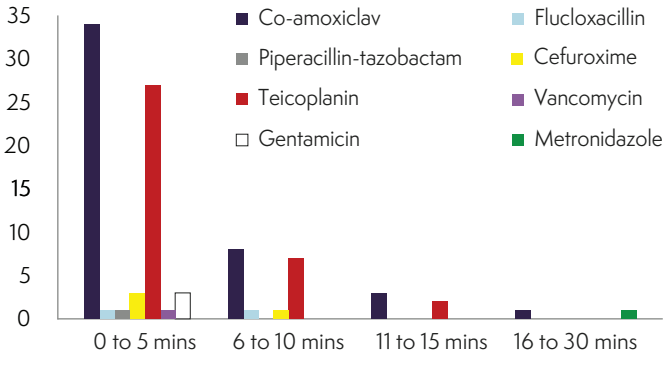
Figure 3. Antibiotic anaphylaxis by surgical specialty



Timing between antibiotic exposure and onset of anaphylaxis

The first clinical feature presented within 5 minutes of exposure in 74% of cases, within 10 minutes in 92.5%. None presented after 30 minutes (Figure 4).

Figure 4. Time interval between exposure to the suspected culprit and appearance of first clinical feature

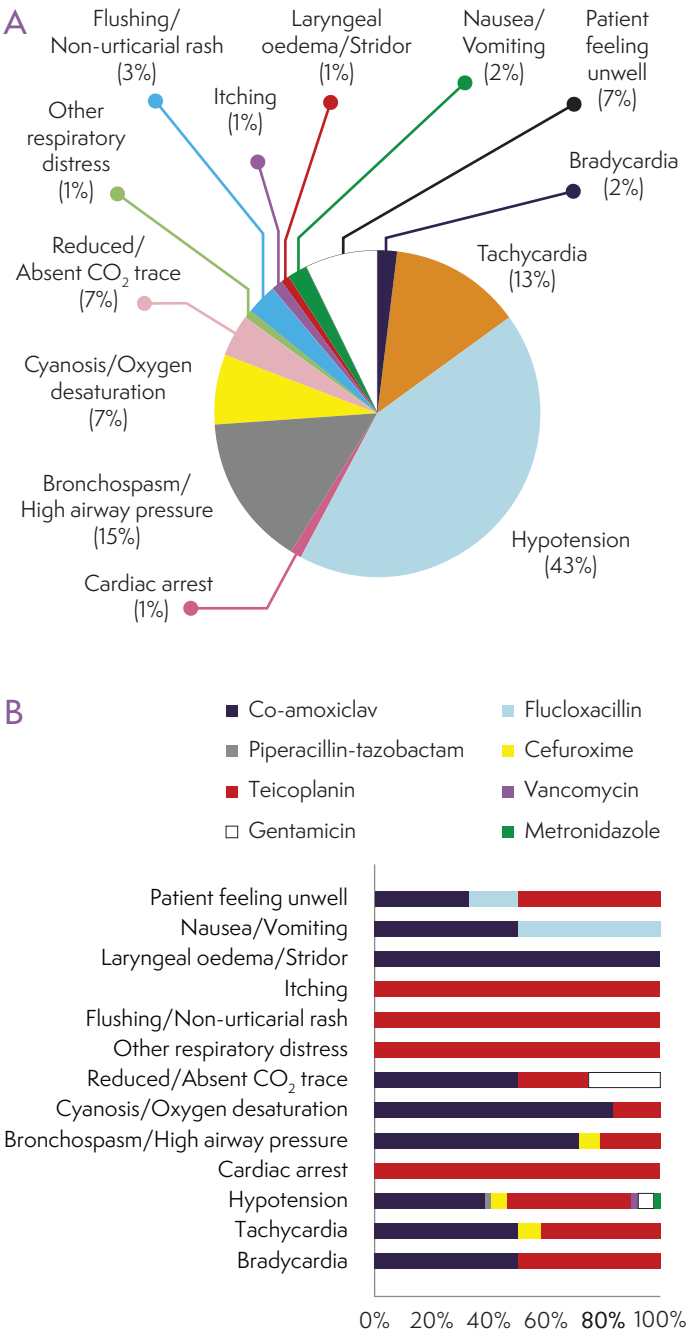


The anaesthetist identified the event as a clinical incident within 5 minutes of antibiotic administration in 65% of cases, and within 10 minutes in 88% of cases. The anaesthetist suspected anaphylaxis within 5 minutes in 53% and within 10 minutes in 85% of cases.

Clinical features

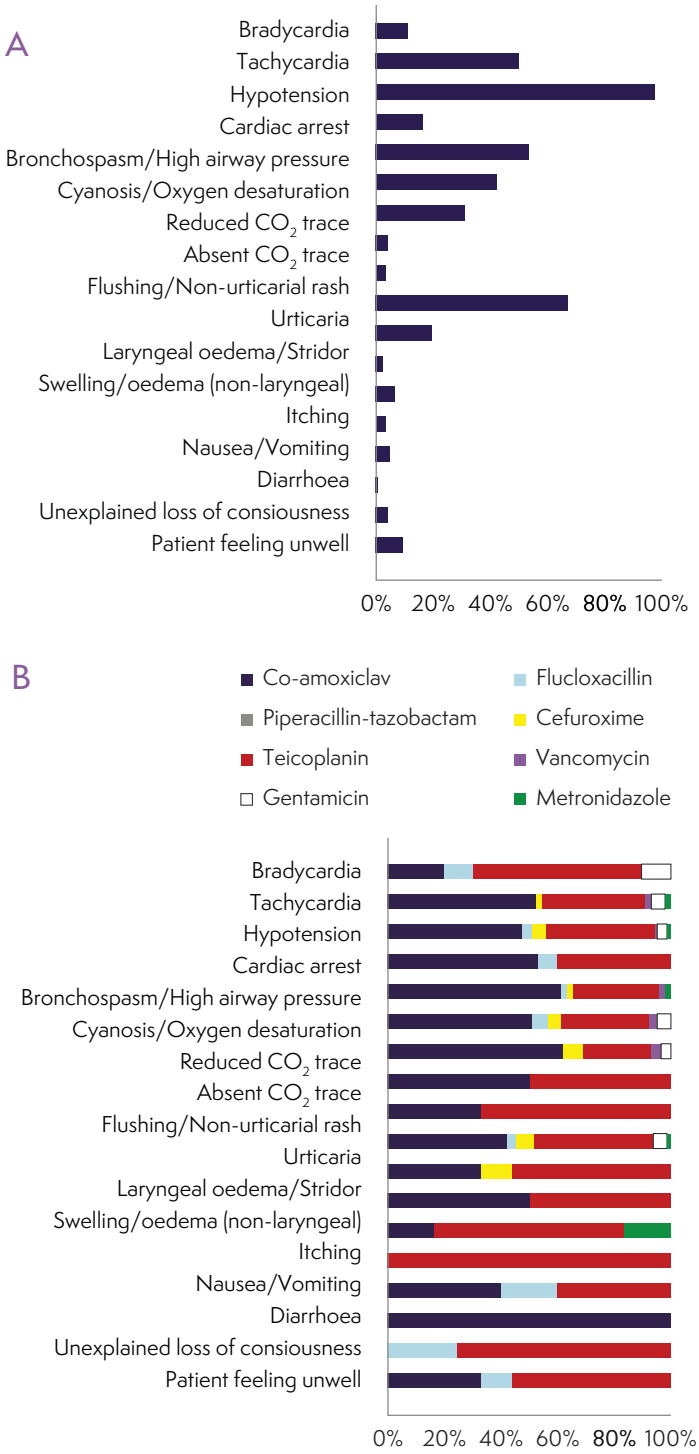
These are discussed in Chapter 10, Clinical features. The most common first-presenting clinical feature (42%) was hypotension followed by bronchospasm/high airway pressure (15%) and tachycardia (13%). During teicoplanin anaphylaxis hypotension was a dominant presenting feature with bronchospasm uncommon (Figure 5).

Figure 5. First clinical feature in anaphylaxis due to antibiotics (panel a), and proportionately by antibiotic (panel b)



Considering clinical features present at any time during the episode, hypotension was universal, and blood pressure was unrecordably low in a quarter of cases. Flushing/non-urticarial rash, bronchospasm/high airway pressure and tachycardia were the next most-common features (67%, 53% and 50%, respectively). Bradycardia was present in 11% of cases (Figure 6).

Figure 6. Clinical features at any time during perioperative anaphylaxis due to antibiotics (panel a) and proportionately by antibiotic (panel b)



Severity

There were 46 (50%) Grade 3 and 43 (47%) Grade 4 reactions. Three (3%) cases were fatal, of which two were due to teicoplanin and one co-amoxiclav. The severity grade of anaphylaxis resulting from each antibiotic is detailed in Table 2.

Table 2. Grade of anaphylaxis for all antibiotics identified by the review panel

Antibiotic	Grade			
	Grade 3 Total	Grade 4 Total	Grade 5 Total	All Total
Co-amoxiclav	24	21	1	**46**
Teicoplanin	18	16	2	**36**
Cefuroxime	0	4	0	**4**
Gentamicin	3	0	0	**3**
Flucloxacillin	1	1	0	**2**
Piperacillin-tazobactam	0	1	0	**1**
Metronidazole	1	0	0	**1**
Vancomycin	1	0	0	**1**
Total	48*	43	3	**94***

**Two cases where teicoplanin and gentamicin were joint probable causes*

Antibiotic test doses and timing of antibiotic administration

A test dose was administered to 82 (35%) of 235 patients who received an antibiotic and 18 (20%) of 92 patients in whom an antibiotic was the cause of the reaction. Of these 18, in ten (53%) cases the patient reacted to the test dose itself, which ranged from 5–30% of the therapeutic dose, and the other eight patients reacted to the full dose, which was given within 1 minute of the test dose in all but one case (given within 10 minutes).

Test doses were commonest with meropenem and co-amoxiclav. A test dose preceded 13 (28%) of 46 cases of co-amoxiclav anaphylaxis; seven of these cases reacted to the test dose (5–30% of the full therapeutic dose). Test doses were given in four (11%) of 36 cases of teicoplanin anaphylaxis. Two reacted after the test dose, and two when the full dose was administered almost immediately after the test dose. The only case receiving a test dose of vancomycin also reacted immediately. Thus, there was no evidence that a test dose prevented a reaction.

There was also no evidence that administration of a 'test dose' of antibiotic reduced the severity of an ensuing reaction. On the contrary, in cases of anaphylaxis caused by an antibiotic where a test dose had been given, a slightly greater proportion of severe reactions (Grades 4 and 5) was seen than if no test dose had been given (58% vs 51%).

Several cases of antibiotic-induced anaphylaxis occurred before the patient had been anaesthetised, enabling prompt diagnosis and management of anaphylaxis prior to administration of other possibly confounding drugs. In addition, investigation was facilitated as there were fewer possible culprits to exclude.

A patient scheduled for elective general surgery and general anaesthesia received a test dose of co-amoxiclav 120 mg after induction, and, 10 minutes later, the full dose. Ten minutes after the full dose the patient developed widespread signs of anaphylaxis, including bronchospasm, oxygen desaturation and hypotension. Anaphylaxis was promptly recognised and treated, leading to a good recovery. Anaphylaxis to co-amoxiclav was confirmed by subsequent allergy investigations.

A patient was scheduled for elective surgery and general anaesthesia. Anaesthesia was induced and a test dose of co-amoxiclav 300 mg was given, followed by the full dose one minute later. The patient developed tachycardia, hypotension, swelling, and oxygen desaturation. Hypotension was prolonged and progressed to PEA cardiac arrest, requiring CPR. The patient was treated for anaphylaxis and successfully resuscitated. Subsequent allergy investigations confirmed anaphylaxis to co-amoxiclav..

A patient was scheduled for elective general surgery and general anaesthesia. Following induction of anaesthesia, a test dose of co-amoxiclav 180 mg was given. The patient reacted to the test dose with bradycardia, profound hypotension and rash. The patient was treated for anaphylaxis, making a good recovery. The allergy clinic diagnosed anaphylaxis to co-amoxiclav after appropriate investigations.

Past medical history and history of antibiotic allergy

Seventy-three patients had a preoperative label of antibiotic allergy – 52 to penicillins (49 penicillin, 2 amoxicillin, 1 piperacillin-tazobactam), of whom three also had a label of cephalosporin allergy. Seven patients had a label of cephalosporin allergy and 16 an allergy to a variety of antibiotics, including trimethoprim, co-trimoxazole, erythromycin, metronidazole, doxycycline and tetracycline. Four of these also had a label of penicillin allergy. One patient had a label of multiple antibiotic allergy to penicillin, cephalosporin and other antibiotics.

The NAP6 Allergen Survey (Chapter 9) demonstrated that the choice of antibiotic was influenced by preoperative allergy history in a quarter of patients who received teicoplanin or vancomycin. Among the 36 patients reported to NAP6 with teicoplanin anaphylaxis, more than half stated preoperatively that they were allergic to penicillin. Among the 20 who were likely to have received teicoplanin because of a history of allergy, eight reactions were Grade 4 and one Grade 5, six developed moderate harm, and one died. In at least three cases of teicoplanin anaphylaxis in patients with a reported history of penicillin allergy, this label was subsequently removed as part of the allergy clinic investigations.

A patient scheduled for elective surgery gave a history of penicillin allergy. Teicoplanin and gentamicin were administered shortly before neuraxial block, five minutes after which the patient felt unwell and nauseated. The patient became, clammy and hypotensive, with tachycardia and flushing/non-urticarial rash. Anaphylaxis was diagnosed and treated promptly and successfully. Subsequent allergy investigations ruled out penicillin allergy and confirmed anaphylaxis to teicoplanin.

Drug errors

In less than 1% of cases, communication failure led to an antibiotic being administered despite a relevant positive allergy history. Two cases were judged preventable by better allergy history communication.

Suspected antibiotics, allergy clinic investigations and diagnosis

Out of the 266 cases of anaphylaxis reported to NAP6, 98 (37%) were suspected by the anaesthetist to be caused by an antibiotic and 92 confirmed by the review panel. The anaesthetist suspected allergy to an antibiotic in 65 (71%) of these 92 cases. Allergy clinics considered 70 cases to have been caused by allergy to an antibiotic. However, in some cases a single culprit was not confirmed and two or more agents were recommended for avoidance.

Diagnostic uncertainty in the allergy clinic was usually caused by incomplete investigations, with either an insufficient panel of skin tests or because drug provocation to exclude possible culprits was not undertaken (Table 3). This is discussed further in Chapter 14, Investigation.

Concordance between the allergy clinic and the review panel

Table 4 compares culprits identified by the review panel with the diagnosis reached by the allergy clinics. Our data suggest that allergy clinics may be underdiagnosing allergy to co-amoxiclav and teicoplanin, potentially placing patients at risk of future reactions.

In one case, the allergy clinic identified co-amoxiclav without skin or challenge testing, but the review panel considered chlorhexidine the most likely culprit. In three cases, the allergy clinic identified gentamicin with intermediate certainty, but the review panel considered teicoplanin the most likely culprit.

Communication with the patient

In two-thirds of cases appropriate advice on future avoidance was not provided by the allergy clinic. This included; no advice given, not all culprits investigated, no culprit identified, no safe alternatives for future surgery stated, and excessive avoidance advice (eg. multiple antibiotics). See also Chapter 14, Investigation.

Table 3. Oral (12) and intravenous (11) challenges NOT undertaken by allergy clinic but considered necessary by the review panel to either exclude or confirm allergy

Antibiotic	Challenges not undertaken when indicated
Co-amoxiclav	7
Teicoplanin	6
Cefuroxime	1
Flucloxacillin	3
Gentamicin	5
Amoxicillin	1
Total	23

A patient scheduled for elective surgery was induced with fentanyl, propofol and atracurium. Levobupivacaine and clonidine were administered in a nerve block. Teicoplanin and gentamicin were given ≈15 minutes afterwards. Widespread signs of anaphylaxis developed within a few minutes. The Grade 3 reaction resolved with treatment. Investigation in the allergy clinic included skin prick tests for atracurium and bupivacaine but no other investigations such as additional skin prick or intradermal tests, drug challenge(s) or measurement of drug-specific IgE. The clinic described no specific tests for teicoplanin or gentamicin and, with negative tests for other drugs, advised the patient to be cautious about teicoplanin and gentamicin.

Discussion

No previous study has undertaken concomitant studies of incidence of anaphylaxis and antibiotic exposure. This is particularly important in the case of some antibiotics, such as teicoplanin, where usage has increased in recent years. This means NAP6 provides a unique opportunity to examine both prevalence of reactions and incidences.

Our findings provide robust evidence that antibiotics are the most common cause of perioperative anaphylaxis in the UK, adding to previously published data (Low 2016, Kemp 2017, Meng 2017). We also unequivocally identify teicoplanin as being associated with the highest per-administration risk, confirming suspicions expressed by the authors of small case series (Asero 2006, Savic 2015, Kemp 2017, Azamgarhi 2018). This is a new and important finding.

Our findings demonstrate that administration of teicoplanin is closely related to patient-reported penicillin allergy, and it is reasonable to assume that in many of the cases of teicoplanin anaphylaxis penicillin would have been the first-line antibiotic choice. Penicillin is the most commonly reported drug allergy in the community, with up to 10% of the population labelled as allergic to it. It is likely that the majority are mislabelled, and that at least 90% could be de-labelled if an adequate description of the original reaction could be obtained or the patient investigated in an allergy clinic (Borch 2006, Dworzynski 2014, Macy 2015). We also identified that in at

Table 4. Culprit antibiotics suspected by anaesthetists, diagnosed by allergy clinics, and identified by the review panel

Antibiotic	Suspected by the anaesthetist	Allergy clinic (high)	Allergy clinic (intermediate)	No clinic culprit	Review panel
Co-amoxiclav	40	24	8	14*	46
Teicoplanin	33	19	8	9*	36
Cefuroxime	6	2	0	2	4
Gentamicin	0	1	2	0	3
Flucloxacillin	6	2	0	0	2
Piperacillin-tazobactam	3	0	1	0	1
Metronidazole	0	1	0	0	1
Vancomycin	2	0	0	1	1
Total	**90**	**50**	**19**	**24**	**94**

**Three patients died and one did not attend the allergy clinic.*

least three cases of teicoplanin allergy in patients with a reported history of penicillin allergy, this label was subsequently removed as part of the allergy clinic investigations. It is currently impractical for all putative penicillin allergy to be investigated in allergy clinics preoperatively, and the process is significantly complex. However, with the ever-increasing importance of antibiotic stewardship, avoidance of a spurious label of 'penicillin- allergic' is an area ripe for research.

Multiple drug allergy may benefit from preoperative investigation. NICE recommends that those with a suspected allergy to beta-lactam antibiotics should be referred if they need treatment for a disease or condition that can only be treated by a beta-lactam antibiotic or are likely to need beta-lactam antibiotics frequently in the future (eg. recurrent bacterial infections or immune deficiency) (NICE 2014). Referral should also be considered where there is suspected allergy to beta-lactam antibiotics and at least one other class of antibiotic. In the elective setting, improved history taking and allergy clinic referral may facilitate de-labelling and the identification of safe alternatives where allergy is confirmed.

We are facing a threat of increasing antibiotic resistance (WHO 2014, WHO 2017), and in addition there is a growing body of evidence showing that use of second-line (often more expensive) antibiotics has significant public health implications and increased healthcare costs, with increased duration of treatment and hospital stay, and higher rates of antibiotic resistance and infections including methicillin-resistant Staphylococcus aureus, Clostridium difficile and vancomycin-resistant enterococcus. Our findings provide additional evidence of the use of second-line antibiotics, driven by drug allergy history, and highlight that substitution with an antibiotic carrying a high anaphylaxis risk is not necessarily a safe solution. This further highlights the need, already raised by the international allergy community, for robust programmes to investigate and de-label, where appropriate, patients with reported history of penicillin allergy, thus improving antibiotic stewardship (Sade 2003, Macy 2014b, Solensky 2014, Krishna 2017).

The most common first clinical feature was hypotension, presenting within five minutes of exposure in three quarters of patients. This is in keeping with published data showing that cardiovascular involvement is the predominant feature (Gonzalez-Estrada 2015, Kuhlen 2016, Low 2016), and confirms the clinical suspicion and available published data that reactions to intravenous drugs, and antibiotics in particular, can be severe and tend to present very quickly after administration (See Chapter 10, Clinical features and Chapter 11, Immediate management and departmental organisation).

The use of antibiotic 'test doses' appears common, and occurs in one fifth of all cases of antibiotic-induced anaphylaxis reported to NAP6. It cannot reasonably be expected that a single test dose will eliminate the risk of anaphylaxis. In the allergy clinic, where challenge testing only takes place after a negative skin test, the starting dose for drug challenge will vary depending on the severity of the index reaction, the dose that is believed to have caused it, the patient's co-morbidities, whether the challenge is oral or intravenous, and the drug itself. With some high-risk drug challenges the test dose can be as low as 10^{-3} of the therapeutic dose, increasing in two-fold to ten-fold increments. A third of UK anaesthetists routinely administer a test dose when administering an intravenous antibiotic (Chapter 7, Baseline survey), despite guidelines from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) advising against their use (Harper 2009). We find no evidence to support the practice.

Considerably more than half of all patients received an antibiotic, and almost all were administered after induction of anaesthesia. Avoiding unnecessary antibiotic administration is certainly one way to reduce the incidence of perioperative anaphylaxis, and adhering to hospital protocols is likely to achieve this. In three quarters of cases, signs of antibiotic-induced anaphylaxis were identified in less than five minutes, and almost all in less than ten minutes. Anaphylaxis-induced hypotension is likely to be exacerbated by general or neuraxial anaesthesia. There is a strong argument for antibiotics to be administered several minutes before induction of anaesthesia. There are several potential benefits: first, lack of allergy can be confirmed with the awake patient immediately before administration; second, the severity of physiological derangement due to anaphylaxis may be lessened; and third, investigation of anaphylaxis is considerably simplified if fewer drugs have been administered.

The NAP6 Allergy clinic baseline survey (Egner 2017, Chapter 13), identified that not all were compliant with national guidelines. Our findings reinforce the need for allergy clinics to follow published guidelines on investigation of possible antibiotic anaphylaxis (Ewan 2010, Dworzynski 2014, NICE 2014, Mirakian 2015).

Allergy clinics did not identify the antibiotic culprits in a quarter of all cases, mostly as a result of investigations that were incomplete in such areas as skin tests and drug provocation challenges. Clinics may be underdiagnosing antibiotic allergy, potentially placing patients at risk of future reactions.

Recommendations

Institutional

- Patients with reported allergy to a beta-lactam antibiotic and at least one other class of antibiotics should be referred for specialist allergy investigation before elective surgery, in line with National Institute for Health and Care Excellence guidelines CG183 (NICE 2014)
- If antibiotic allergy is suspected despite negative skin tests, challenge testing should be performed
- Trust guidelines on antibiotic prophylaxis for surgery should be immediately available to anaesthetic and surgical teams in theatre.

Individual

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

IV drug challenging may be required to exclude penicillin allergy

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