

CLINICAL INVESTIGATION

Penicillin allergy de-labelling ahead of elective surgery: feasibility and barriers

L. Savic^{1,*}, L. Gurr², V. Kaura³, J. Toolan⁴, J. A. T. Sandoe^{2,5},
P. M. Hopkins^{1,3} and S. Savic^{2,4}

¹Anaesthetic Department, Leeds Teaching Hospitals NHS Trust, Leeds, UK, ²University of Leeds School of Medicine, Leeds, UK, ³Leeds Institute of Biomedical and Clinical Sciences, Leeds, UK, ⁴Department of Clinical Immunology and Allergy, Leeds Teaching Hospitals NHS Trust, Leeds, UK and ⁵Microbiology Department, Leeds Teaching Hospitals NHS Trust, Leeds, UK

*Corresponding author. E-mail: louise.savic@nhs.net

Abstract

Background: Around 10–15% of the in-patient population carry unsubstantiated ‘penicillin allergy’ labels, the majority incorrect when tested. These labels 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 the feasibility of a rapid access de-labelling pathway for surgical patients, using direct oral challenge.

Methods: ‘Penicillin allergic’ patients, recruited from a surgical pre-assessment clinic, were risk-stratified using a screening questionnaire. Patients at low risk of true, immunoglobulin E (IgE)-mediated allergy were offered direct oral challenge using incremental amoxicillin to a total dose of 500 mg. 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 of 19 patients received appropriate antimicrobial prophylaxis during surgery. Only three of 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.

Clinical trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=AN17/92982): AN17/92982.

Keywords: allergy; anaphylaxis; antibiotics; de-labelling; perioperative; preoperative assessment

Editor's key points

- Direct oral challenge appeared to be safe and effective in patients at low risk of true penicillin allergy.
- Removal of the allergy label resulted in appropriate use of penicillin during surgery.
- Widespread adoption of this model has the potential to reduce the burden of incorrect penicillin allergy labels in this population.

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 aureus* (MRSA), *Clostridium difficile*, and vancomycin-resistant *Enterococcus* (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 perioperative 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](https://www.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 immunoglobulin E (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, dependent on their availability.

Eligible patients attended a dedicated de-labelling clinic, where a direct oral challenge was performed using oral amoxicillin, after written consent was obtained. The clinic had the facility to test for alternatives, should the index penicillin

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
Do not know/cannot remember	Wheeze, shortness of breath
	Collapse or dizziness
	Itchy rash
	Symptoms required hospital admission and treatment

be different. An incremental dosing regimen of 10%, 50%, and 100% full dose (500 mg) was used, with 20 min intervals between doses. This is the protocol used for low risk patients who undergo challenge testing in the Immunology Department in Leeds Teaching Hospitals, Leeds, UK. Patients were observed for a further 1 h 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 antibiotics 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 the hospital. The results of testing were confirmed in writing to the patient, general practitioner (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.

Table 2 Eligibility criteria. *These three criteria were amended after high demand for testing amongst otherwise eligible patients

Eligible	Ineligible
Low risk symptoms	High risk symptoms
Reaction occurred >15 yr ago*	Reaction <15 yr ago
Sufficient time for testing before operation*	No time for testing
Wants to be tested	Declines testing
Requires penicillin for surgery*	Doesn't require penicillin for surgery
Aged >18 yr	Pregnant, breastfeeding
	Unstable asthma (oral steroids required in the past 6 months)

Midway through the study, the eligibility criteria were amended in response to high patient demand for testing (substantive amendment October 31, 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 after operation.

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 were ineligible. See Figure 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 patients 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 patients completed the course of antibiotic therapy.

Among the 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 of patients, 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 because of high risk co-morbidities.

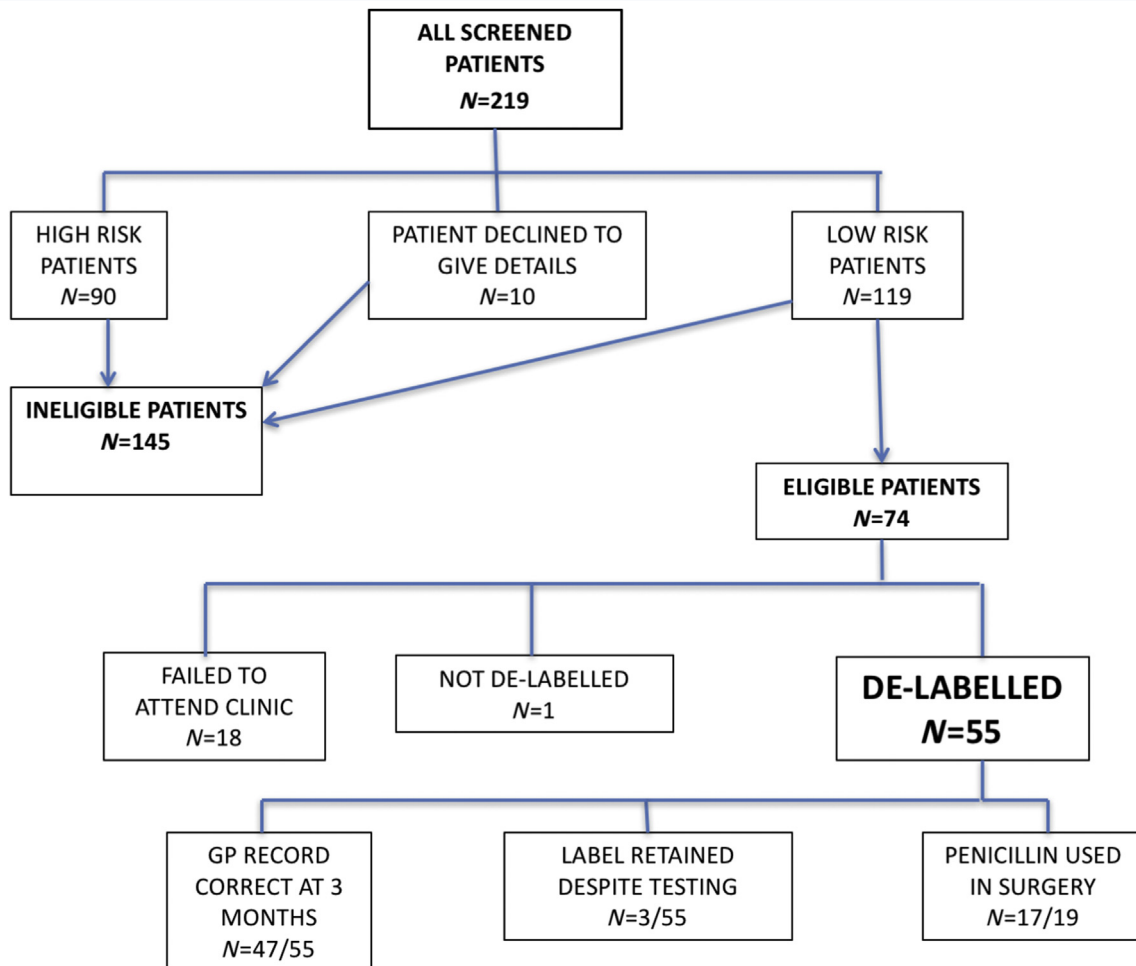


Fig 1. Outcomes of all screened patients.

Table 3 Symptoms of index reaction in 119 patients in the low risk group. GI, gastrointestinal. The total number of symptoms exceeds 119 as some patients had more than one symptom

Symptom	GI upset	Red rash Flushing	Rash (unspecified)	Don't know Can't remember	Thrush	Miscellaneous (e.g. 'convulsions')
n	32	41	25	41	1	2

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 patients), 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; six of them wished to be tested.

Among the 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) of patients 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 re-labelled 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 the 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 preoperative 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 the 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%. In addition to 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 test, intradermal test, 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

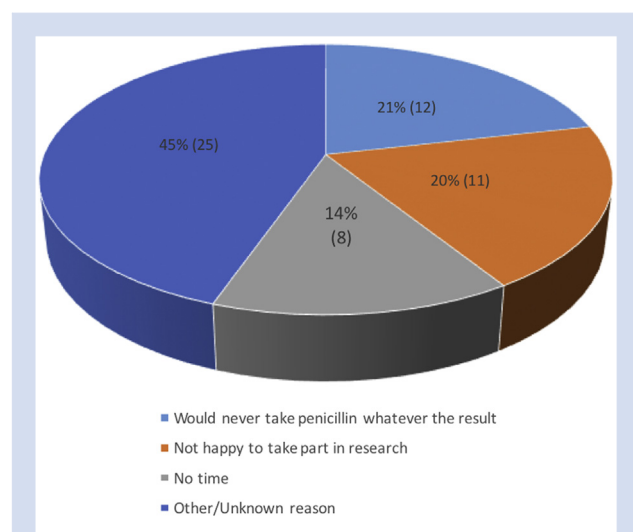


Fig 2. Reasons why patients with a label of 'penicillin allergy' declined testing.

not offered a challenge test and so the positive predictive value (PPV) is difficult to determine. The PPV is generally accepted to be less than 50% based on a limited number 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 preoperative setting, with subsequent reduced use of intraoperative 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. Although 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 because of 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 used in several centres in the USA; 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 (Drug Rash with Eosinophilia and Systemic Symptoms) and TENS (Toxic Epidermal Necrolysis), are also high risk and must avoid penicillin.

The barriers to implementing this on a large scale are twofold: 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 during the course of the operation, 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 after 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 USA 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 intraoperative dose of a more expensive alternative antibiotic.

Finally, this study addressed the question of acceptability of de-labelling without formal testing—that is, on the basis of history alone. In those with histories clearly consistent with side-effects (e.g. 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 3 months after 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 500 mg amoxicillin. The utility of this has been confirmed in a study of 500 sequential patients in the USA,⁴ and a cohort of Marine recruits also in the USA,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 1 h and 45 min, to about 1 h, 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 January 5, 2018), 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, as 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.

Authors' contributions

Study design: L.S., S.S., P.H., J.S.

Writing of the manuscript: L.S., S.S., P.H., J.S.

Patient recruitment: L.S., L.G., V.K., J.T.

Conduct of challenge testing: L.S., L.G., V.K., J.T.

Declaration of interest

The authors declare no competing interests.

Funding

Leeds Teaching Hospital NHS Trust.

Acknowledgements

The authors are grateful to N. Glover, A. Rose, and A.-M. Jones for invaluable help in screening patients in pre-assessment; to S. Farooque, who provided critical review of the protocol; and to the Immunology and Anaesthetic departments of Leeds Teaching Hospitals for their support for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2018.09.009>.

References

- Mirakian R, Leech SC, Krishna MT, et al. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy* 2015; **45**: 300–27
- Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 2014; **133**: 790–6
- Mistry AMD, Corps C, Savic S, Savic L. Feasibility and utility of testing for penicillin allergy status in patients attending for elective surgery. *Clin Exp Allergy* 2016; **46**: 1625–74
- Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. *J Allergy Clin Immunol Pract* 2013; **1**: 258–63
- Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010; **105**: 259–73
- Knezevic B, Sprigg D, Seet J, et al. The revolving door: antibiotic allergy labelling in a tertiary care centre. *Intern Med J* 2016; **46**: 1276–83
- Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. *Pharmacotherapy* 2011; **31**: 742–7
- van Dijk SM, Gardarsdottir H, Wassenberg MW, Oosterheert JJ, de Groot MC, Rockmann H. The high impact of penicillin allergy registration in hospitalised patients. *J Allergy Clin Immunol Pract* 2016; **4**: 926–31
- Blumenthal K, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis* 2017; **66**: 329–36
- McDaniel DL, Azar AE, Dowden AM, et al. Screening for beta-lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *J Arthroplasty* 2017; **32**: S101–8
- Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
- Savic LC, Garcez T, Hopkins PM, Harper NJ, Savic S. Teicoplanin allergy — an emerging problem in the anaesthetic allergy clinic. *Br J Anaesth* 2015; **115**: 595–600
- Blumenthal KG, Li Y, Banerji A, Yun BJ, Long AA, Walensky RP. The cost of penicillin allergy evaluation. *J Allergy Clin Immunol Pract* 2017; **6**: 1019–27
- National Clinical Guideline Centre (UK). *Drug allergy: diagnosis and management of drug allergy in adults, children and young people*. London: National Institute for Health and Care Excellence (UK); 2014 Sep (NICE Clinical Guidelines, No. 183.) 5, Guideline summary
- Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of suspected and challenge-verified penicillin allergy in a university hospital population. *Basic Clin Pharmacol Toxicol* 2006; **98**: 357–62
- Confino-Cohen R, Rosman Y, Meir-Shafir K, et al. Oral challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. *J Allergy Clin Immunol Pract* 2017; **5**: 669–75
- Iammatteo M, Alvarez Arango S, Ferastraoaru D, et al. Safety and outcomes of oral graded challenges to amoxicillin without prior skin testing. *J Allergy Clin Immunol Pract* 2018. <https://doi.org/10.1016/j.jaip.2018.05.008>. Advance Access published on May 23
- Tucker MH, Lomas CM, Ramchandran N, Waldram JD. Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. *J Allergy Clin Immunol Pract* 2017; **5**: 813–5
- UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018. Available from: <https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018>. [Accessed 4 October 2018].
- Krishna MT, Huissoon AP, Li M, et al. Enhancing antibiotic stewardship by tackling "spurious" penicillin allergy. *Clin Exp Allergy* 2017; **47**: 1362–73
- Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs — an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; **68**: 702–12
- Torres MJ, Blanca M, Fernandez J, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003; **58**: 961–72
- del Real GA, Rose ME, Ramirez-Atamoros MT, et al. Penicillin skin testing in patients with a history of beta-lactam allergy. *Ann Allergy Asthma Immunol* 2007; **98**: 355–9
- Park MA, Solensky R, Khan DA, Castells MC, Macy EM, Lang DM. Patients with positive skin test results to penicillin should not undergo penicillin or amoxicillin challenge. *J Allergy Clin Immunol* 2015; **135**: 816–7
- Macy E, Burchette RJ. Oral antibiotic adverse reactions after penicillin skin testing: multi-year follow-up. *Allergy* 2002; **57**: 1151–8

26. Tannert LK, Mortz CG, Skov PS, Bindslev-Jensen C. Positive skin test or specific IgE to penicillin does not reliably predict penicillin allergy. *J Allergy Clin Immunol Pract* 2017; **5**: 676–83
27. Macy E, Schatz M, Lin C, Poon KY. The falling rate of positive penicillin skin tests from 1995 to 2007. *Perm J* 2009; **13**: 12–8
28. Blanca M, Torres MJ, Garcia JJ, et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. *J Allergy Clin Immunol* 1999; **103**: 918–24
29. Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA* 2001; **285**: 2498–505
30. Goldberg A, Confino-Cohen R. Skin testing and oral penicillin challenge in patients with a history of remote penicillin allergy. *Ann Allergy Asthma Immunol* 2008; **100**: 37–43
31. Solensky R, Earl HS, Gruchalla RS. Penicillin allergy: prevalence of vague history in skin test-positive patients. *Ann Allergy Asthma Immunol* 2000; **85**: 195–9
32. Padial A, Antunez C, Blanca-Lopez N, et al. Non-immediate reactions to beta-lactams: diagnostic value of skin testing and drug provocation test. *Clin Exp Allergy* 2008; **38**: 822–8
33. Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol* 2011; **127**: 218–22
34. Mill C, Primeau MN, Medoff E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. *JAMA Pediatr* 2016; **170**: e160033
35. Ibanez MD, Del Rio PR, Lasa EM, et al. Prospective assessment of diagnostic tests for pediatric penicillin allergy, from clinical history to challenge tests. *Ann Allergy Asthma Immunol* 2018; **121**: 235–44.e3
36. Moussa Y, Shuster J, Matte G, et al. De-labeling of B-lactam allergy reduces intraoperative time and optimises choice in antibiotic prophylaxis. *Surgery* 2018; **164**: 117–23
37. Sacco KA, Bates A, Brigham TJ, Imam JS, Burton MC. Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis. *Allergy* 2017; **72**: 1288–96
38. Trubiano JA, Thursky KA, Stewardson AJ, et al. Impact of an integrated antibiotic allergy testing program on antimicrobial stewardship: a multicenter evaluation. *Clin Infect Dis* 2017; **65**: 166–74
39. Trubiano J, Phillips E. Antimicrobial stewardship's new weapon? A review of antibiotic allergy and pathways to 'de-labeling'. *Curr Opin Infect Dis* 2013; **26**: 526–37
40. Leis JA, Palmay L, Ho G, et al. Point-of-care beta-lactam allergy skin testing by antimicrobial stewardship programs: a pragmatic multicenter prospective evaluation. *Clin Infect Dis* 2017; **65**: 1059–65
41. Frigas E, Park MA, Narr BJ, et al. Preoperative evaluation of patients with history of allergy to penicillin: comparison of 2 models of practice. *Mayo Clin Proc* 2008; **83**: 651–62
42. Park M, Markus P, Matesic D, Li JT. Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. *Ann Allergy Asthma Immunol* 2006; **9**: 681–7
43. Aberer W, Macy E. Moving toward optimizing testing for penicillin allergy. *J Allergy Clin Immunol Pract* 2017; **5**: 684–5
44. Rimawi RH, Shah KB, Cook PP. Risk of redocumenting penicillin allergy in a cohort of patients with negative penicillin skin tests. *J Hosp Med* 2013; **8**: 615–8
45. Patel SV, Tarver SA, Alvarez KS, Lutek KE, Schlebus J, Khan DA. Effectiveness of interventions to maintain penicillin allergy label removal as part of an inpatient penicillin allergy testing protocol. *J Allergy Clin Immunol* 2017; **139**: AB183

Handling editor: J.G. Hardman

Pre-assessment Screening Questionnaire - Eligibility for PADLES

1. Date:

2. Name of assessor:

3. Patient details (addressograph):

4. Are you allergic to penicillin?.....Yes / No

5. When did you have an allergic reaction to penicillin?

In the last 5 years

Between 5 and 15 years ago

More than 15 years ago

In childhood

Don't know/can't remember

6. Do you know the name of the penicillin drug you were given?
(eg benpen, amoxicillin, augmentin, flucloxacillin, etc)

7. What happened when you took penicillin?

Upset stomach (eg nausea, cramps, diarrhoea)

Red rash or flushing (not itchy)

Itchy rash (hives)

Rash (don't know what sort)

Severe blistering rash (Stephens-Johnson, DRESS etc)

Swelling of face/tongue/lips

Wheezing or difficulty breathing

Anaphylaxis

Don't know/can't remember

Other symptoms or problems not listed above? (please detail on this page and overleaf)

7B. Were you admitted to hospital after you took penicillin?.....Yes / No

8. Do you have poorly controlled asthma.....Yes / No
(needing to use oral steroids in the last 6 months)

9. Are you pregnant, planning to become pregnant, or breastfeeding?.....Yes / No

10. Would you like to undergo testing for penicillin allergy?..... Yes / No
If not, what is the reason? (please circle all which apply)

Would not feel happy taking penicillin whatever the result of testing

Do not want to take part in research

No time

Do not wish to answer this question

Other (please comment below)

.....
STUDY TEAM TO ANSWER

11. Is the patient undergoing a surgical procedure requiring penicillin as first line antimicrobial prophylaxis?.....Yes / No
(Patient can still be tested if 'No')

13. Does the patient require antihistamines or oral steroids? If so, can these be omitted for **4 days** prior to testing?.....Yes / No

14. Is the patient eligible for inclusion?.....Yes / No

15. If eligible, what is the BEST contact number for the patient?

16. If eligible, has the patient been given an information leaflet and a provisional date for de-labelling clinic?.....Yes / No

V7 28/9/2017

IRAS number 222993