

REVIEW ARTICLE

Management of a surgical patient with a label of penicillin allergy: narrative review and consensus recommendations

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Summary

Unsubstantiated penicillin-allergy labels are common in surgical patients, and can lead to significant harm through avoidance of best first-line prophylaxis of surgical site infections and increased infection with resistant bacterial strains. Up to 98% of penicillin-allergy labels are incorrect when tested. Because of the scarcity of trained allergists in all healthcare systems, only a minority of surgical patients have the opportunity to undergo testing and de-labelling before surgery. Testing pathways can be modified and shortened in selected patients. A variety of healthcare professionals can, with appropriate training and in collaboration with allergists, provide testing for selected patients. We review how patients might be assessed, the appropriate testing strategies that can be used, and the minimum standards of safe testing.

Keywords: allergy; drug provocation testing; penicillin; prophylaxis; surgery; surgical site infection

The recommendations developed in this article concern the management of surgical patients with a label of penicillin allergy. We aimed to provide a practical guide for anaesthetists and other healthcare professionals in the perioperative setting.

To provide context, a literature search was performed to examine the existing evidence and current practices. The search was initially performed in June 2018 and repeated in September 2018, using the following criteria: English language only; humans; last 10 yrs; PubMed search engine; MESH key words: penicillin allergy (yields 904 articles), AND testing, de-labelling, AND health costs, implications, health benefits, AND pre-operative patients, surgical patients, surgery, AND testing strategies. A 10 yr limit was set on the basis that much of the work informing these guidelines has arisen in this period of time. A total of 301 articles were selected; 93 were deemed relevant after a review by the writing group. Additional articles were included on the basis of relevance, including some from more than 10 yr ago where these were judged to be of seminal importance.

Epidemiology of a penicillin-allergy label

Penicillin is the most common drug allergy recorded in medical records, with a prevalence ranging from 6 to 15% in recent large studies throughout the world.^{1–4} Whilst frequently listed in the medical record, the incidence of confirmed penicillin allergy is much lower and appears to be decreasing. Longitudinal studies from a large health plan in the USA found the rate of positive penicillin skin tests to have decreased from 15% in 1995 to 3% in 2007.⁵ In 2013, the same group reported that only 1.6% of penicillin-allergy histories from 500 patients could be confirmed.⁶ A work in France has demonstrated a higher rate of immediate (immunoglobulin E [IgE]-mediated) penicillin allergy, although testing was only performed in those with a history already suggestive of an allergic reaction, rather than an unselected group of all patients with the label.⁷

Recent large studies from other countries have confirmed low rates (5–6%) of confirmed penicillin allergy in both children and adults.^{8,9}

Nevertheless, penicillin remains a leading cause of drug-induced hypersensitivity and anaphylaxis. A recent US study of a large electronic health record database of more than 1.7 million patients determined that 1.1% reported drug-induced anaphylaxis, with the most common culprit being penicillin.¹⁰ Cases collected by the French Allergy Vigilance Network between 2010 and 2012 determined that penicillins (especially amoxicillin) were the most commonly identified cause of severe drug-induced anaphylaxis.¹¹ Amongst fatal drug-induced anaphylaxis, penicillin was the most commonly identified culprit drug in a recent US study,¹² and a recent study of suspected perioperative anaphylaxis in the UK found that antibiotics were the commonest cause of life-threatening anaphylaxis, with amoxicillin clavulanate (co-amoxiclav) the most frequently causal agent.¹³ Aside from anaphylaxis, penicillins may more rarely cause severe cutaneous adverse reactions, such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These severe blistering skin conditions can result in organ failure and be fatal.

Evidence of harm from the label

Over the past 10 yr, the clinical and economic ramifications of the ‘penicillin allergy’ label have been well defined. These include infection and antimicrobial resistance, hospital readmission rates, length of hospital stay, use of critical care beds, and healthcare costs. For surgical patients, postoperative surgical site infections (SSIs) are major contributors to patient morbidity and mortality, and therefore, costs. Antibiotic prophylaxis is a key strategy to prevent SSI, with beta-lactam antibiotics the preferred antibiotic for many procedures.¹⁴ Several studies have assessed SSI in patients labelled as penicillin allergic. A retrospective cohort study of 8385 patients undergoing 9094 procedures showed that 11% reported

penicillin allergy, and those with the label had 50% increased odds of SSI attributable to the use of second-line antibiotics.¹⁵ In approximately 250 patients undergoing head and neck surgery, clindamycin was substituted for a cephalosporin in those labelled penicillin allergic, and this was associated with a four-fold increase in SSI.¹⁶ In a retrospective study of 18 830 elective primary arthroplasties, the use of vancomycin as a sole agent was associated with more SSIs than prophylaxis with cefazolin as a sole agent; penicillin-allergy labels accounted for 54% of the vancomycin group.¹⁷ However, increased SSI was not demonstrated in another study, where arthroplasty patients received vancomycin alone attributable to the penicillin-allergy label, compared with those receiving cefazolin.¹⁸

Given the use of beta-lactam alternative antibiotics in those labelled penicillin allergic, the focus has turned to associated infection, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* infection. In a large population-based cohort study from the UK of more than 300 000 adults, those labelled with penicillin allergy were compared with matched controls¹⁹; penicillin allergy was associated with an increased risk of MRSA (hazard ratio: 1.69) and *C. difficile* (hazard ratio: 1.26). Increased use of beta-lactam alternatives accounted for 55% of the increased risk of MRSA and 35% of the increased risk of *C. difficile*. In a large cohort US study of more than 50 000 inpatients, those labelled penicillin allergic were treated with significantly more fluoroquinolones, clindamycin, and vancomycin compared with control subjects, and had 23.4% more *C. difficile*, 14.1% more MRSA, and 30.1% more vancomycin-resistant enterococcus infections.⁴ In addition, penicillin-allergy-labelled patients averaged 0.59 more hospital days during an average of 20 months of follow-up compared with control patients.

The effect of a penicillin-allergy label on hospital readmissions has also been quantified. In a West Australian adult tertiary hospital, more than 600 patients were surveyed, with 18% labelled penicillin allergic. Those with the label had significantly more hospital readmissions within 4 weeks and 6 months of discharge compared with controls; the majority of readmitted patients had major infections.²⁰ In a large prospective matched cohort study from a Dutch university medical centre of more than 17 000 patients, of whom 5.6% were labelled penicillin allergic, the penicillin allergic group had a significantly higher risk of being re-hospitalised at 12 weeks (27% vs 22%), although there was no significant difference at 4 weeks between the groups.³

Current guidelines for penicillin-allergy testing and their limitations

In most countries, testing for penicillin allergy is performed predominantly under the supervision of allergy specialists and, typically, when there is a need for penicillin-based therapy. Given the morbidity associated with a spurious label of penicillin allergy and the low likelihood of a label of penicillin allergy being correct, it has now been recommended to perform such testing routinely in labelled patients, regardless of acute need.²¹

Standard testing guidelines

The gold standard test with which to establish tolerance to penicillin is a graded drug provocation test (DPT) using the

index penicillin to which the patient reacted. Current guidelines from Europe and North America recommend that patients should first be skin tested using skin prick tests (SPTs) and intradermal tests (IDTs).^{22–26} In the context of a patient who has had a clinical reaction, a positive skin test, with readings taken immediately, can identify the presence of IgE sensitisation. The skin test, therefore, provides a way of risk stratifying patients for a DPT. Skin tests for penicillin have a negative predictive value approaching 100%, and patients who do not react to SPT or IDT are therefore unlikely to have a severe immediate reaction on the DPT.^{26,27} However, the interpretation of a positive skin test is less well defined, as these patients are not offered a DPT for obvious ethical reasons. The positive predictive value is generally accepted to be <50% based on limited numbers of prospective studies and outcomes from accidental re-exposure.^{28–30} It is important to note that delayed readings are required for the diagnostic work-up of non-immediate type i.v. hypersensitivity reactions, although the predictive value of these readings is not well established and their utility may be lower.²² Any subsequent DPT may also demonstrate delayed reactions such as these.

The panel of reagents used for skin testing varies geographically. In particular, the experience of using minor determinant mixtures (MDMs) and benzylpenicilloyl poly-L-lysine (PPL) is mixed, not least, because for many years in the USA, these reagents were not commercially available. The utility of PPL/MDM is best defined for immediate-type hypersensitivity reactions to penicillin, where the addition of each reagent increases the sensitivity of testing by 15% and 47%, respectively.^{31,32} In Southern Europe, with its greater use of amoxicillin, the value of adding this drug to the skin-test panel has been well documented.³³ The British Society for Allergy and Clinical Immunology recommends that patients are tested against PPL, MDM, amoxicillin, and the index penicillin if known (and different), and penicillin G (benzylpenicillin) if this is not contained in the PPL/MDM reagent kits.²²

There are some important limitations to the utility of skin tests. Many studies have commented on reduced sensitivity over time in the diagnosis of immediate reactions,^{5,34,35} and low sensitivity and specificity in patients with non-severe, non-immediate, and vague reactions.^{36–38} Reactions in childhood, typically delayed onset, and unspecified rashes can result in lifelong unnecessary avoidance of penicillin, and yet are only rarely associated with positive skin or DPT testing.³⁹

Another testing modality that can be used is the serum-specific IgE assay. Although the sensitivity and specificity of this test are low, it is recommended by European guidelines. There have been cases where skin testing was negative but serum-specific IgE positive, and the patient went on to have anaphylaxis when exposed to the drug.²⁵ Its use as a sole test is not recommended.

The cost of performing a standard penicillin-allergy evaluation varies according to multiple local factors. A study in the USA examined the cost of testing using time-driven activity-based costing, which measures cost through calculation of time spent using a given resource and the per unit cost of the resource. They found that base-case penicillin-allergy evaluation costs \$220 (2016), with a range of \$40–537.⁴⁰ The skin testing component of testing is typically the most expensive, requiring highly trained personnel and relatively expensive consumables.

Direct penicillin challenge in low-risk patients

Where symptoms are mild and not suggestive of an IgE-mediated reaction, the utility of skin tests is low and a direct oral DPT may be appropriate. Although a recent work has shown that the risk of true allergy cannot be predicted with high sensitivity and specificity on the basis of clinical history alone,⁴¹ a growing body of evidence suggests that the clinical history can nevertheless be used to risk stratify patients for a direct DPT. In a US study, 328 young military recruits with non-severe histories of penicillin allergy underwent a direct amoxicillin DPT with only 1.5% having objective reactions, none of which were life-threatening anaphylaxis.⁴² An Israeli study of 642 patients (two-thirds were children and some had reactions not suggestive of true allergy) with delayed reactions (>1 h after the last dose) underwent skin testing and a 5 day amoxicillin DPT even if skin tests were positive, with only 6% displaying mild reactions and no cases of anaphylaxis.⁴³ Almost one-third of patients had equivocal skin tests and 5% had positive skin tests, yet the majority tolerated the DPT. It is worth noting that immediate readings of skin tests were used even though the index reactions were in keeping with delayed hypersensitivity. In a prospective study from Canada, 818 children underwent an amoxicillin DPT without skin testing, with 94% tolerating amoxicillin.⁸ The immediate reactions were all mild, although a few developed serum-sickness-like reactions, as this was not an exclusion criterion. Of 17 children with immediate reactions to the DPT, only one (5.9%) had a positive penicillin skin test 2–3 months later. A prospective study from Spain evaluated 766 children with histories of penicillin allergy who underwent skin testing and DPT (regardless of skin-test results), and found around 5% to be allergic.⁹ Penicillin-allergy skin tests had very low sensitivity (2.9% had positive immediate skin tests), but had good specificity. A study of 155 adults and children, with non-severe histories of penicillin allergy and who underwent placebo-controlled amoxicillin DPTs without skin testing in an allergy clinic, found 2.6% with true allergic reactions and 10% reacting to placebo.⁴⁴

The primary advantage of this approach is that the lack of need for skin testing reduces time and cost. A direct DPT is also quick and non-invasive, which is more convenient for patients. There are disadvantages, however. Firstly, the data appear to be strongest in children; secondly, it is not yet known whether non-allergists will be able to adopt this approach with the safety and outcomes seen in studies to date. Finally, there is also no clear consensus on which patients can be considered low risk and forgo skin testing, although several groups have proposed criteria for this.⁴⁵

Advice for de-labelled patients

Patients evaluated with skin tests, DPT, or both, and found not to be sensitised to penicillin should be advised that they have the same risk as the general population for developing new allergy to penicillin in the future. This statement acknowledges that any individual may become sensitised to penicillin during their lifetime and that negative testing is not a lifelong guarantee of tolerance. It must also be recognised, however, that a DPT for a single penicillin does not entirely preclude allergy to all other penicillins because of side-chain sensitivity, which might be missed with a single-drug DPT. For example, a patient whose index reaction was to flucloxacillin, but who does not remember this and has a negative DPT with

amoxicillin remains at risk from re-exposure to flucloxacillin. However, this does not appear to be a significant problem given the lack of reports in the literature of this occurring, and current guidelines do not recommend multiple DPTs in cases where the index penicillin is not known.

Finally, the risk of re-sensitisation must be considered for any patient undergoing a DPT. This risk appears to be lower than initially reported in the USA, however, with the results of recent studies suggesting that repeating skin tests after an oral DPT in order to check for re-sensitisation is unnecessary.⁴⁶ Patients who have been tested and de-labelled should instead be monitored clinically for evidence of re-sensitisation. Repeating the skin tests may be of use in patients with confirmed severe reactions as a means of periodically reassessing whether the patient remains sensitised, but this is less the case in those with initial histories not suggestive of allergy.²⁴

Novel testing strategies and pathways

As the impact of the 'penicillin allergic' label on antimicrobial stewardship and health costs becomes clearer, the need to find ways of reducing the burden of incorrect labels has become imperative. A key part of the problem is poor understanding of allergy amongst non-specialists (and patients) leading to incorrect labelling, and limited knowledge of the services available for allergy testing,^{47,48} although there is evidence that knowledge can be improved through training.⁴⁹ These aspects are beyond the scope of this article.

Different strategies around the world have been used to address the expanding and unmet need for allergy testing; some of these are detailed next.

Inpatient-based penicillin skin testing programmes

Large numbers of hospitalised patients are treated with antibiotics, often requiring prolonged courses and including broad-spectrum antibiotics. The inpatient setting is therefore ideal for penicillin-allergy testing, and numerous studies have demonstrated the improved use of antibiotics after penicillin skin tests. Of ~1000 patients with self-reported penicillin allergy, same-day penicillin skin testing and consultation reduced the vancomycin use from 30% in historical controls to 16% in those judiciously evaluated.⁵⁰ In an ICU setting, a prospective study of 96 patients labelled as penicillin allergic were skin tested⁵¹; of the group receiving therapeutic antimicrobials, 82% were changed to a beta-lactam after a negative skin test with no adverse events. Long-term follow-up of 308 subjects evaluated with skin tests and matched with 1251 unique controls (labelled penicillin allergic; not evaluated) found that those tested received significantly more penicillins and first- and second-generation cephalosporins than controls, with less clindamycin and macrolides. Those evaluated also had fewer outpatient and emergency department visits, and 0.553 less hospital days per year than the controls. The authors estimated that testing 308 of the controls may have saved the health system more than \$2 million over 3.6 yr.⁵²

A recent systematic review described several studies, including six in the intensive care setting.⁵³ Penicillin skin tests were negative in 95% of patients overall, and increased use of penicillins and cephalosporins was noted, with rare reports of life-threatening anaphylaxis after amoxicillin challenge at an incidence of <1%. The largest reported inpatient experience is from the USA and utilises allergy-trained pharmacists to perform penicillin skin tests and amoxicillin

challenge.⁵⁴ To date, 98% of more than 700 penicillin allergic inpatients have been found to test negative (D. Khan, personal communication). Another large US study of inpatient penicillin-allergy skin testing (with 90% performed by a nurse) found a much higher rate (20%) of positive skin tests, but utilised minor determinant skin tests with different criteria for a positive skin test.⁵⁵ Another study utilised telemedicine to reduce the need for on-site allergy specialists, with skin testing performed by physician assistants.⁵⁶ Some studies have performed penicillin-allergy testing in the emergency department; however, higher than typical rates of positive skin tests (15.5%) might suggest that the 30 min training session for testers was inadequate.⁵⁷ The benefits of testing as an inpatient include a readily accessible high-risk population and immediate impact on antimicrobial stewardship outcomes. The main drawback to this approach is a lack of trained providers who can perform skin tests and allergists who can assist with setting up such programmes.

Clinical algorithms to guide the use of beta-lactams in penicillin allergy

An alternative approach to encourage a more appropriate use of antibiotics is through the use of clinical guidelines, which provide advice on the use of beta-lactams based on the history of the penicillin allergy. A recent study in the UK demonstrated proof of concept for guideline-based selection of patients suitable for a direct DPT using an algorithm suitable for use by non-specialists.⁴⁵ The use of guidelines such as these in an inpatient setting has demonstrated an increased use of beta-lactams (primarily cephalosporins) and a reduction in the use of vancomycin, aztreonam, and fluoroquinolones.^{58,59} A study comparing usual care, penicillin skin tests, and a clinical guideline with additional web-based clinical decision support found that both penicillin skin testing and the guideline led to an increased use of penicillins or cephalosporins, although not penicillins alone.⁶⁰ The methodology for implementing this type of approach at a hospital level has been published.⁶¹ The benefits are that guidelines can potentially be used to change antibiotic prescribing patterns in penicillin allergic patients without the need for additional personnel. Drawbacks to this approach are that a primary effect is to increase the use of cephalosporins in penicillin allergic patients,⁶² a practice that may already be commonplace in some hospitals⁶³ and, which when used alone, typically does not allow de-labelling of the penicillin allergy.

Preoperative penicillin-allergy testing

Patients with a history of penicillin allergy often receive vancomycin for surgery. In the UK, the commonest alternative is now teicoplanin. Aside from the risks of increased SSI, longer hospital stay, and higher readmissions, there is also the risk of allergy to the alternative antibiotic used.¹³ In order to reduce the use of alternatives in the perioperative setting, penicillin-allergy tests can be performed before surgery. The surgical population represents a large pool of accessible patients with an immediate need for good antibiotic stewardship. A recent UK study demonstrated that penicillin-allergy testing can be incorporated into the preoperative journey for a patient with a subsequent improved use of SSI prophylaxis.⁶⁴ The largest experience with preoperative testing comes from the Mayo Clinic in the USA, where a preoperative evaluation clinic was established in 2001.⁵⁰ To date, this programme has performed >29 000 penicillin-allergy tests with only 1% being positive (M.

Park, personal communication). Recent studies have used electronic best practice alerts to identify patients with penicillin allergy who are scheduled for orthopaedic surgery and to facilitate referral to a specialised clinic for penicillin-allergy testing.⁶⁵ The benefit of a preoperative testing approach is that patients are de-labelled at the time of antibiotic need. Drawbacks are the requirement for personnel to perform the tests and the time pressures associated with surgery.

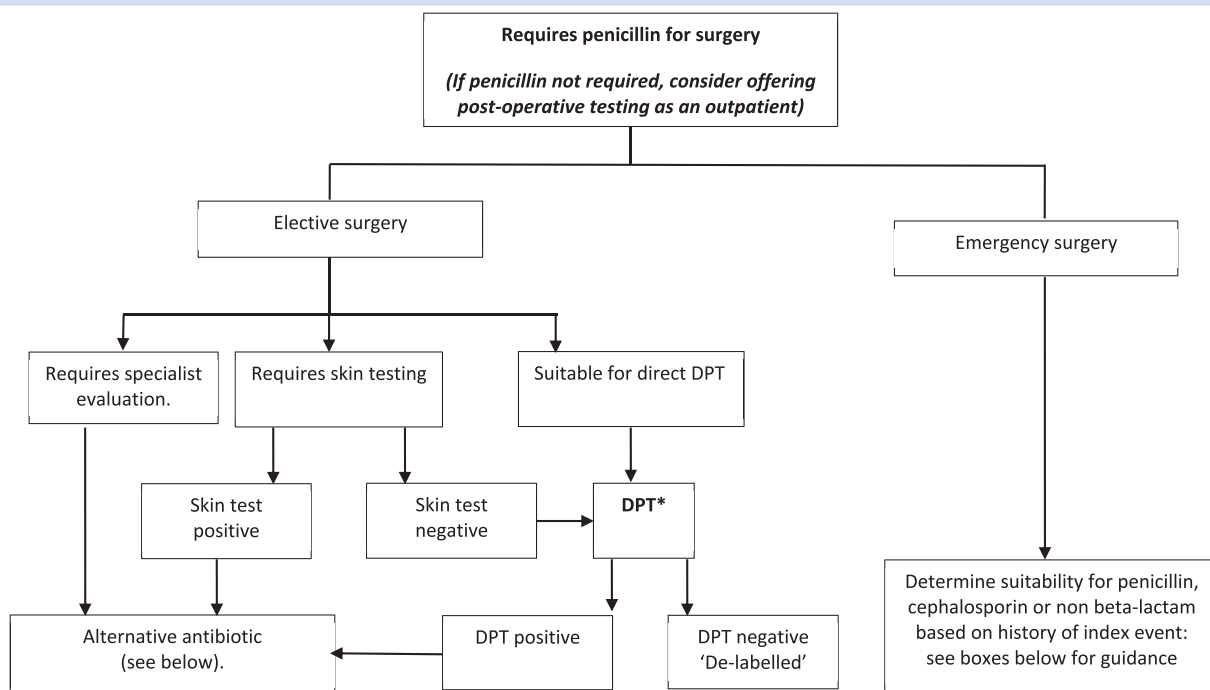
Use of alternative beta-lactam antibiotics in penicillin-allergic patients

Alternative beta-lactams include the cephalosporins, carbapenems, and monobactams, of which cephalosporins appear to be the most relevant. Carbapenem cross-reactivity with either penicillins or cephalosporins appears to be very low.^{66–68} There is no apparent cross-reactivity between monobactams and penicillins,⁶⁸ although there may be between ceftazidime and aztreonam, partly because they share an R1 side chain.⁶⁹ The earliest studies of penicillin and cephalosporin cross-reactivity from the 1970s were tainted by the presence of trace amounts of benzylpenicillin in the cephalosporins, falsely increasing the apparent degree of cross-reactivity. The figure of 10% cross-reactivity stems from this work and is still quoted in the US Food and Drug Administration descriptions of the cephalosporins.

The true incidence of cross-reactivity between penicillins and cephalosporins, and between different cephalosporins, is likely to be lower, but has been difficult to quantify or predict. Partly, this is because of differences in study methodology; this is compounded by the rarity of allergy to cephalosporins. The incidence of anaphylaxis to cephalosporins is estimated at 0.00002% and 0.00016% for oral and parenteral administration, respectively.⁷⁰ This is at least one order of magnitude less frequent than anaphylaxis to penicillin, which is about 0.005% and 0.002% with oral and parenteral administration, respectively.⁷¹

Variation in the degree of cross-reactivity between penicillin and cephalosporins is determined by structural differences amongst cephalosporins. All share with penicillin a four-membered beta-lactam ring, which is adjacent to a five-membered thiazolidine ring or a six-membered dihydrothiazine ring in cephalosporins. The penicillins and cephalosporins undergo different beta-lactam ring degradation patterns; breakdown of the penicillin beta-lactam ring results in the formation of haptens capable of allergenicity, whereas the cephalosporins undergo rapid breakdown that does not predictably produce haptens. Therefore, cross-reactivity between the penicillins and cephalosporins has focused on the R1 and R2 side-chain moieties that vary between the generations of cephalosporins, with side-chain similarity likely to contribute to cross-reactivity. Of note, cephazolin, used perioperatively in many parts of the world, does not have similar R1 or R2 side chains to either penicillins or other cephalosporins except for ceftazole. Cephazolin also offers superior Gram-positive antimicrobial activity compared with cephalosporins of later generations, and has been shown after testing not to cross-react with a number of other cephalosporins from all generations.^{72,73} Thus, despite being a first-generation cephalosporin, it may be an option for a penicillin-allergic patient. It is worth noting that the R1 and R2 side chains are not always the antigenic determinant, and cross-reactivity may still exist.⁷⁴

Studies on cephalosporin allergy can be broadly divided into two groups: large observational studies and smaller



*Drug provocation test (DPT), using index penicillin if known, otherwise the most commonly used penicillin in that country. Absolute contra-indications to DPT include history of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN) and other severe cutaneous reactions, severe ischaemic heart disease, pregnancy

**Patients suitable for direct DPT:
Initial reaction consisted of:**

- GI disturbance only
- Thrush;
- Family history only;
- Minor, non-specific, non-allergic symptoms (e.g. headache)
- Benign rash >10 years ago (non-itchy, non-blistering, >1 hour after first dose;
- Uncertain history but has since taken penicillin with no reaction.

**Patients requiring skin test prior to
consideration for DPT:
Initial reaction consisted of:**

- Rash, with no further details
- Urticarial rash
- Uncertain history but told reaction was severe requiring treatment.

**Patients requiring specialist
evaluation:
Initial reaction consisted of:**

- History of severe immediate systemic reaction with any of the following: wheeze, dyspnoea, collapse, angioedema, swelling, loss of consciousness.
- Patients with a history of severe and/or blistering rash or confirmed diagnosis DRESS, SJS, TENS

Advice on selection of alternative antibiotics

1. Confirmed penicillin allergy:
 - Skin test (ST) to establish tolerance to other beta-lactams, followed by DPT
2. Unconfirmed penicillin allergy:
 - History suitable for initial DPT: give penicillin (or any cephalosporin if patient refuses penicillin)
 - History suitable for initial ST (+/- DPT): give cephalosporin with different R1 and R2 side chain if index penicillin known. If index penicillin not known, consider using cephazolin if available **and after advice from local allergist**; otherwise avoid all beta-lactams
 - History not suitable for testing: avoid all beta-lactams

Fig 1. Flow chart for management of a surgical patient with a label of penicillin allergy.

studies with well-documented IgE-mediated hypersensitivity to penicillins undergoing evaluation with cephalosporins. A weakness of the large observational studies is the inclusion of self-labelled penicillin-allergic patients. As the vast majority

of patients labelled penicillin allergic in medical charts and electronic medical records are not truly penicillin allergic, these studies automatically underestimate true penicillin cross-reactivity with cephalosporins. In addition, selection

bias would potentially exist in these studies, as clinicians would be unlikely to prescribe cephalosporins to a patient with a severe reaction to penicillin. In a compilation of eight observational studies, the range of cross-reactivity was 0–8%.^{75–77} In a meta-analysis of cross-reactivity between penicillin and cephalosporin allergy that included nine studies of patients with reported history of penicillin allergy, the odds ratio of an allergic reaction to any cephalosporin was lower than that to first-generation cephalosporins,⁷⁴ emphasising the importance of cephalosporin structure, with higher cross-reactivity amongst the first-generation cephalosporins and minimal cross-reactivity with second and third generations.

The largest prospective study assessing penicillin and cephalosporin cross-reactivity included 252 subjects who experienced 319 immediate reactions to penicillins and had positive skin tests to at least one penicillin reagent.⁷⁸ Of the 39% with positive allergy tests to cephalosporins, 96% of these were to the amino-cephalosporins or cefamandole. This study demonstrated that skin testing, although helpful, does not always detect sensitivity to cephalosporins with similar side chains. However, DPT to cephalosporins with different side-chain determinants to penicillin (and negative skin tests) was tolerated. Further evidence that side-chain analysis alone without testing (both skin tests and DPT) is not 100% predictive in ruling out cross-reactivity was seen in a study with cefuroxime, where 2.9% cefuroxime sensitivity was seen in 69 patients with prior histories involving penicillin sensitivity only, despite dissimilar side chains.⁷⁹ It is worth noting that cross-reactivity was calculated only when the specific penicillin was known and patients with positive skin tests did not undergo a DPT; the rate of cross-reactivity may therefore be an overestimate.

In general, the risk of a reaction to a cephalosporin is higher in those with true penicillin allergy, and is estimated to be 2–5%.⁷⁷ When confronted with the rare patient with a genuine penicillin allergy who requires a cephalosporin, sensitivity to a cephalosporin with dissimilar R1 and R2 side chains should be explored with skin tests and a graded DPT if this is negative. The significance of positive skin testing in this context remains poorly understood. Two recent comprehensive overviews of side-chain cross-reactivity, including useful tables detailing this, are available.^{62,80}

Consensus recommendations for management of surgical patients with a label of penicillin allergy

These recommendations are based on the results of a Delphi consensus process and were developed with reference to the Appraisal of Guidelines for Research & Evaluation 2 checklist.⁸¹ All members of the writing group are experienced in this field and have published work in this area. A total of four rounds of questionnaires were completed, with 18–23 members participating in each round. Questions were amended or removed at each stage depending on the degree of consensus, and modified according to comments received from the group. Each statement was rated for appropriateness on a scale of 1 (completely inappropriate) to 9 (completely appropriate). The median score for each statement was calculated and used to rate each statement as appropriate (median score: 7–9), uncertain (3.5–6.9), or inappropriate (1–3.4). The disagreement index (DI) was used to determine the degree of consensus for

each statement, with consensus defined as a $DI < 0.5$; this approach is adapted from Fitch and colleagues.⁸² For a full list of all statements where a consensus was reached and some of the key areas where it was not reached, see [Supplementary Appendix 1](#).

For the purposes of these recommendations, the term *allergist* has been used to describe a medical professional whose primary specialisation is in allergy, or who trained in allergy as part of his/her specialty. It is accepted that the nomenclatures for the specialties of immunology and allergy vary across the world.

Defining the most appropriate testing strategy for an individual labelled as penicillin allergic

Risk stratification is a key aspect of investigating patients with a label of penicillin allergy. As discussed in earlier sections, there is no accepted consensus in the literature on how to define risk or group patients into different levels of risk. It is easiest to define those who lie at either end of the spectrum; for example, patients reporting thrush with penicillin use are easily defined as low (or indeed 'no') risk above the risk of penicillin allergy in the general population; patients who give a clear history of anaphylaxis or severe cutaneous reactions are easily categorised as being at high risk. Between these, however, fall myriad intermediate reactions that are harder to categorise, including the very common history of 'no recollection of the event'.

Initial rounds attempted to define risk groupings into no, low, medium, and high compared with risk in the general population. However, it proved difficult to reach a consensus on what constituted 'low risk' and how this group should be approached. Ultimately, it is probably more useful and practical to define instead the appropriate approach to testing for an individual based on the specific reaction reported. The algorithm in [Figure 1](#) defines the pathway that patients may take, depending on whether they are suitable for a direct oral DPT, require skin testing before consideration for a DPT, do not require testing, or should not be tested. The terms *low*, *medium*, and *high* risk, which are open to different interpretations, have thus been avoided.

The definition of what constitutes an appropriate testing strategy for an individual was refined further to take into account the degree of urgency of the surgery, the time available, the level of expertise of the available personnel, and concomitant co-morbidities and medications. This provides a more practical approach to the management of patients in a variety of settings, and may help avoid the blanket avoidance of beta-lactams in both elective and emergency surgery.

In all statements that follow, it is assumed that the patient has no cognitive impairment that might impact recollection of the index event.

Group 1: Direct oral DPT

The following patients are suitable for a direct oral DPT, if lack of time or local expertise precludes prior skin testing (see [Section Definition of the minimum standards required for penicillin-allergy testing](#) below for details of who can perform this testing). Those with an asterisk (*) are patients who could be de-labelled without any formal testing based on their history. It is recognised that a significant proportion of these patients will be reluctant to have the label removed in

this way because of a longstanding belief in their allergic status, and for them a DPT is then the appropriate test.

- (i) History only of thrush*
- (ii) History only of minor gastrointestinal upset*
- (iii) Family history of penicillin allergy, but no personal history*
- (iv) Patient cannot remember why the label was given, but has had at least one course of penicillin antibiotic since then without adverse effects*
- (v) History of only minor symptoms, which are not suggestive of any type of allergic reaction (e.g. headache and arthralgia), and did not require treatment*
- (vi) History of benign rash (all of the following must apply: non-itchy, non-blistering, non-severe, and occurring >1 h after first dose) more than 10 yr ago, provided this did not require treatment

Group 2: Skin testing with or without DPT

The following patients require skin testing before consideration for a DPT (see Section D below for details on who is able to perform the skin testing):

- (i) History of rash, but no details of this are remembered (including childhood rash)
- (ii) History of itchy rash (urticaria) at any time during course of penicillin
- (iii) Index reaction not remembered
- (iv) Other symptoms, not detailed in Groups 1 or 3, and which required treatment

Group 3: Specialist evaluation

The following patients should not be tested or should be referred to an allergist for specialist investigation. This might include the need for desensitisation, an area that is beyond the scope of these guidelines.

- (i) Clear history of immediate and severe reaction with any of the following problems: wheeze, shortness of breath, angioedema, tachycardia, swelling, low blood pressure, collapse, cardiac arrest, and loss of consciousness; these patients may be considered for penicillin desensitisation if there is an absolute indication for penicillin; this would not result in de-labelling of the patient
- (ii) Patients with a history of severe or blistering rash appearing at any time during the course of penicillin or in the weeks afterwards, or a formal diagnosis of drug reaction with eosinophilia and systemic symptoms syndrome, SJS, or TEN are contraindicated from receiving penicillins in the future and should not be offered testing

Medical exclusion criteria for DPT (unrelated directly to symptoms of index reaction)

In addition to the patients in Group 3, the following were agreed as exclusion criteria:

- (i) Severe or unstable ischaemic heart disease
- (ii) Pregnancy (breastfeeding was not considered an exclusion criterion)

We were unable to reach a consensus on whether an airway disease, such as severe asthma or chronic obstructive pulmonary disease, should constitute an exclusion criterion.

Ultimately, this decision must be at the discretion of the team performing the testing, and will be a balance between the need for penicillin and the likelihood of harm from a severe allergic reaction.

Patients undergoing cancer chemotherapy should not be excluded from testing, but the consensus view was that there is a greater chance of a false-negative DPT testing because of the immunosuppressive effects of the treatment.

One additional exclusion criterion, severe aortic stenosis, was suggested by a co-author during the editing phase. Although this was not formally agreed on during the consensus process, it is nevertheless a safe practice to avoid a DPT in such patients unless the risk–benefit analysis strongly favours proceeding.

Ideal timing of testing

There was a clear consensus within the group that testing of perioperative patients is ideally performed before the day of surgery, which may help mitigate both surgical flow issues and medico-legal concerns amongst anaesthetists. A recent work in the UK demonstrates that, when anaesthetists are confronted with a label of penicillin allergy that they consider highly unlikely to be correct, up to 60% will avoid giving penicillin where this is the first-line SSI prophylaxis. Concern about potential medico-legal issues was one of the predominant barriers (L. Savic, personal communication). By testing patients ‘upstream’ of surgery, the anaesthetist is presented with an already de-labelled patient, and subsequent antibiotic use in theatre is likely to be improved. There will be circumstances where testing cannot be performed in a timely manner and a decision needs to be made on the day of surgery. In these circumstances, the following recommendations were agreed:

- (i) Patients who require penicillin for surgery
 - (a) If surgery is elective, it may be appropriate to offer testing on the day, provided this does not delay surgery. This is most likely to apply to patients who are suitable for a direct oral DPT as a result of logistical problems around provision of skin testing.
 - (b) If surgery is urgent or emergent, it should not be delayed in order to test the patient, and alternatives should be used.
- (ii) Patients who do not require penicillin for surgery
 - (a) Testing on the day of surgery is not recommended. However, if the patient wishes to be tested, this could be performed after operation as an outpatient.

Choice of reagents for skin-test panel and DPT

The choice of reagents for skin testing was not explored through a consensus process, as regional variations in standard practice and availability of reagents are likely to make recommendations redundant. This is also true of dosing regimens for a DPT, which should be decided based on locally existing practice.

In terms of drug choice for a DPT, a consensus was reached on the following:

- (i) If the index penicillin is known, testing should be to this drug.
- (ii) If the index penicillin is not known, testing should be with the penicillin most commonly used in that country (e.g. amoxicillin in the UK).

There was no agreement as to whether an i.v. DPT was more appropriate in patients due to receive i.v. penicillin during surgery, and therefore, this cannot be recommended.

Definition of the minimum standards required for penicillin-allergy testing

In this section, we explored how testing should proceed in practical terms. There was a clear consensus that any programme of testing and de-labelling should be set up and overseen by an allergist, but that the day-to-day running of the programme could be performed by a healthcare professional who had received training to a level deemed appropriate by the allergist. This leaves open the possibility that preoperative testing could be performed by a variety of appropriately trained healthcare professionals and that the allergist need not be physically present for all testing. Given the scarcity of these specialists in most healthcare systems around the world, testing is likely to take place at a site geographically separate from the allergist. However, it must be possible to contact the lead allergist for advice when required.

We have not defined in these guidelines what constitutes 'adequate training' for the healthcare professional providing the testing; this must be stipulated by the allergist and will vary between regions. The key area for training, aside from history taking, is in the use of skin tests. The healthcare professional performing these tests is likely to require extensive experience and be able to demonstrate proficiency on a regular basis. This requirement is likely to be a limiting factor for many healthcare settings and may in turn limit the provision of testing to only those patients who are suitable for a direct oral DPT.

The following provision was considered mandatory for the safe testing of patients:

- (i) Basic life support training for the healthcare professional performing the testing
- (ii) Immediate access to a resuscitation team, including an anaesthetist
- (iii) Access to on-site critical care facilities
- (iv) Equipment for i.v. and intra-osseous access
- (v) Immediate access to epinephrine (for i.m. or i.v. use)
- (vi) Immediate access to a defibrillator
- (vii) Equipment for airway management, including oxygen, suction, and oral/supraglottic/tracheal airways

Use of prolonged DPT testing

There are geographical variations in the use of a prolonged DPT after an oral challenge. Broadly speaking, patients in the USA tend not to undergo a prolonged DPT, whilst practice in Europe is mixed.^{83,84} There are also variations in the length of a DPT considered necessary. Ultimately, this is a decision for the allergist overseeing any programme of testing and de-labelling in the perioperative period. The following areas of agreement were reached:

- (i) If used, a prolonged DPT should last for as many days as it took for the symptoms to appear in the index reaction, if this is known.
- (ii) If it is not known how many days it took for the symptoms to appear in the index reaction, a prolonged DPT of 3–5 days is generally sufficient.

- (iii) Patients suitable for de-labelling without any formal testing, but who choose to undergo a DPT (see definitions presented earlier) do not require prolonged challenge.

Advice on alternatives

There will be situations where testing either cannot be performed or is positive. For these situations, practical advice on the use of alternatives is offered in the algorithm in [Figure 1](#). These recommendations are based on a consensus within the group and the evidence base described in earlier sections. The following are the key points:

- (i) In patients who undergo testing and are found to be allergic to penicillin, tolerance to other beta-lactams should be explored with skin testing, followed by a DPT if negative.
- (ii) In patients who require penicillin for SSI prophylaxis but cannot be tested for any reason, the choice of alternative is dictated by the degree of likelihood of true allergy. Please note that the use of cephazolin was not agreed via the formal Delphi consensus process, but arose after a discussion amongst the group when the first draft of the paper was disseminated. All members of the writing group had the opportunity to comment on this section of the guideline, which was highlighted in an e-mail correspondence for ease of review.
 - (a) Patients from Group 1 (direct oral DPT): administer penicillin (or if patient declines penicillin, a cephalosporin of any generation).
 - (b) Patients from Group 2 (skin test with or without DPT): if index penicillin is known, choose a cephalosporin with different R1 and R2 side chains. If not known, consider using cephazolin, if available, after a discussion with a local allergist. Otherwise, avoid all beta-lactams.
 - (c) Patients from Group 3 (specialist evaluation): avoid all beta-lactams.

Dissemination of results after testing

A key component of penicillin-allergy testing is the effective dissemination of the results to the patient and their healthcare providers. Pharmacy-led counselling and provision of a wallet card detailing the results and implications of testing have been successfully used in some areas.⁸⁵ Whilst a consensus was not sought on this topic, the authors recommend that, as a minimum, written evidence of testing is provided to the patient and their primary care physician, and the electronic hospital record is updated accordingly. A wallet card that is standardised across geographical regions and becomes embedded in local practice might help prevent relabelling.

Summary

These guidelines provide a consensus-based outline of how to manage the surgical patient with a label of penicillin allergy across a wide spectrum of reported allergic reactions, urgency of surgery, and available facilities. Acknowledging the extremely limited resources available for allergy testing in most healthcare settings and increasing evidence that not all patients with the label require all elements of standard allergy testing, we have included strategies that reduce the need for

specialist input from allergists in selected circumstances. This allows the appropriately trained non-specialist to assess and test patients, working within agreed frameworks. Further work is needed to assess the utility and impact of such programmes.

Authors' contributions

Study conception: all authors.

Study design: LCS, GWV, DAK, PK.

Data collection: all authors.

Data analysis: all authors.

Data interpretation: all authors.

Drafting of manuscript: LCS, GWV, DAK, PK, SDM.

All authors reviewed the drafts of the manuscript and approved the final version.

Declarations of interest

PD has received lecture and travel fees from MSD France (Courbevoie, France), lecture and travel fees from Bracco Imaging France (Courcouronnes, France), and from Agence Nationale de Sécurité du Médicament et des Produits de Santé (Saint-Denis, France). He was an expert for a task force group dedicated to 'neuromuscular blocking agents and anaphylactic reactions' (until 2016) and is an MSD Expert Board on 'neuromuscular blocking agents and fast-tracking anesthesia' (until October 2019). LHG is a consultant and adjudication committee member for Merck (Kenilworth, NJ, USA) and Novo Nordisk (Gatwick, West Sussex, Denmark). PMH is an Editorial Board Member of the *British Journal of Anaesthesia*. PMM is a scientific advisor for the Allergy to Neuromuscular Blocking Agents and Pholcodine Exposure study (NCT02250729), funded by a consortium of pharmaceutical companies: Zambon, URGO, Pierre Fabre, Boots, Hepatoum, Biocodex, Sanofi, LBR, GSK, APL, Bell's Healthcare, Pinewood, T & R, and Ernest Jackson. PK has received lectures fees from Novartis Pharma Services Inc. and Shire Pharmaceuticals Group Plc. SDM is in receipt of an Australian National Health and Medical Research Council ECR Fellowship for the investigation of cognitive aids in emergencies. All other authors confirm that they have no interests to declare.

Disclaimer

The guidelines and recommendations included in this paper represent the views of the authors. They are based on careful consideration and interpretation of the available evidence at the time that they were agreed, along with a formal consensus development process. They are intended principally for clinicians involved in the management of patients scheduled for surgery who give a history of penicillin allergy, and these clinicians are encouraged to take the guidelines and recommendations fully into account when exercising their clinical judgement. The guidelines and recommendations do not override the individual responsibility for clinicians to make appropriate decisions and give the best care according to the circumstances of individual patients. Where appropriate, decisions should be made in consultation with the patient and, where relevant, their guardian.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2019.01.026>.

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Delphi consensus: Management of the surgical patient labelled as penicillin allergic.

Below are listed the statements for which agreement was reached among the group. For each statement the median score and the disagreement index (DI) are given

The remaining statements where agreement was not reached have not been included. Where this was in key areas in which lack of agreement merits attention, further details are given.

Who should be considered for testing?	Median	DI
Patients scheduled for elective surgery, who require penicillin-based SSI prophylaxis*	9	0.23
Patients scheduled for emergency/urgent surgery should be considered for testing, regardless of the need for penicillin-based SSI prophylaxis	2.5	0.16
Patients who present for surgery but state they would continue to avoid penicillin even if testing is negative, should be considered for testing	2	0.22

*No agreement on whether elective patients NOT requiring penicillin for surgery should be offered testing, however it was determined in a later question that these patients could be tested post-operatively – see statement 5b.

At what point in the surgical pathway should patients be offered testing?	Median	DI
Patients undergoing elective surgery should be tested prior to admission	8	0.19
Testing should be undertaken post-operatively, but before discharge	3	0.37
Testing should take place after surgery, as an outpatient*	7	0.20

*There was commentary from some respondents that they were unclear whether this statement referred to patients undergoing emergency or elective surgery.

Risk stratification:	Median	DI
The following patients are at ‘no’ increased risk above general population		
Family history only	9	0
Thrush only	9	0
Mild Gastro-intestinal upset only	9	0.13
Minor symptoms not suggestive of any type of allergic reaction	9	0
The following patients at are ‘low’ increased risk above general population		
Non-itchy, non-blistering rash more than 1 hour after first dose	7	0.03
Unspecified rash more than 1 hour after first dose, not requiring treatment	7	0.11
Patient doesn’t know/can’t remember, but was told not serious and didn’t require treatment	7	0.23
The following patients are ‘medium’ increased risk above general population		
History suggestive of immediate allergic reaction but not severe	7	0.16
Can’t remember but told it was severe	7.5	0.16
The following patients are ‘high’ risk above general population		
History suggestive of IgE mediated problem temporally related to administration of penicillin	9	0
Severe and/or blistering skin rash during or following a course of penicillin	9	0

Determining the appropriate strategy for testing:	Median	DI
Patients at ‘no’ increased risk		
The most appropriate approach is to remove the label without testing, if the patient accepts this	9	0

In patients who request to have testing, the most appropriate approach is direct DPT without prolonged challenge	9	0.14
In patients who request testing, but cannot have this before admission for surgery, the most appropriate approach is a single dose DPT on the day of surgery	9	0.19
Patients at 'low' increased risk: see text below*		
Patients who cannot be tested due to eczema or other medical condition listed in 'exclusion criteria', should have oral graded DPT	8	0.47
Elective patients not tested prior to surgery, and who do not need penicillin SSI prophylaxis, should have testing post-operatively, as an outpatient	9	0.13
Patients at 'medium' increased risk		
The most appropriate approach is direct DPT	3	0.37
The most appropriate approach is graded, direct DPT	3	0.39
The most appropriate approach is skin testing +/- DPT	8	0.14
Patients not tested pre-op, who require penicillin for surgery, should have skin test +/- DPT on the day of surgery if this doesn't delay surgery	7	0.14
Patients not tested prior to admission, and who do not need penicillin for surgery, should be offered post operatively, as an outpatient	9	0.13
Patients at 'high' increased risk		
These patients should be referred to an allergy specialist for assessment	9	0

*No clear consensus on the general approach to testing in low risk patients. Comments from respondents included being unsure what 'low risk' means, or not agreeing with the definitions of low risk as set out in the questionnaire.

Anaesthetists and allergists answered some of the questions differently. For example:

- The appropriate testing strategy is skin tests +/- DPT (no overall consensus, but allergists gave a median of 8, DI 0.29)

- The appropriate testing strategy is a single dose DPT (anaesthetists 7.5/0.37, allergists 4/0)
- patients not tested prior to admission, who need penicillin, should undergo skin test +/- DPT on the day of admission, providing this does not delay surgery (anaesthetists 3/0.35, allergists 7/0.49)

Use of prolonged drug provocation test (DPT)	Median	DI
Prolonged challenge is not required in 'no' risk patients	9	0
Prolonged challenge is required in low and medium risk patients if their reaction occurred >1 hour after first dose	7	0.25
Prolonged challenge should last for as many days as it took for the index symptoms to appear, if the patient can remember this	7	0.37
Prolonged challenge should last for 3-5 days if the patient cannot remember how long it took for index symptoms to appear	8	0.16
If a 'no' or 'low' risk patient receives penicillin during surgery, follow up with a prolonged challenge is required	4	0.47

Which drug should be used for DPT?	Median	DI
If the index penicillin is known, DPT should be with that drug	9	0.13
If the index penicillin is not known, DPT should be with the amoxicillin, or the most commonly used penicillin for that country	0	0.13
If the index penicillin is not known, it is appropriate to test with cephalosporins rather than penicillin	3	0.51
If the index penicillin is known and the patient tests negative for this, further investigation of other b-lactam tolerance is not required	8	0.13
In patients with positive DPT, tolerance to other b-lactams should be explored with skin testing, followed by DPT if negative	8	0.29

Exclusion criteria for DPT	Median	DI
Severe or unstable coronary artery disease (angina occurring most days or myocardial infarction in the last 3 months) (8/0.11)	8	0.11
Pregnancy *	8	0.16
A history of severe and/or blistering skin rash with any penicillin, or a formal diagnosis of SJS, DRESS or TENS	9	0
Patients undergoing immunosuppressive therapy can undergo DPT but have greater likelihood of false negative	7	0.42
Patients with clear history IgE-mediated allergic reaction, but negative skin tests, should have DPT	7	0.37

* no agreement on whether breastfeeding should be an exclusion criteria

Advice on alternatives for patients undergoing elective surgery, who cannot be tested, or decline testing.	Median	DI
'No' risk patients		
These patients should be given penicillin if they accept this (9/0)	9	0
It is safe to give a cephalosporin of any generation (9/0.04)	9	0.04
A non b-lactam should be advised (2/0.29)	2	0.29
'Low' risk patients		
It is safe to give a second generation cephalosporin	8	0.16
It is safe to advise the use of a third or later generation cephalosporin	7	0.31
'Medium' and 'high' risk patients		
In patients with medium or high risk histories, a non b-lactam should be advised	7	0.38

Patients presenting for urgent surgery	Median	DI
'No' risk patients		
It is appropriate to advise the use of a penicillin if required for surgery	9	0.13
A non b-lactam should be advised	1	0.13
'Low' risk patients		
A non b-lactam should be advised	3	0.51
'Medium' risk patients*		
'High' risk patients		
A non b-lactam should be advised	8	0.13

*no agreement reached for this group

Advice for patients with a clinical history which requires skin testing prior to consideration for DPT (Group 2 in) but who cannot be tested pre-operatively, for any reason.	Median	DI
If the index penicillin is known, is safe to advise the use of a cephalosporin with a different R1 and R2 side chain*	8	0.16
If the index penicillin is not known, is safe to advise the use of cephazolin	8	0.16
It is better to avoid all beta-lactams	3	0.40

*no agreement on the use of second or later generation cephalosporins, if index penicillin not known

<i>The following statements relate to specific examples of the history a patient might give, and the appropriate testing strategy for this</i>	Median	DI
For a patient with a rash which was non-itchy, non-blistering, and not severe, and occurred > 10 years ago, graded direct DPT is better than	7	0.47

avoiding penicillin		
For a patient whose reaction was >10 years ago, but who has had at least one course of penicillin since then without problems, the label should be removed without testing	8	0.49
For a patient whose reaction was >10 years ago, but who has taken at least one course of penicillin since then, should be offered DPT if the patient specifically requests testing	8	0.13

Mandatory requirements for the safe provision of a penicillin allergy testing service	Median	DI
Any program of screening and testing of patients should be set up and overseen by or with an allergist	8.5	0.13
The screening and testing of patients should be undertaken by a healthcare professional who has been trained to a level deemed appropriate by the allergist overseeing the programme	8	0.19
The healthcare professional undertaking the screening and testing of patients requires, as a minimum, the remote supervision of an allergist whom they can contact for advice	8	0.29
The healthcare professional undertaking the testing must be trained in basic life support	9	0
There must be immediate access to a crash team including an anaesthetist	9	0
Adrenaline of IM or IV use must be immediately available	9	0
Equipment for IV or IO access must be immediately available	8.5	0.13
Equipment for airway management including suction, oral/supraglottic/endotracheal airways must be immediately available	9	0.4
Provision of on-site critical care facilities must be available	9	0.19