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

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Special Article

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

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Abbreviated title: Management of surgical patients labelled 'penicillin allergic'

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Abstract:

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. Due to the scarcity of trained allergists in all healthcare systems, only a minority of surgical patients have the opportunity to undergo testing and de-labelling prior to surgery.

Testing pathways can be modified and shortened in selected patients and a variety of healthcare professionals can, with appropriate training and in collaboration with allergists, provide testing for selected patients.

In this paper we set out how patients might be assessed, appropriate testing strategies which may be employed and the minimum standards of safe conduct for these.

Introduction

The recommendations developed in this article concern the management of the surgical patient with a label of penicillin allergy, and aim 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 years; 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 ten-year 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 following review by the writing group. Additional articles were included on the basis of relevance and included some from more than 10 years ago, where these were judged to be of seminal importance.

A. Epidemiology of a Penicillin Allergy Label

Penicillin is the most common drug allergy listed in medical records, with a prevalence ranging from 6-15% 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 falling. Longitudinal studies from a large health plan in the U.S. found the rate of positive penicillin skin tests to have decreased from 15% in 1995, to 3% in 2007 [9]. In 2013, the same group reported that only 1.6% of penicillin allergy histories from 500 patients could be confirmed [10]. Work in France has demonstrated a higher rate of immediate (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 [11]. Recent large studies from other countries have confirmed low rates (5-6%) of confirmed penicillin allergy in both children and adults [12,13].

Nevertheless, penicillin remains a leading cause of drug-induced hypersensitivity and anaphylaxis. A recent U.S. study of a large electronic health record database of over 1.7 million patients determined that 1.1% reported drug-induced anaphylaxis, with the

most common culprit being penicillin [5], and cases collected by the French Allergy Vigilance Network between 2010-12 determined that penicillins (especially amoxicillin) were the most commonly identified cause of severe drug-induced anaphylaxis [6]. Amongst fatal drug-induced anaphylaxis, penicillin was the most commonly identified culprit drug in a recent U.S. study [7], 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 occurring causal agent [8]. As well as 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.

B. Evidence of harm from the label

Over the past 10 years the clinical and economic ramifications of the 'penicillin allergy' label have been well defined. These include infection sequelae and antimicrobial resistance, hospital readmission rates, length of hospital stay, use of critical care beds, and healthcare costs.

For the surgical patient, postoperative surgical site infections (SSI) 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 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 fourfold increase in SSI [16]. In a retrospective study of 18,830 elective primary arthroplasties, use of vancomycin as a sole agent was associated with more SSI 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 due to the penicillin allergy label, compared to those receiving cefazolin[18].

Given the use of beta-lactam alternative antibiotics in those labelled penicillin allergic, focus has turned to associated infection, particularly methicillin resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* (*C. difficile*) infection. In a large population-based cohort study from the United Kingdom of over 300,000 adults, those labelled with penicillin allergy were compared to matched controls [19]; 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 MSRA and 35% of the increased risk of *C. difficile*. In a large cohort U.S. inpatient study of over 50,000 patients, 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 enterococci 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 over 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 to controls; the majority of readmitted patients had major infections [20]. In a large prospective matched cohort study from a Dutch university medical centre of over 17,000 patients, of whom 5.6% were labelled penicillin allergic, the penicillin allergic group had a significantly higher risk of being re-hospitalized at 12 weeks (27% vs 21.9%), though there was no significant difference at four weeks between the groups [3].

C. 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].

1. Standard testing guidelines

182 The gold standard test with which to establish tolerance to penicillin is a graded drug
183 provocation test (DPT) using the index penicillin to which the patient reacted. Current
184 guidelines from Europe and North America recommend that patients should first be skin
185 tested using skin prick tests (SPT) and intradermal tests (IDT) [22-26]. In the context of a
186 patient who has had a clinical reaction, a positive skin test, with readings taken
187 immediately, can identify the presence of IgE-sensitisation. The skin test therefore
188 provides a way of risk stratifying patients for a DPT. Skin tests for penicillin have a
189 negative predictive value approaching 100% and patients who do not react to SPT or IDT
190 are therefore unlikely to have a severe immediate reaction on DPT [26, 27]. However, the
191 interpretation of a positive skin test is less well defined, since these patients are not
192 offered a DPT for obvious ethical reasons. The positive predictive value is generally
193 accepted to be less than 50% based on limited numbers of prospective studies, and
194 outcomes from accidental re-exposure [28-30]. It is important to note that delayed
195 readings are required for the diagnostic work-up of non-immediate type IV
196 hypersensitivity reactions, although the predictive value of these readings is not well
197 established and their utility may be lower [22]. Any subsequent DPT may also demonstrate
198 delayed reactions such as these.
199 The panel of reagents used for skin testing varies geographically. In particular, the
200 experience of using minor determinant mixtures (MDM) and benzylpenicilloyl poly-L-
201 lysine (PPL), is mixed, not least because for many years in the US these reagents were
202 not commercially available. Utility of PPL/MDM is best defined for immediate-type
203 hypersensitivity reactions to penicillin, where 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), as well as 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 [9, 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 life-long unnecessary avoidance of penicillin~~,~~ and yet are only rarely associated with positive skin or DPT testing [39].

Another testing modality which may be employed is the serum specific IgE assay. Although sensitivity and specificity of this test is low it is still 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 will vary according to multiple local factors. A study in the US 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 to $537 [40]. The skin

testing component of testing is typically the most expensive, requiring highly trained personnel as well as relatively expensive consumables.

2. 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 recent work has shown that 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 direct DPT . A U.S. study, 328 young military recruits with non-severe histories of penicillin allergy underwent direct amoxicillin DPT with only 1.5% having objective reactions, none of which were life-threatening anaphylaxis [42]. An Israeli study of 642 patients (2/3 were children and some had reactions not suggestive of true allergy) with delayed reactions (>1 hour after 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 amoxicillin DPT without skin testing, with 94% tolerating amoxicillin [12]. 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 DPT only 1 (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 [44]. 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 underwent placebo-controlled amoxicillin DPTs without skin testing in an allergy clinic found 2.6% with true allergic reactions and 10% reacting to placebo [45].

The primary advantage of this approach is that the lack of need for skin testing reduces time and cost. 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 [46].

3. Advice for de-labelled patients

Patients evaluated with skin tests, DPT or both and found not to be sensitized to penicillin should be advised that they have the same risk as the general population for developing new allergy to a penicillin in the future. This statement acknowledges that any individual may become sensitized to penicillin during their lifetime and that

negative testing is not a lifelong guarantee of tolerance. It must also be recognised, however, that DPT for a single penicillin does not entirely preclude allergy to all other penicillins because of side chain sensitivity which might be missed with 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 DPT. This risk appears to be lower than initially reported in the US however, with the results of recent studies suggesting that repeating skin tests following an oral DPT in order to check for re-sensitisation is unnecessary [47]. Patients who have been tested and de-labelled should instead be monitored clinically for evidence of resensitisation. Repeating the skin tests may be of use in patients with confirmed severe reaction, 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].

D. 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 among non-specialists (and patients) leading to incorrect labelling, and limited

knowledge of the services available for allergy testing [48, 49], although there is evidence that knowledge can be improved through training [50]. These aspects are beyond the scope of this article.

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

1. *Inpatient-based penicillin skin testing programmes*

Large numbers of hospitalized 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 improved use of antibiotics following penicillin skin tests. Of approximately 1,000 patients with self-reported penicillin allergy, same day penicillin skin testing and consultation reduced vancomycin use from 30% in historical controls to 16% in those judiciously evaluated [51]. In an intensive care unit setting a prospective study of 96 patients labelled as penicillin allergic were skin tested [52]; of the group receiving therapeutic antimicrobials, 82% were changed to a beta-lactam after the 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 as well as 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 years [53].

A recent systematic review described several studies including six in the intensive care setting [54]. 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 in-patient experience is from the U.S. and utilizes allergy-trained pharmacists to perform penicillin skin tests and amoxicillin challenge [55]. To date, 98% of over 700 penicillin allergic inpatients have been found to test negative (D. Khan, personal communication). Another large U.S. study of inpatient penicillin allergy skin testing (with 90% performed by a nurse) found a much higher rate (20%) of positive skin tests but utilized minor determinant skin tests with different criteria for a positive skin test [56]. Another study utilized telemedicine to reduce the need for on-site allergy specialists, with skin testing performed by physician assistants [57]. 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 minute training session for testers was inadequate [58]. 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 programs.

2. Clinical Algorithms to Guide Use of Beta-Lactams in Penicillin Allergy

An alternative approach to encourage 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 direct DPT using an algorithm suitable for use by non-specialists [46]. Use of guidelines such as these in an inpatient setting has demonstrated increased use of beta-lactams (primarily cephalosporins) and reduction in use of vancomycin, aztreonam, and fluoroquinolones [59, 60]. 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 increased use of penicillins or cephalosporins, although not penicillins alone [61]. Methodology for implementing this type of approach at a hospital level has been published [62]. 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 use of cephalosporins in penicillin allergic patients [63], a practice that may already be commonplace in some hospitals [64] and which when used alone, typically does not allow de-labelling of the penicillin allergy.

3. Pre-Operative Penicillin Allergy Testing

Patients with a history of penicillin allergy often receive vancomycin for surgery. In the UK the commonest alternative is now teicoplanin. As well as the risks of increased SSI, longer hospital stay and higher readmissions, there is also the risk of allergy to the

alternative antibiotic used [8]. In order to reduce use of alternatives in the preoperative setting, penicillin allergy tests can be performed prior to surgery. The surgical population represents a large pool of accessible patients with immediate need for good antibiotic stewardship. In the UK a recent study demonstrated that penicillin allergy testing can be incorporated into the pre-operative journey for the patient with subsequent improved use of SSI prophylaxis [65]. The largest experience with pre-operative testing comes from the Mayo Clinic in the U.S. where a preoperative evaluation clinic was established in 2001 [51]. 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 facilitate referral to a specialized clinic for penicillin allergy testing [66]. 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.

E. 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 [67-69] and there is no

apparent cross-reactivity between monobactams and penicillins [69], although there may be between ceftazidime and aztreonam, partly because they share an R1 side chain [70].

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 US Food and Drug Administration (FDA) 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 due to 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 [71]. This is at least one order of magnitude less frequent than anaphylaxis to penicillin which is approximately 0.005% and 0.002% with oral and parenteral administration respectively [72].

Variation in the degree of cross-reactivity between penicillin and cephalsporins is determined by structural differences among cephalosporins. All share a four membered beta lactam ring with penicillin which is adjacent to a five membered thiazolidine ring in penicillin, and 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 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 ceftezole. Cephazolin also offers superior gram positive antimicrobial activity compared to cephalosporins of later generations, and has been shown after testing not to cross-react with a number of other cephalosporins from all generations [73, 74]. Thus despite being a first generation cephalosporin it may be an option for a penicillin allergic patient, although it is worth noting that as the R1 and R2 side chains are not always the antigenic determinant, cross-reactivity may still exist [75].

Studies on cephalosporin allergy can be broadly divided into two groups; large observational studies and smaller 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. Since the vast majority of patients labelled penicillin allergic in medical charts and electronic medical records are not truly penicillin allergic, these studies will 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% [76-78].

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 [75], emphasizing 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 [79]. Thirty-nine percent had positive allergy tests to cephalosporins, 96% of these were to the aminocephalosporins and/or cefamandole. This study demonstrated that skin testing, though 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 a 2.9% cefuroxime sensitivity was seen in 69 patients with prior histories involving penicillin sensitivity only, despite dissimilar side chains [80]. 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 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% [78]. When confronted with the rare patient with

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 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, can be found in the referenced articles [63, 81].

F. Consensus recommendations for management of the surgical patient with a label of penicillin allergy.

Methods

These recommendations are based on the results of a Delphi consensus process, and were developed with reference to the AGREE 2 checklist [82]. 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 between 18 and 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 was defined as a DI of < 0.5. This approach is adapted from Fitch et al [83]. For a full list of all statements where consensus was reached, and some of the key areas where it was not reached, please see Supplementary Online Appendix 1.

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

Fig. 1. Flowchart for management of the surgical patient with a label of penicillin allergy

A. 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. However 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; e.g. 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 categorized as being at high risk. Between these however fall myriad intermediate reactions which are harder to categorize, including the very common history of 'no recollection of the event'.

Initial rounds of the consensus attempted to define risk groupings into no, low, medium and high, comparing to risk in the general population. However it proved difficult to reach consensus on what constituted 'low risk' and how this group should be approached. Ultimately, it is probably more useful and practical to instead define the appropriate approach to testing for an individual, based on the specific reaction reported. The algorithm in Fig. 1 defines the pathway which patients may take, depending on whether they are suitable for direct oral DPT, require skin testing prior to consideration for 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 below, it is assumed that the patient has no cognitive impairment that might impact recollection of the index event.

1. Group 1 - Direct Oral DPT

The following patients are suitable for direct oral DPT, if lack of time or local expertise precludes prior skin testing (see section D 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.

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

2. Group 2 - Skin testing +/- DPT

The following patients require skin testing prior to consideration for DPT:

(See section D below for details on who is able to perform the skin testing)

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

3. 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 desensitatisation, an area which is beyond the scope of these guidelines:

- 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, loss of consciousness. These patients may be considered for penicillin desensitization if there is an absolute indication for penicillin; this would not result in de-labelling of the patient.

Patients with a history of severe and/or blistering rash appearing at any time during the course of penicillin or in the weeks afterwards, or a formal diagnosis of DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome , SJS (Stevens-Johnson syndrome), or toxic epidermal necrolysis 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 above, the following were agreed as exclusion criteria:

- Severe or unstable ischaemic heart disease
- Pregnancy (breast feeding was not considered an exclusion criterion)

We were unable to reach consensus on whether 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 false negative DPT testing because of the immunosuppressive effects of treatment.

One additional exclusion criteria, 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 safe practice to avoid DPT in such patients unless the risk-benefit analysis strongly favours proceeding.

B. Ideal timing of testing

There was clear consensus within the group that testing of perioperative patients is ideally performed prior to the day of surgery, which may help mitigate both surgical flow issues and medico-legal concerns among anaesthetists. Recent work in the UK demonstrates that when anaesthetists are confronted with a label of penicillin allergy which 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 'up-stream' 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:

1. *Patients who require penicillin for surgery:*

1a. If surgery is elective it may be appropriate to offer testing on the day, providing this does not delay surgery. This is most likely to apply to patients who are suitable for direct oral DPT due to logistical problems around provision of skin testing.

1b. If surgery is urgent or emergent, surgery should not be delayed in order to test the patient and alternatives should be used.

2. Patients who do not require penicillin for surgery:

2a. Testing on the day of surgery is not recommended. However, if the patient wishes to be tested, this could be performed post-operatively as an outpatient.

C. Choice of reagents for skin test panel and DPT

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

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

1. If the index penicillin is known testing should be to this drug
2. 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 intravenous (IV) DPT was more appropriate in patients due to receive IV penicillin during surgery and therefore this cannot be recommended.

D. Definition of the minimum standards required for penicillin allergy testing

In this section we explored how testing should proceed in practical terms. There was 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 pre-operative testing could be performed by a variety of appropriately trained healthcare professionals and that the allergist need not be physically present for all testing. Indeed 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 direct oral DPT.

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

- Basic life support training for the healthcare professional performing testing
- Immediate access to a resuscitation team, including an anaesthetist
- Access to on-site critical care facilities
- Equipment for intravenous and intra-osseous access
- Immediate access to epinephrine (for intra muscular or intravenous use)
- Immediate access to a defibrillator
- Equipment for airway management including oxygen, suction, oral/supraglottic/endotracheal airways

E. Use of prolonged DPT testing

There are geographical variations in the use of prolonged DPT following oral challenge. Broadly speaking, patients in the US tend not to undergo prolonged DPT, whilst practice in Europe is mixed [84, 85]. There are also variations in the length of 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 however:

1. 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

2. If it is not known how many days it took for the symptoms to appear in the index reaction, prolonged DPT of 3-5 days is generally sufficient
3. Patients suitable for de-labelling without any formal testing, but who choose to undergo DPT (see definitions above) do not require prolonged challenge.

F. Advise 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 Fig. 1. These recommendations are based on consensus within the group, and the evidence base described in earlier sections. The key points are as follows:

1. 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 DPT if negative.
2. 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 following discussion among the group when the first draft of the manuscript was disseminated. All members of the writing group had the opportunity to comment on this section of the guideline, which was highlighted in email correspondence for ease of review.

- Patients from Group 1 (Direct oral DPT): administer penicillin (or if patient declines penicillin, a cephalosporin of any generation)
- Patients from Group 2 (skin test +/- DPT): If index penicillin known choose cephalosporin with different R1 and R2 side chains. If not known consider using cephazolin if available, after discussion with local allergist. Otherwise, avoid all beta-lactams.
- Patients from Group 3 (Specialist evaluation): avoid all beta-lactams

G. Dissemination of results following 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 employed in some areas [86]. 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 which is standardized across geographical regions and becomes embedded in local practice might help prevent re-labelling.

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 the elements of standard allergy testing, we have included strategies which 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.

Disclaimer

The guidelines and recommendations included in this article 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 over-ride 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.

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