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Penicillin Allergy De-Labelling Ahead of Elective Surgery – Is it Feasible and What are the Barriers?

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Abstract

Background:

Around 10-15% of the inpatient population carry unsubstantiated 'penicillin allergy' labels, the majority incorrect when tested. These label are associated with harm, from use of broad-spectrum non-penicillin antibiotics. Current testing guidelines incorporate both skin and challenge tests; this is prohibitively expensive and time-consuming to deliver on a large scale. We aimed to establish feasibility of a rapid access de-labelling pathway for surgical patients, using direct oral challenge.

Methods

'Penicillin allergic' patients, recruited from surgical pre-assessment clinic, were risk-stratified using a screening questionnaire. Patients at low risk of true, IgE-mediated allergy were offered direct oral challenge, using incremental amoxicillin to a total dose 500mg. A 3-day course was completed at home. De-labelled patients were followed up to determine antibiotic use in surgery, and attitudes towards de-labelling were explored.

Results

Of 219 patients screened, 74 were eligible for inclusion and offered testing. We subsequently tested 56 patients; 55 were de-labelled. None had a serious reaction to the supervised challenge, or thereafter. On follow-up, 17/19 received appropriate antimicrobial prophylaxis during surgery. Only 3/33 de-labelled patients would have been happy for the label to be removed without prior specialist testing.

Conclusion

Rapid access de-labelling, using direct oral challenge in appropriately risk-stratified patients, can be incorporated into the existing surgical care pathway. This provides immediate, and potential long-term benefit for patients. Interest in testing is high among patients, and clinicians appear to follow clinic recommendations. Patients are unlikely to accept removal of their allergy label on the basis of history alone.

Key words: penicillin; allergy; de-labelling; peri-operative.

An estimated 5-10% of people carry a label of penicillin allergy, [1, 2] with a higher incidence of around 15% observed in the inpatient population [2, 3]. At least 92-95% of unsubstantiated penicillin allergy labels are incorrect when tested [4, 5]with side effects and other non-allergic phenomena misattributed to allergy by patients, clinicians or both. It is now widely recognised that the 'penicillin allergic' label is associated with increased morbidity, greater healthcare costs, increased rates of methicillin resistant *Staphylococcus aureas* (MRSA), *Clostridium difficile* and vancomycin resistant enteroccocus (VRE) infection, longer hospital stays, increased readmission rates, and more critical care admissions [2, 6-8]. This is most likely through the avoidance of 'best first-line' antimicrobial therapy with penicillins, and use of broad-spectrum alternatives. In surgical patients, there is evidence of increased risk of wound infections when penicillins are replaced with non-beta lactam alternatives [9, 10] and of peri-operative anaphylaxis from the alternatives used [11, 12]

Testing patients for penicillin allergy, according to current guidelines, is a relatively time-consuming and expensive process.[13] As a result, it is generally only accessible to a minority of patients. In the UK, this is typically those in whom penicillin is the only therapeutic option or those likely to require multiple courses of antibiotics. [14]

In this study, we tested the feasibility of incorporating a rapid access, and abbreviated, de-labelling programme into the existing surgical care pathway. This involved a direct oral challenge, in patients identified as being at low risk of a true penicillin allergy. We assessed the acceptability of this intervention among patients and clinicians, and the impact on prescribing during their surgery.

Methods

The study was approved by the Leeds East Research Ethics Committee (ref: 17/YH/0096), and registered with ClinicalTrials.gov (protocol ID: AN17/92982). It took place in a single centre, tertiary care setting in the UK, between May 2017 and June 2018.

Patients were recruited by the surgical pre-assessment clinic nurses, who identified 'penicillin allergic' patients and administered a screening questionnaire. The questionnaire risk stratified them for likelihood of IgE-mediated penicillin allergy, (see appendix 1), and also identified suitability for inclusion into the study. See tables 1 and 2 for details of risk stratification and eligibility criteria. Only a small proportion of pre-assessment nurses were trained to undertake this screening, so recruitment was undertaken on an 'ad-hoc' basis, dependant on their availability

Eligible patients attended a dedicated de-labelling clinic, where a direct oral challenge was performed using oral amoxicillin, after gaining written consent. The clinic had the facility to test for alternatives, should the index penicillin be different. An incremental dosing regimen of 10%, 50%, 100% full dose (500mg) was used, with 20 minute intervals between doses. This is the protocol used for low risk patients who undergo challenge testing in the Immunology department in Leeds Teaching Hospitals. Patients were observed for a further one hour after the full dose, before being allowed home. Baseline blood pressure, heart rate and oxygen saturations were measured, but only repeated if the patient became unwell during testing. Full resuscitation equipment and personnel were immediately available.

Challenge negative patients were given a 3-day course of antibiotic to complete at home, with an information sheet containing advice and contact details in the event of problems. The team contacted patients by telephone at

the end of the course, and checked for delayed symptoms. This was generally at a minimum of 5-7 days after the patient had left hospital. The results of testing were confirmed in writing to the patient, GP and surgeon, and the hospital electronic record updated accordingly. Feedback was sought during the phone consultation, on several aspects of the testing process.

Where appropriate, notes were reviewed to determine which antibiotics had been administered for surgical prophylaxis. Three months after testing, the GP was contacted by telephone to check the patient's allergy status on their primary care record.

Midway through the study, the eligibility criteria were amended in response to high patient demand for testing (substantial amendment 31/10/2017). From this point, all patients with low risk symptoms were offered testing, including those with recent reactions (if symptoms were clearly remembered by the patient), those not requiring penicillin for surgery, and those who could only be tested post-operatively.

Results

During the study period, a total of 219 patients with the 'penicillin allergic' label were screened. Of these, 74 patients were eligible for testing, and 145 ineligible. See Fig. 1 for outcome of screening for all patients.

A total of 56 patients underwent a direct oral challenge. No patient suffered any immediate adverse reactions, and none suffered any serious delayed reactions subsequent to leaving hospital. One patient developed urticaria in her hands after the second dose and stopped taking the amoxicillin. On questioning, it was discovered that her index reaction had been of widespread urticaria, but she had chosen not to disclose this to the study team previously as she was keen to be tested. Four patients experienced mild non-allergic symptoms during the prolonged antibiotic course. Two were considered to be unrelated to the amoxicillin (sore throat and a cough in one patient, and a worsening of existing arthralgia in the other); another two experienced mild nausea. All four completed the course of antibiotic.

Among patients who did not attend clinic (n=18), five were unable to attend because of ongoing illness and treatment, or a change of surgical date. The remainder simply did not turn up for their appointments. This was despite the study team attempting to contact all patients a few days ahead of the appointments to confirm attendance.

A total of 119 patients had 'low risk' symptoms, described in Table 3. Not all of these were eligible for testing, however, as they did not meet other eligibility criteria. In around half, the reason for ineligibility was refusal to undergo testing; the remainder were ineligible because penicillin was not required, or the operation was too soon to have time to be tested. These eligibility criteria were removed midway through the study in response to high patient demand. One patient was ineligible due to high risk co-morbidities.

All screened patients were asked if they would like to undergo testing. Overall, 74% (163/219) stated they would like to be tested. Within the 'low risk' population 82% (98/119) requested testing; in the 'high risk' group 66% (59/90) requested it. In patients who declined testing (56), the reasons for this were explored (Fig. 2). There were 10 patients for whom no information was available except whether they would like to be tested; 6 of these wished to be tested.

Among patients who were successfully de-labelled, feedback was sought on levels of satisfaction with the process. Although a majority stated they would have preferred testing to be performed on the same day as pre-assessment (70%, 30/47), it was broadly considered to be a 'smooth process' (85%, 40/47). Low levels of anxiety about the testing were noted, with 81% (35/43) stating they had little or no anxiety on the day. Patients were asked if they would have been happy for their label to be removed without any testing at all, on the basis that their index reaction did not indicate allergy. The majority, 70% (30/43) would not have been happy to have their allergy label removed in this way. Comments included: "The security of supervision takes away the anxiety"; "In case I had a bad reaction"; "I would worry about having a bad reaction without support, in case help was needed", and "You can't undo 30 years of being allergic to penicillin with a quick conversation".

In the follow-up of patients subsequently undergoing surgery, 17/19 were given appropriate penicillin-based surgical prophylaxis uneventfully; penicillin was avoided in two patients despite negative testing. In patients successfully de-labelled, the GP confirmed that the correct allergy status was present on the primary care record in 47/55 patients. The reason for re-labelling in our current cohort is only known in one patient; this patient was discovered to have relabelled himself, when he was incidentally anaesthetised

for an emergency operation by a member of the study team. This patient's recollection of the testing was that he had been told he had "suffered a severe allergic reaction and must continue to avoid penicillin at all costs". Despite reassurance, he was adamant he would not wish to receive penicillin for surgery, and instead received teicoplanin.

Discussion

In this study, a rapid access and abbreviated de-labelling test was integrated into the existing pre-operative care pathway. Patients were risk stratified on the basis of history alone, and those at low-risk of IgE-mediated hypersensitivity, in whom skin testing was unlikely to offer additional diagnostic value, underwent a direct oral challenge test. Recall of exact timing of the index reaction by patients is accepted to be poor, especially when from many years ago.[15] Instead, we focused on the symptoms of the reaction, and their severity. In particular, we asked about requirement for hospitalisation and treatment of the index event, as a marker of severity. None of the patients tested suffered serious adverse events during testing. This is consistent with the findings of similar studies, which demonstrate the safety of this approach when patients are appropriately risk stratified [16-18].

The incidence of unsubstantiated penicillin allergy labels in hospital inpatients is around 10-15%. As well as potential harm for individuals, there exists the wider problem of multi-resistant bacterial strains that are promoted by the use of broad-spectrum antibiotics, and an ever-decreasing pool of antimicrobial options to treat these. Improving stewardship through more rational antibiotic use, is a key strategy for healthcare systems[19]. Reducing the number of people inappropriately denied penicillin contributes to this, and novel strategies should be developed to allow wider access to de-labelling and promote effective use of penicillins where possible. [20]

Current guidelines advise that patients are referred to specialist services for testing. The gold standard test with which to establish tolerance to penicillin is a challenge, using the index penicillin to which the patient reacted. According to current UK and European guidelines, patients should first be skin

tested, using prick or intradermal tests, or both [1, 21, 22]. This identifies patients who are IgE-sensitised, and provides risk stratification for progression to the next step in the diagnostic pathway, a challenge test.[1, 21] Skin tests have a negative predictive value (NPV) approaching 100%, and patients who do not react to prick or intradermal tests are therefore unlikely to have a severe reaction on challenge. [5, 23] However the interpretation of positive skin tests is less clear; these patients are generally not offered a challenge test and so the positive predictive value (PPV) is hard to determine. The PPV is generally accepted to be less than 50% based on a limited numbers of prospective studies, and on outcomes from accidental re-exposure [24-26].

There are significant limitations to skin testing. Many studies have commented on reduced sensitivity over time,[3, 27, 28] and low sensitivity and specificity in patients with non-severe, non-immediate, and vague reactions. [29-32] Reactions in childhood, typically delayed onset and unspecified rashes which can result in life long allergy labels, are only rarely associated with positive skin or challenge testing.[33]

Increasingly, the evidence demonstrates that patients can be risk stratified for a challenge test on the basis of history alone. Where symptoms are not severe, not suggestive of an IgE-mediated reaction, are vague, or historic, the utility of skin testing is low and a direct oral challenge may be safe and appropriate. This approach is already used routinely for children in the UK, [34, 35] and several studies have demonstrated safety and efficacy in adults. [16-18].

A number of antimicrobial stewardship programmes have been successful at reducing the burden of unsubstantiated penicillin allergy labels, and have demonstrated benefits from doing so.[10, 36-40] Some programmes have been used specifically in the pre-operative setting, with subsequent

reduced use of intra-operative vancomycin and other beta-lactam alternatives. [41, 42] The majority of these programmes administer skin tests initially, and only proceed to challenge testing if these are negative. Whilst this is an accepted and valid strategy, the skin-testing component has implications for the overall cost and convenience of the pathway. Skin testing kits are relatively expensive and require trained personnel for their use and interpretation. There is also the potential for over-diagnosis due to false positive skin tests, and continued unnecessary avoidance of penicillin in such patients. The use of direct oral challenge in low risk patients is recent in Europe, but has been successfully employed in several centres in the US; this gap in practice has recently been commented[43].

Although not all labels can be removed using this pathway, we estimate from this study that at least one third of 'penicillin allergic' patients would be suitable for direct oral challenge. Patients with labels more suggestive of IgE-mediated allergy continue to require skin testing as part of their diagnostic work-up, or should be advised to continue avoiding penicillins. Patients with histories of severe, widespread skin reactions, including delayed and blistering eruptions such as DRESS and TENS, are also high risk and must avoid penicillin.

The barriers to implementing this on a large scale are two-fold; human factors leading to anxiety around allergy labels, and financial implications. We were able to explore some of the human factors in this study.

The first perceived barrier was a lack of interest in testing. However, patients appeared keen to be tested, irrespective of the severity of their presenting symptoms. The change to our eligibility criteria was indeed made in direct response to demand among patients with low risk labels, but who were ineligible for other reasons - most commonly lack of time, or lack of immediate need for penicillin.

A second potential barrier was lack of acceptance among clinicians (primarily anaesthetists) that the abbreviated pathway provided conclusive evidence of tolerance to penicillin. However, clinic advice was generally accepted by anaesthetists on the day of surgery. In the two patients denied penicillin peri-operatively, it is not known whether the anaesthetist actively disregarded the test result or was simply unaware of it.

Lastly, it has been demonstrated previously that a high proportion of patients re-label themselves following negative testing for penicillin allergy, or are re-labelled by healthcare providers.[44] However, the rate of 're-labelling' in our population appeared to be very low. Only the longer term follow-up of this cohort will determine whether this is indeed true. It is likely that behavioural change interventions will be required in addition to the de-labelling itself, in order to address this issue. There is little literature in this field to date, although one centre in the US has used pharmacist counselling and wallet-cards with confirmation of test results, to good effect.[45]

The financial barrier to widespread testing is likely to be significant. Although long term cost benefits are likely to be realised through de-labelling patients, there is an 'upfront' cost to perform the testing. Omitting skin tests helps with this, but even abbreviated pathways using direct oral challenge have a cost attached, which is not immediately offset by the avoidance of a single intra-operative dose of a more expensive alternative antibiotic.

Finally, this study addressed the question of acceptability of de-labelling without formal testing; i.e. on the basis of history alone. In those with histories clearly consistent with side effects (eg nausea, or thrush), those who have received penicillin uneventfully since their index reaction, and those with only a family history of allergy, there is no requirement for allergy testing. In the authors' institution, guidelines recommend that penicillin can be administered

without prior testing in such patients, although these are rarely followed. Our results indicate that patients may be reluctant to receive penicillin without formal testing under supervision.

The limitation of this study is primarily its small size, and further work is needed to corroborate our findings. In addition, we only have follow up data from three months post-testing. It would be informative to identify the rate of re-labelling several years after testing, and explore the reasons for this. Nevertheless, our results are encouraging in terms of potential uptake in future studies. Based on our work, uptake could be maximised by offering 'opportunistic' testing of all patients attending for surgical pre-assessment irrespective of the need for penicillin during surgery, offering testing as part of the initial pre-assessment visit rather than a separate clinic appointment, and reducing the time required for testing. The last of these could be achieved by moving from an incremental, to single dose challenge, using 250 or 500mg amoxicillin. The utility of this has been confirmed in a study of 500 sequential patients in the US,[4] and a cohort of Marine recruits also in the US, [18] where low risk patients received a single dose oral challenge with none having a severe life threatening reaction. Using this protocol, the time for testing would be reduced from one hour 45, to around one hour, increasing both the likelihood of uptake among patients, and the turnover in clinic. In the last few months of this study, the protocol was altered to allow single dose challenge (substantial amendment 5/1/18), although none received this before the end of the study period. A single dose approach will be taken in future de-labelling programs at the host site.

It is increasingly clear that the burden of 'en masse' de-labelling cannot be shouldered by specialist services in isolation, since these are relatively small groups with already scarce resources. Our protocol is one example of how

testing might be integrated into an existing patient pathway, and delivered by non-specialists working in close collaboration with allergy/immunology specialists.

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Declaration of interests:

The authors declare no competing interests

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Authors contributions

LS, SS, PH, JS designed the study the and wrote the paper. LS, LG, VK, JT recruited the patients and conducted the challenge testing.

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Table 1: Definition of 'high risk' and 'low risk' symptoms.

'LOW RISK' SYMPTOMS	**'HIGH RISK' SYMPTOMS**
Nausea, vomiting, diarrhoea	Anaphylaxis
Non-itchy rash	Angioedema
Thrush	Swelling of face/body
Not admitted to hospital	Severe blistering skin rash
'Don't know/can't remember	Wheeze, shortness of breath
	Collapse or dizziness
	Itchy rash
	Symptoms required hospital admission and treatment

Table 2 – Eligibility criteria

ELIGIBLE	INELIGIBLE
Low risk symptoms	High risk symptoms
Reaction occurred > 15 years ago*	Reaction < 15 years ago
Sufficient time for testing pre-operatively*	No time for testing
Wants to be tested	Declines testing
Requires penicillin for surgery*	Doesn't require penicillin for surgery
Aged >18 years	Pregnant, breastfeeding
	Unstable asthma (oral steroids required in the last 6 months)

*These three criteria were amended following high demand for testing amongst otherwise eligible patients.

Table 3: Symptoms of Index Reaction in 119 Low Risk Group

SYMPTOM	GI* UPSET	RED RASH FLUSHING	RASH (UNSPECIFIED)	DON'T KNOW CAN'T REMEMBER	THRUSH	MISCELLANEOUS (EG 'CONVULSIONS')
N	32	41	25	41	1	2

* Gastrointestinal; GI. NB Total number of symptoms exceeds 119 as some patients had more than 1 symptom

Fig 1. Outcomes of All Screened Patients

Fig 2. Reasons why patients with a label of 'penicillin allergy' declined testing

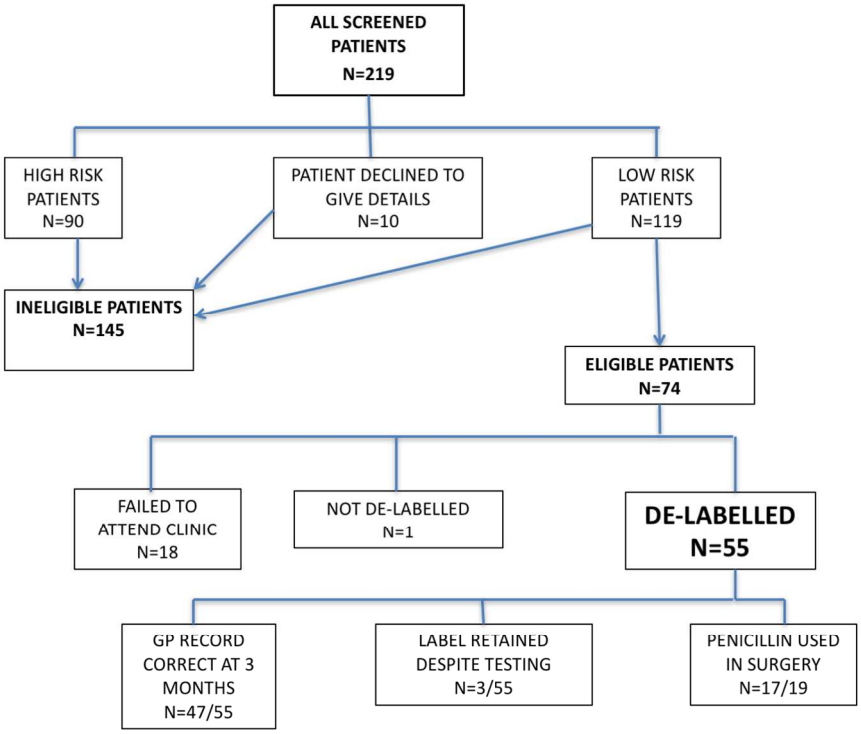

Figure1. Outcomes of All Screened Patients

549x412mm (72 x 72 DPI)

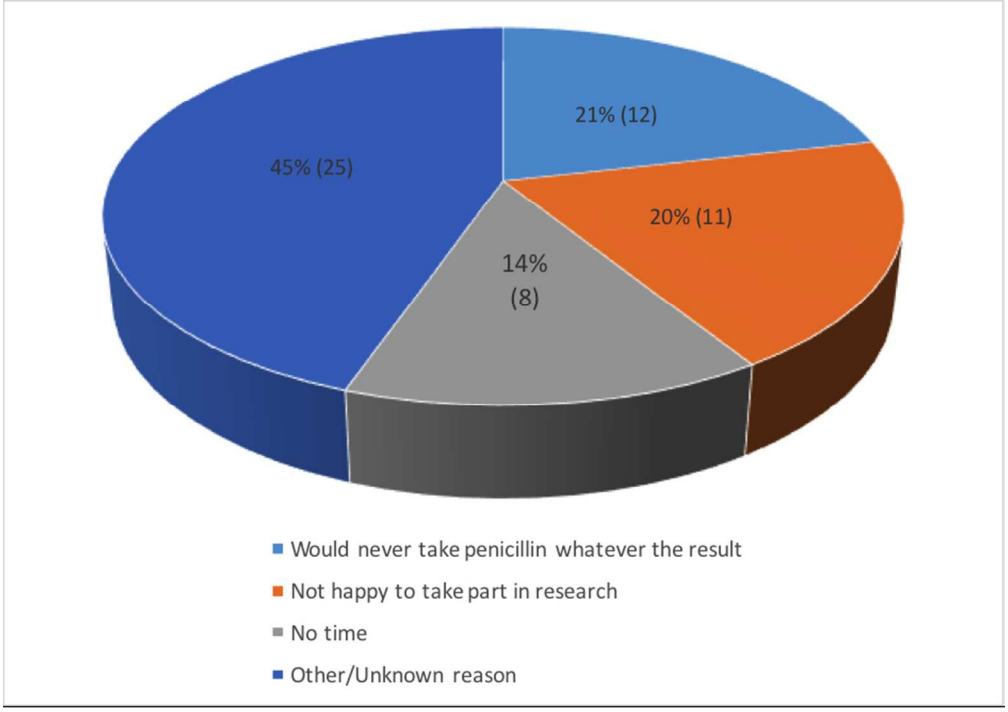

Figure 2.Reasons why patients with a label of 'penicillin allergy' declined testing