

ORIGINAL RESEARCH

De-labelling self-reported penicillin allergy within the emergency department through the use of skin tests and oral drug provocation testing

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Abstract

Objective: Self-reported penicillin allergy is common among patients attending the ED, but is a poor predictor of true immunoglobulin E-mediated hypersensitivity to penicillin. We hypothesise that with a combination of skin testing and drug provocation testing, selected patients can be safely de-labelled of their allergy.

Methods: This prospective study enrolled a sample of patients presenting to an urban academic ED between 2011 and 2016 with a self-reported allergy to penicillin. Standardised skin prick and intradermal testing with amoxicillin and both major and minor determinants of penicillin was performed in the department. If negative, testing was followed by a graded oral challenge of amoxicillin over 9 days. The primary end point was the allergy status of participants at the end of the study.

Results: A total of 100 patients (mean age 42; standard deviation 14 years; 54% women) completed the testing. Of these, 81% (95% confidence interval 71.9–88.2) showed no hypersensitivity to

penicillin and were labelled non-allergic. The majority (16/19) of allergies were confirmed by skin testing, with three suspected allergies detected by the oral challenge. Women were more likely than men to have a true penicillin allergy, with odds ratio of 4.0 (95% confidence interval 1.23–13.2). There were no serious adverse events.

Conclusion: Selected patients in the ED who self-report an allergy to penicillin can be safely tested there for penicillin allergy, using skin tests and oral drug provocation testing. This testing allows a significant de-labelling of penicillin allergy, with the majority of these patients able to tolerate penicillin without incident.

Key words: allergy, emergency medicine, hypersensitivity, penicillin, skin test.

Introduction

Penicillin is widely known to be the first discovered antibiotic.¹ Despite the continuing spread of antibiotic resistance in general,² penicillin and its derivatives remain recommended as efficacious first-line medications in

Key findings

- Selected patients reporting penicillin allergy can be safely tested in the ED for the presence of true hypersensitivity.
- The majority of patients tested can have their label of “penicillin allergy” removed.

a wide range of infections requiring emergency treatment.³

A significant percentage of patients presenting to the ED report an allergy to penicillins, with prevalence in the range of 8–12%,^{4,5} corresponding with similar levels of self-reporting in general practice and outpatient clinics.^{6,7}

Allergic reactions to penicillin of immediate concern are generally immunoglobulin E (IgE) mediated. Symptoms can include pruritus, urticaria, angioedema and bronchoconstriction.⁸ Anaphylaxis refers to a systemic hypersensitivity reaction with potentially life-threatening severity, typically through IgE mechanisms.⁹

To avoid the possibility of serious adverse effects including anaphylaxis, patients self-reporting an allergy to penicillin are usually prescribed alternative antibiotics, often with a broader spectrum of antimicrobial action, additional potential complications of antibiotic use¹⁰ and at greater expense.¹¹ This prescribing of second-line therapies in lieu of penicillin therefore confers risk of harm to the patient, increased cost to the healthcare

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system and a selection pressure favouring multidrug-resistant organisms.

Self-reporting of penicillin allergy is notoriously unreliable, with up to half of patients reporting vague or even unlikely histories of allergy.¹² Testing of patients who self-report reveals that a majority have no demonstrable allergy. A 2001 meta-analysis of 9528 inpatients and outpatients found a self-reported history of penicillin allergy had a positive predictive value of only 14% (95% confidence interval [CI] 12–18%) when allergy was subsequently assessed by skin testing,¹³ considered a reliable method of assessing the presence of an immune-mediated allergy.

Penicillin skin testing has been in regular use by immunologists since the early 1960s.¹⁴ Testing detects an IgE-mediated response to the spontaneous breakdown products of penicillin, in the form of haptens. Haptens bind with carrier proteins to form the 'major' (90%) and 'minor' (10%) determinants of the immune response.¹⁵

Penicillin skin tests are well tolerated and safe – a 2000 study of 1710 patients undergoing skin prick and intradermal (ID) testing demonstrated a systemic reaction rate of 0.12%, including one case of mild anaphylaxis.¹⁶ A 1993 study of 5063 patients had a rate of 0.26%, although the increased rate was likely attributable to a protocol proceeding with ID testing in patients with positive skin prick results.¹⁷

Use of penicillin skin tests allows patients to be safely challenged with larger oral doses of penicillin. A review of 6739 patients with self-reported penicillin allergy but negative skin tests reported 103 (1.49%) IgE-type reactions; 43 (0.63%) delayed-type reactions and no episodes of anaphylaxis on subsequent penicillin challenge.¹³

Penicillin allergy testing in Australia is normally carried out in allergy clinics, which often have extensive waiting lists,¹⁸ and rely on referral systems. This excludes patients who are not highly motivated to be tested. Using the ED as a capture setting will allow testing to reach a larger group

of patients reporting a penicillin allergy, and with suitably rapid testing, could influence the prescribing of antibiotics for their treatment plan, if required.

To date there has been only one prospective study examining the feasibility of penicillin skin testing in an ED. In a study carried out in the USA by Raja *et al.*,¹⁹ 150 patients were tested without significant adverse events, demonstrating a high false-positive rate of self-reporting (91.3%; 95% CI 85.3–95.1). The study was unable to incorporate the administration of a drug provocation test (DPT) in the form of an oral challenge with penicillin, following negative skin test results, considered the gold standard for exclusion of an immediate hypersensitivity reaction.²⁰

The aim of this study was to determine whether comprehensive allergy testing conducted within an Australian ED could safely de-label selected patients presenting for emergency care reporting a penicillin allergy.

This is the first such study carried out in an Australian ED, and the first in any ED to utilise a DPT in addition to skin testing. We hypothesised a de-labelling of penicillin allergy of 80–90% following allergy testing, a smaller effect than suggested in the study by Raja *et al.*¹⁹ due to the addition of the DPT.

The de-labelling of penicillin allergy in patients presenting to the ED should allow improvement in current or future antibiotic treatment options, while reducing the spread of antibiotic resistance and the risks of inappropriate broad spectrum use.

Methods

A prospective study of penicillin allergy testing at an urban, academic ED using standardised criteria was undertaken between 2011 and 2016.

The study was approved by the hospital's Human Research Ethics Committee (HREC09/SVH/149), and written informed consent was obtained from all participants.

Patients 18–85 years of age presenting to the ED self-reporting a history of penicillin allergy were eligible for inclusion in the study.

Patients were excluded if they were pregnant or unable to consent, presented with severe illness (unstable vital signs or clinician concern that a systemic allergic reaction or its treatment could cause significant morbidity), a clear history of severe anaphylaxis, or were taking beta-blocker, corticosteroid, antihistamine or cromolyn medications. The reported reaction and duration between reaction and presentation were not recorded. Recruitment was performed by study investigators when patients were flagged for penicillin allergy by triage and other nurses. Three patients were tested during their initial presentation to the ED, with 100 recalled for testing in batches to maximise the yield of testing reagents and clinician testing time.

Standardised skin prick and ID testing was performed by one emergency physician (GA), one registrar (JM) and one senior resident (Jordan Sandral), after each received 30 min training in administering and interpreting the skin prick test (SPT) and ID test from an allergy specialist (JR).

Reagents used for skin prick and ID testing were DAP kits (Diater Laboratories penicillin/amoxycillin allergy kits, Australasian Medical and Scientific Ltd), major determinant mix 'PPL' (benzylpenicilloyl polylysine), minor determinant mix 'MDM' (sodium benzyl penicillin, benzylpenicilloic acid and sodium benzylpenicilloate) and amoxycillin (20 mg/mL), with a cost of AUD \$265 per kit. The initial reported shelf life of the reagents was 24 h following reconstitution. In August 2013 the manufacturers increased this shelf life to 15 days, allowing significantly improved flexibility in testing. It is estimated four patients were tested per kit.

Skin prick testing was performed on the volar surface of the forearm, using major and minor determinant penicillin reagents and amoxicillin, along with a negative control of 0.9% saline solution and positive control of histamine dihydrochloride (10 mg/mL) (Fig. 1). If skin prick results were negative after 15 min, ID testing was carried out using 0.02 mL of the major and minor

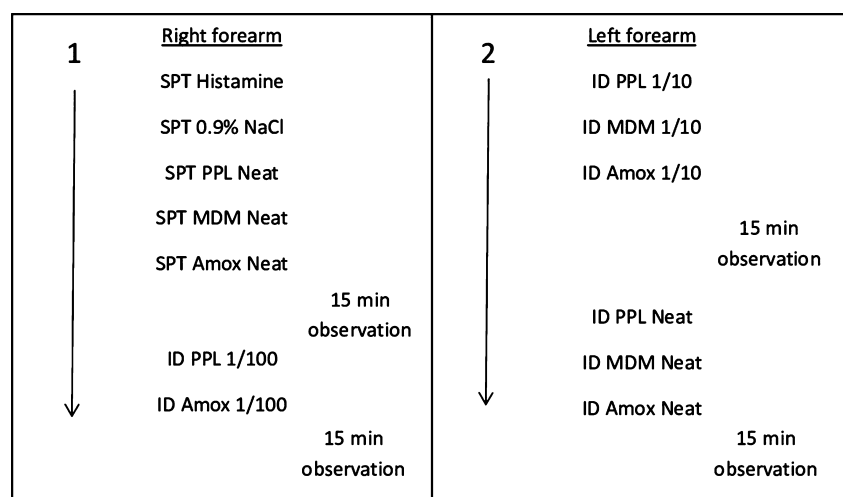


Figure 1. Layout of skin prick and intradermal testing. Amox, amoxicillin; ID, intradermal test; MDM, minor determinant; PPL, major determinant; SPT, skin prick test.

reagents and amoxicillin, initially 1/100 dilution (major determinant and amoxicillin only), then 1/10 dilution, followed by neat reagents, with 15 min of observation between each series. Each ID bleb in the skin was traced with pen to delineate its margins for measurement.

Wheal-and-flare reaction was measured on the skin, and a positive result was recorded with a wheal diameter >3 mm larger than the negative control (SPT) or 3 mm larger than the initial marked bleb (ID testing). If all skin prick and ID tests were negative, participants started drug provocation testing through a graded oral amoxicillin challenge, using two strength syrups of 12.5 and 125 mg/5 mL, beginning with a daily dose of 2.5 mg, reaching 250 mg after 9 days (Table S1). Patients were observed in the ED after their initial dose for 30 min. Resuscitation equipment was available in case of anaphylaxis.

Syrups were prepared by the Clinical Trials Pharmacy at a cost of \$55 per patient. The cost of all testing equipment, reagents and take-home packs was estimated at \$195 per patient.

Total testing time in the ED was 120 min, including 30 min for skin prick and ID testing and 90 min for observation. For a senior registrar at \$55/h this would imply labour costs of \$110 per patient, although this is

reduced by batching patients in twos or threes, and by the study clinicians attending to departmental patients between phases of testing when on a clinical shift.

The primary end point was the perceived allergy status at the end of testing, with adverse events summarised overall and individually by subject. At the conclusion of testing, patients and their general practitioners were informed of their penicillin allergy status, and note was made on the patient's electronic record. Patient willingness to take penicillin following de-labelling was not recorded in the study, but may be sought in future follow up.

We hypothesised a reduction in prevalence of 80–90%. Using McNemar's test of paired proportions, a study of 100 subjects was determined to provide approximately 99% power to detect a reduction from the self-reported to the actual prevalence of allergy, at a two-sided level of 5%. Statistical analysis was conducted with Stata Version 14.1 (StataCorp, College Station, TX, USA). We calculated the reduction in true prevalence of penicillin allergy and exact binomial 95% CI. Formal comparisons were made using McNemar's test. We thereafter used logistic regression to assess whether true penicillin allergy differed by age and sex. Age was modelled in quartiles because it was not linear against the logit function.

Results

From 2011 to 2016, it is expected the ED saw 20 000–30 000 patients reporting a penicillin allergy (8–12% of 250 000 who presented). This included periods where no testing or enrolment was performed due to staff rotations or reagent supply.

A total of 103 patients aged from 19 to 69 years (54% women) met eligibility criteria and consented to testing. Their characteristics are summarised in Table 1.

One patient declined to proceed with the oral challenge after suffering a headache during SPT, and two patients were lost to follow up after undergoing SPT and ID testing. Of note, one positive ID test was delayed – this patient had been unable to start on the DPT on the day of her skin test and was due to return, but 48 h later developed wheal and flare at all neat ID test sites, so subsequent DPT was not undertaken.

Of the 100 patients who completed the study, 81 tolerated penicillin without evidence of allergy. A total of 17 patients had evidence of IgE hypersensitivity, and two developed a delayed rash, likely caused by non-IgE mechanisms (Fig. 2).

This equated to a de-labelling of 81% (95% CI 71.9–88.2) of patients reporting a penicillin allergy, $P < 0.001$ (Table 2). For women, the percentage de-labelled was significantly less than for men: 72.2 (95% CI 58.4–83.5) *vs* 91.3 (95% CI 79.2–97.6), as women were more likely to have a true penicillin allergy with an odds ratio of 4.0 (95% CI 1.23–13.2). In univariate logistic regression screening there were no associations between having a true penicillin allergy and triage category, discharge destination or antibiotic prescription for the index presentation.

There were no serious adverse events. One patient was advised to cease the DPT after reporting an urticarial rash and tingling lips on day 2, thought to be an IgE-mediated reaction. Two patients reported developing a rash at the end of the DPT. The list of reported reactions to DPT is detailed in Table 3.

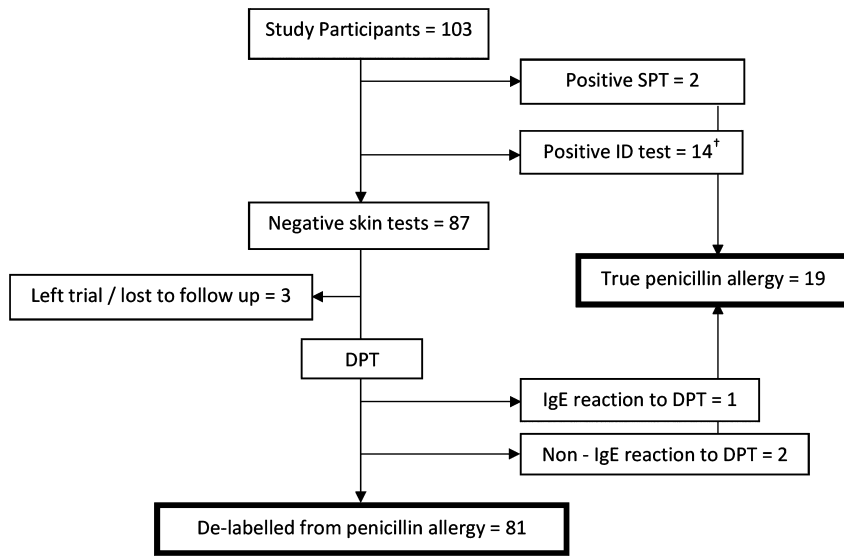


Figure 2. Flow-through study. DPT, drug provocation testing; ID, intradermal test; SPT, skin prick test. †Including one delayed by 48 h.

TABLE 1. Demographic, triage and discharge characteristics

Characteristic			
All enrolled subjects	N = 103		
Women, <i>n</i> (%)	56 (54)		
Median (interquartile range) age (years)	43 (30–55); min = 19, max = 69		
Subjects with outcome data	N = 100		
Women, <i>n</i> (%)	54 (54)		
Median (interquartile range) age (years)	42.5 (30–54.5); min = 19, max = 69		
Antibiotics prescribed	N = 100		
Yes	30		
No	70		
Discharge destination	N = 100		
Home	65		
Ward	10		
Emergency Medical Unit†	25		
Australasian Triage Scale	Study patients	ED profile 2011–2016 ²¹	
	N = 100	N = 253 982	N = 100%
Category 1 – Immediate	0	6183	2.4
Category 2 – Emergency	16	30 956	12.2
Category 3 – Urgent	41	118 754	46.8
Category 4 – Semi-urgent	25	86 363	34.0
Category 5 – Non-urgent	18	11 726	4.6

†For emergency medicine admissions <24 h duration.

Discussion

This study demonstrated a significant reduction in apparent prevalence of penicillin allergy following testing, with 81% of the tested patients initially reporting an allergy able to safely tolerate an oral challenge of 250 mg amoxicillin. This indicates that the prevalence of patients falsely reporting penicillin allergy in Australia is similar to those in studies performed overseas.

The study demonstrated that allergy testing including DPT can be safely performed in adult, non-pregnant emergency patients who are not critically unwell or taking beta-blocking, anti-histamine, corticosteroid or cromolyn medications. These findings are consistent with studies performed in outpatient settings¹³ and in an ED study performed without DPT.¹⁹

This study provided additional information about the utility of DPT testing in the ED. Of the 84 patients with negative skin tests who took part in the DPT, only one (1.2% [95% CI 0.03–6.4]) had a result suggesting IgE hypersensitivity and three (3.6 [95% CI 0.7–10.1]) suggestive of any allergic reaction. Consistent with previous studies,¹³ this suggests that although of low yield for those with negative skin testing, the DPT revealed genuine allergy that might otherwise have been labelled as false, with potentially harmful consequences.

However, a 9 day DPT protocol is problematic for patients being admitted to hospital, and safe use of rapid challenge doses following negative skin testing has been described in previous studies.^{22,23} An accelerated DPT may be adequate to exclude IgE-mediated penicillin allergy,¹⁵ potentially during the first 24 h of a patient's admission, allowing early administration of the most suitable antibiotics.

Modifications to the protocol employed in this study could be made to expedite testing in a presenting emergency patient so that, when followed by an accelerated DPT, these patients could be tested, and treated with penicillin if indicated, during their index presentation.

TABLE 2. Prevalence of true penicillin allergy and associations between age and sex (logistic regression model)

Grouping	n/N with true allergy	True prevalence (95% confidence interval)	Odds ratio (95% confidence interval)	P-value
All subjects	19/100 (19%)	19 (11.8–28.1)%		
Sex				
Male	4/46 (8.7%)	8.7 (0.0–20.8)%	1.0 (reference)	0.02
Female	15/54 (27.8%)	27.8 (16.5–41.6)%	4.0 (1.23–13.2)	
Age group (years)				
≤30	7/28 (25.0%)	25.0 (10.7–44.9)%	1.0 (reference)	0.44
31–43	2/24 (8.3%)	4.2 (0.1–26.9)%	0.27 (0.05–1.47)	
44–55	5/24 (20.8%)	20.8 (7.1–42.2)%	0.79 (0.21–2.91)	
≥56	5/24 (20.8%)	20.8 (7.1–42.2)%	0.79 (0.21–2.91)	

The current study employed a comprehensive testing procedure (involving 2 h in the ED and 9 days of self-medication) to minimise the risk of injuring a patient during rapid escalation of antigen exposure, or falsely de-labelling their allergy status. The safety of abbreviating this testing regime – for example by removing the 1/100 ID dilutions – could be observed in future studies. This would reduce the labour costs of the clinicians trained to perform the testing, improve patient compliance with testing and cause less disruption to patient flow through the ED. Previous research has demonstrated the benefit of stratifying histories of patients reporting penicillin allergy, predicting the likelihood of IgE-mediated reaction, with a correlation in prevalence of allergy demonstrated by skin testing.¹² Future research might observe whether those with vague or unlikely histories could

in particular be safely subjected to a shorter testing course.

Our finding that women were more likely to have a true penicillin allergy (odds ratio 4.0 [95% CI 1.23–13.2]) mirrors the finding of an American study from 2007 of 1759 pre-operative patients with history of penicillin allergy who underwent SPT and ID testing.⁷ However, this was not observed in the 2009 study by Raja *et al.*¹⁹

Using an electronic prescribing system with displayable and searchable allergy data would increase capture of potential patients, and along with batch-testing, reduce wastage and thus minimise the cost of reagent per patient. Further study into patient-level costings and potential savings from allergy de-labelling through an abbreviated skin test and DPT protocol could help justify a business case for

implementation of formal penicillin allergy testing in the ED.

Limitations

The total study duration was significantly increased due to challenges with enrolment and testing, including dormant enrolment periods due to inter- and intra-hospital rotations of the testing clinicians, as well as a lack of searchable allergy records: hence, the enrolment of 103 patients out of a potential 25 000 may suggest a risk of selection bias.

A potential cause for selection bias may be a requirement for significant motivation to take part in the study, with a majority of patients returning to the ED for testing and likely undertaking a potentially injurious medicine for 9 days, all for the potential future benefit of allergy de-labelling. We also did not record the numbers of patients reporting a penicillin allergy that were approached to participate in the study and subsequently declined. However, it is unclear in what direction this would impact results.

Our study population differed from the background ED profile, mostly due to a higher number of non-urgent presentations in the study. However, no association was found between acuity of triage and presence of true allergy.

It is important to note that this study examined the presence or absence of an IgE-mediated “type

TABLE 3. Reported reactions during drug provocation testing

Reported reactions during drug provocation testing	De-labelled	N = 6
Urticarial rash and tingling lips†	No	1
Delayed rash	No	2
Pruritus	Yes	1
Diarrhoea	Yes	1
Nausea	Yes	1

†Likely IgE mediated.

1" hypersensitivity reaction only. Other types of reactions not generally associated with an IgE hypersensitivity were reported by patients, and these may result in intolerance of penicillin use.

Patients with a clear history of severe anaphylaxis were also excluded on grounds of safety and these patients would be likely to have a higher rate of positive tests.

Conclusion

Selected patients in the ED who self-report an allergy to penicillin can be safely tested for the presence of true allergy, using skin tests and drug provocation testing. This testing allows a significant de-labelling of reported penicillin allergy, with the majority of these patients tolerating penicillin without incident. However, the gold-standard level of testing is time consuming, and testing is more cost and time-effective when performed in batches.

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Author contributions

JM was the study lead and involved in clinical testing and manuscript preparation. GA was involved in study design, clinical testing and manuscript review. SK was involved in statistical analysis and manuscript review. SAW was involved in study design and manuscript review. JR was involved in supervision, study design and manuscript review.

Competing interests

None declared.

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Supporting information

Additional supporting information may be found in the online

version of this article at the publisher's web site:

Table S1. Drug provocation test schedule.