Title:

An algorithm for safe de-labelling of antibiotic allergy in adult hospital in-patients

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Key findings

- Ninety of 112 (80%) patients with a reported penicillin allergy were safely de-labelled
- No concerning allergic reactions occurred
- Clinicians and patients gave positive feedback about the process and outcomes

Tackling inappropriate penicillin allergy labelling is important because a “penicillin allergy” label potentially leads to the use of sub-optimal alternative antibiotics (e.g. vancomycin instead of flucloxacillin) and is associated with poorer outcomes including increased risk of *Clostridioides (C) difficile*, antimicrobial resistant infections, longer hospital stay and other adverse events\(^1,2\). It is therefore beneficial to assess whether patients have experienced a true allergic reaction and to consider removing their allergy label. Increasing evidence supports removal of penicillin allergy status by non-specialists using an oral challenge test. The Scottish Antimicrobial Prescribing Group (SAPG) therefore convened a multi-professional steering group including lay representatives to scope, develop and test a process for penicillin allergy de-labelling (PADL) across several hospitals. The scoping work involved audits (supplementary material) to confirm the prevalence and nature of reported penicillin allergy in the Scottish in-patient population and a systematic review of the safety and efficacy of oral challenge\(^3\). Risk assessment development involved development of a risk algorithm (Figure 1) using an iterative process along with supporting information for clinical teams and patients (Additional Figure 1 supplementary material). Pilot of PADL process involved in-patients in medical wards (Infectious Diseases, Respiratory, Medical Admissions) or attending pre-operative assessment clinics. Patients who were immunocompromised were not included. Suitable patients were identified using the algorithm, and provided written consent for oral challenge after reading an information leaflet and discussing with the clinical team. These teams included training grade medical staff and the majority of the PADL oral challenges were supervised by infectious disease teams (consultants, registrars and nurses). Clinicians involved in the pilot and patients who participated were given the opportunity to provide feedback on their experience of the process.

**Figure 1 Risk algorithm to identify suitable patients**
A total of 112 adults (61% female) with a mean age of 61 years (SD 18) were assessed for eligibility to receive direct oral penicillin challenge. Details of allergy history and outcome of challenge are shown in Supplementary Table 1 and Additional Figure 2 (supplementary material).
Based on patient history 11 (9.8%) patients were deemed to possibly/probably have Type 1 allergy and were excluded. A further nine patients were excluded (4 due to being clinically unstable or acutely unwell as measured by elevated National Early Warning Score (NEWS), 3 did not consent, and for two no reason was documented) and 92 (82.1%) patients consented to direct oral challenge. The test involved administration of a single oral dose of amoxicillin 500mg or flucloxacillin 500mg followed by close observation for 1 hour. Of those who received a direct oral challenge 90 (97.8%) were deemed negative and, considering all patients assessed as suitable for oral challenge, 80.4% were judged to be negative. There was one mild positive reaction (erythematous rash occurring more than one hour after administration of the challenge dose, and not considered to be an allergic reaction) but no episodes of anaphylaxis. Outcome from challenge was not available for one patient.

Some training grade medical staff were involved in the de-labelling process as this was the proposed model for wider implementation after the pilot was evaluated. Eleven clinicians, at various grades, who were not Steering group members, provided feedback and all toolkit documents received a score of ≥3 on a Likert scale of 1 to 5 with 10/11 clinicians rating them as 4 or 5. The greatest barrier reported was time within the working day. Other issues identified were knowledge and skills within the clinical team, initial anxiety of nurses involved and space within a busy clinic.

Sixteen patients who completed the direct oral challenge provided feedback. All rated the patient information leaflet as excellent (Likert scale score 5) with no suggestions for improvement. Four (25%) respondents indicated that they were anxious as they feared having a reaction. However, during the test most patients experienced subjective self-reported very low or low levels of anxiety.

An erroneous penicillin allergy label is associated with sub-optimal patient outcomes, therefore a safe and reliable PADL process is a key antimicrobial stewardship goal. As well as direct patient/clinical benefits, potential savings in drug costs and bed days associated with PADL via oral challenge have been reported.4

Through a survey across 9 of the 14 health boards in Scotland we estimated reported penicillin allergy prevalence to be 10% in hospitalised adults which correlates with literature reports in the general population. Importantly, the majority of those who reported an allergy either could not recall the nature of the allergy or experienced gastrointestinal symptoms. Timing of allergy in relation to the suspected antibiotic was also infrequently recalled, and the penicillin allergy label had been present for at least 10 years or was unknown in three quarters of patients. We
estimated that 84% of patients with reported penicillin allergy had a low risk of either a Type IV or an immediate Type I hypersensitivity reaction to penicillin and would therefore be suitable for a supervised oral penicillin challenge. Further evaluation of allergy in the remaining patients would constitute higher risk and require specialist allergy/immunology input. Penicillin allergy prevalence was higher (17.4%) in an audit in Day Surgery in one large hospital, however this is consistent with other studies of hospital patients.

The pilot of the toolkit was led by steering group members within their own clinical teams and this approach worked well with different models of deployment. Whilst it was a weakness of the pilot that a limited number of training grade medical staff were involved, the majority of the PADL oral challenges were performed by non-allergy/immunology specialists within acute hospitals. The very low rate of non-severe reactions (1%) following challenge is encouraging and will support and encourage other clinical teams to utilise the toolkit. In the Scottish hospital setting, clinical pharmacy-led PADL oral challenge\(^5\) was not feasible, however the key role for pharmacists in identifying, screening and referring patients is recognised. Similarly, nursing staff can identify and highlight patients for PADL and in some centres were central to the organisational and monitoring aspects of the pilot. Positive feedback from clinicians and patients involved in the pilot provided reassurance that the process is acceptable to both parties and will support spread to other hospitals and patient groups. The key limitation of our study is the relatively small numbers of participants, given how common mislabelling of drug allergy is, and further work is needed to confirm the safety of this approach when used at scale.

Communication of test results to participants' GPs and written information for patients were key components of the PADL process. Standard GP letters were developed and will support de-labelling across records held by other community healthcare professionals e.g. dentists, community pharmacists. Changing allergy status and maintaining the changes within electronic records systems will be an ongoing challenge and follow up of both hospital and community records is required to confirm that de-labelling has been maintained. Behaviour change is crucial to all aspects of antimicrobial stewardship including effective PADL. Limited experience/knowledge of referral criteria for penicillin allergy testing, lack of knowledge of the benefits of testing and lack of motivation to get tested amongst patients (though not in our cohort) have been identified as key behavioural barriers.\(^6\) Even after the formal removal of a penicillin allergy label, ongoing concerns regarding the relative safety of penicillin may persist\(^6\), emphasising the importance of a comprehensive well communicated and reinforced de-labelling process to address behavioural barriers. Fewer than half of UK anaesthetists surveyed would be happy to prescribe or give a penicillin after de-labelling\(^7\).
This study suggests there is a population of hospitalised patients in Scotland with a reported penicillin allergy who are suitable for our PADL process delivered via appropriately trained clinical teams. Several larger studies have shown similar success with direct de-labelling approaches based on allergy history alone\(^8\,^9\) and/or oral challenge tests\(^9\,^10\). Further work is needed to provide a standardised approach to training and to map out the roles of various staff in the process to provide an efficient process utilising the skills of medical, nursing and pharmacy staff while ensuring professional liability is considered. It is also important to follow up patients who have been de-labelled to check whether label removal is maintained.

In conclusion, a risk-based process to remove penicillin allergy labels from patients with unverified allergic reactions tested across several hospitals in a variety of clinical areas has been shown to be safe and feasible for use by non-allergy specialists. Effective PADL through oral challenge improves future antibiotic treatment options, minimises antibiotic related harm and potentially reduces healthcare associated costs.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**AUTHOR CONTRIBUTIONS**

RAS and NR conceived and designed the study. JS, LC, NR, CS, MS, ZD, RS, EK and RAS acquired, analysed, and interpreted the data. JS, LC and RAS drafted the manuscript. NR, CS, MS, ZD, RS, EK and JM critically revised the manuscript for important intellectual content. LC performed the statistical analysis.
DATA AVAILABILITY STATEMENT

Anonymised participant data was collated and stored by the study team in Healthcare Improvement Scotland for the purposes of the study only and is not available for other research.

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