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Safety and efficacy of de-labelling penicillin allergy in adults using direct oral challenge: a systematic review

Lesley Cooper[1]*, Jenny Harbour[2], Jacqueline Sneddon[1] and R. Andrew Seaton[1,3,4]

[1]*Scottish Antimicrobial Prescribing Group, Healthcare Improvement Scotland, Delta House, 50 West Nile Street, Glasgow G1 2NP, UK;* [2]*Healthcare Improvement Scotland, Delta House, 50 West Nile Street, Glasgow G1 2NP, UK;* [3]*Queen Elizabeth University Hospital, Govan Road, Glasgow, UK;* [4]*NHS Greater Glasgow and Clyde, Glasgow, UK*

*Corresponding author. E-mail: lesley.cooper17@nhs.scot

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Background: Approximately 10% of people have an unverified penicillin allergy, with multiple personal and public health consequences.

Objectives: To assess the efficacy and safety of direct oral challenge, without prior skin testing, in this population.

Methods: MEDLINE, EMBASE, CINAHL, the Cochrane Library and Google Scholar were searched from inception to 28 June 2020 (updated November 2020) to find published and unpublished studies that reported direct oral challenge for the purpose of removal of penicillin allergy labels. Population weighted mean was used to calculate the proportion of patients who developed an immediate or delayed reaction to direct oral challenge across the studies.

Results: Thirteen studies were included in the review, with a sample size of 1202 (range 7–328). Studies included inpatient and outpatient cohorts assessed as low risk for true allergy. In pooled analysis of all 13 studies there were 41/1202 (3.41%) mild immediate or delayed reactions to direct oral challenge. The population-weighted mean incidence of immediate or delayed reaction to an oral challenge across studies was also 3.41% (95% CI: 2.38%–4.43%). There were no reports of serious adverse reactions, 96.5% of patients could be de-labelled and many were subsequently successfully treated with penicillin.

Conclusions: Direct oral challenge is safe and effective for de-labelling patients assessed as low risk for true allergy. Non-specialist clinicians competent in using an assessment algorithm can offer evaluation of penicillin allergy labels using direct oral challenge in appropriate patients. These measures will facilitate optimal infection treatment for patients, support antimicrobial stewardship, and minimize antimicrobial resistance.

Introduction

Approximately 10% of people carry an unverified penicillin allergy label on their medical record. However, the true prevalence of penicillin hypersensitivity reaction based on allergy history is unknown.[1,2] It is likely that only 10%–20% of self-reported penicillin allergies will be confirmed with formal evaluation.[3,4] Patients in hospital are particularly likely to report a penicillin allergy.[1] Studies show that 35.7% and 50% of hospitalized patients in Scotland and the US, respectively, receive at least one course of antibiotic treatment during their admission.[5,6] Therefore, it is important to ensure accuracy of a penicillin allergy label to prevent unnecessary penicillin avoidance and inappropriate use of alternative non-β-lactam antibiotics which may be less effective.[7] Injudicious use of alternative broad-spectrum antibiotics is associated with increased direct costs to the healthcare service, longer duration of patient stay in hospital, increased risk of adverse effects, and development of antimicrobial resistance (AMR).[7–11]

Oral challenge (OC) is deemed the gold standard test for the removal or verification of penicillin allergy, as skin and *in vitro* tests do not demonstrate 100% sensitivity or specificity.[12] Assessment of penicillin allergy is usually carried out by allergy specialists starting with skin prick testing (SPT) and intradermal testing (IDT). These procedures are time-consuming and expensive, furthermore, specialist allergy assessment services are not widely available across the UK.[13]

Recent studies have shown that patients' risk of true allergy can be assessed using a decision algorithm and those deemed low risk can be offered a direct oral challenge with low incidence of adverse events.[14–17] The objective of this review was to assess the safety (i.e. number of people who experience a reaction) and efficacy of direct oral challenge with amoxicillin or the culprit penicillin for supporting de-labelling in adults with an unverified penicillin allergy label.

Methods

This systematic review is reported in accordance with the Joanna Briggs Institute (JBI) Reviewers Manual.[18] The objectives, inclusion criteria and methods of analysis were specified in advance and published in a protocol (PROSPERO CRD42020176432).

Inclusion/exclusion criteria

Studies that met the following criteria were included in the systematic review: (i) adult inpatients or outpatients with a documented penicillin allergy on their medical record; (ii) objectively or subjectively reported reactions to direct oral challenge with amoxicillin or the culprit penicillin to rule out or confirm allergy; (iii) reported subsequent treatment of infection with a penicillin after direct oral challenge, including adverse events associated with treatment; (iv) any study design; and (v) studies that reported SPT/IDT prior to direct OC were excluded, even if results were ignored.

Search strategy

An initial limited search of Ovid MEDLINE and Ovid EMBASE was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the articles. A second search using all identified keywords and index terms was then undertaken using the following databases: the Cochrane Library, CINHAL, Ovid EMBASE, Ovid MEDLINE and Google Scholar, from inception to 28 June 2020. The Ovid MEDLINE search was updated on the 2 November 2020. The search strategy was reviewed by an experienced librarian. Search terms included index terms as well as keywords for the concepts penicillin, penicillin allergy, reaction, hypersensitivity, de-labelling, provocation testing, and oral challenge (the full search strategy is provided as Supplementary data at *JAC-AMR* Online). Reference lists of included publications were checked for additional relevant studies. Following removal of duplicates, all titles and abstracts were screened by two authors (L.C. and J.H.). Disagreements were resolved by consensus or by discussion with a third author if required. Full text was retrieved for all records deemed to meet the inclusion criteria.

Assessment of methodological quality

Studies selected for critical appraisal were assessed independently by two authors (L.C. and J.H.) using standardized critical appraisal instruments from the JBI.[18] Disagreements were resolved by consensus or by discussion with a third author if required.

Data extraction

Two authors (L.C. and J.H.) independently extracted data using a standardized data extraction tool. The data extracted included study design,

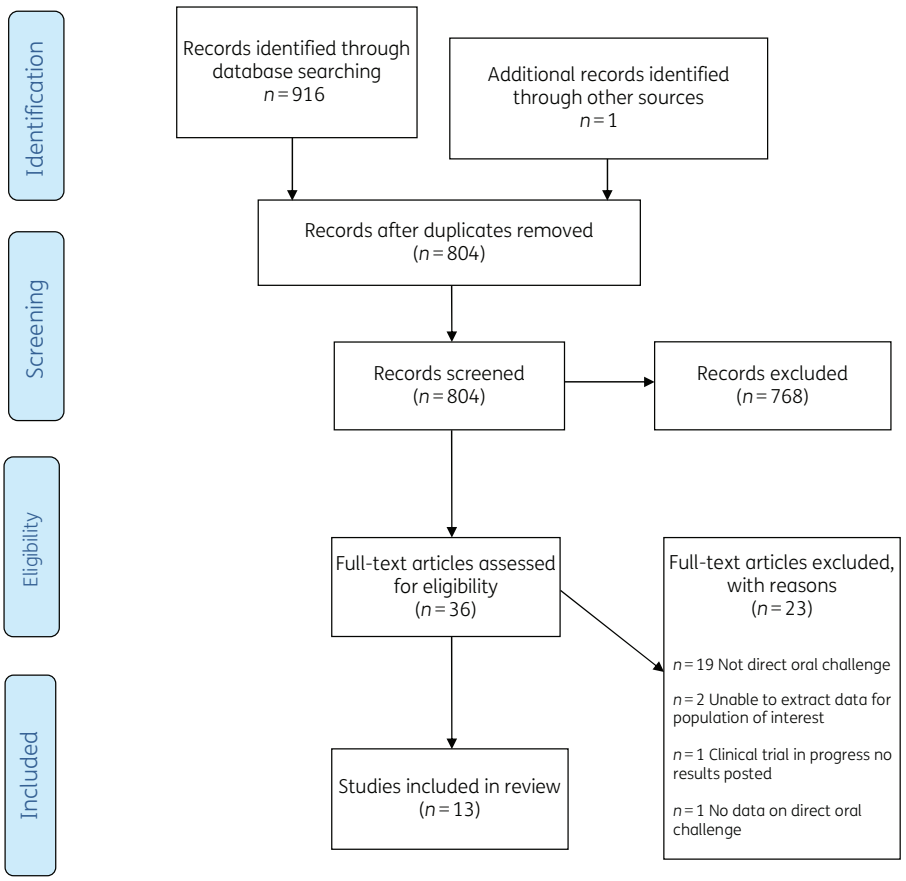

Figure 1. Flow diagram of searches and study selection process.

setting and sample size, criteria used to define low risk of true allergy, details about the direct oral challenge method, duration of challenge and follow-up, number of patients showing an immediate or delayed allergy response, number of patients de-labelled, and subsequent treatment with penicillin (including any delayed reactions to penicillin).

Data synthesis

The primary statistic extracted from each study was the number of participants who developed any immediate or delayed reaction to the OC. Population-weighted analysis was conducted on individual studies reporting the rate of positive direct OCs to produce a population weighted mean. The 95% confidence interval (CI) was calculated using Excel.

Results

Following removal of duplicates and addition of one study found by checking references, a total of 804 citations were identified. Review of titles and abstracts led to the full text for 36 potentially relevant papers being obtained and evaluated against the inclusion criteria by L.C. and J.H. Twenty-three publications were excluded at this stage, resulting in 13 studies being included in the systematic review. Figure 1 details the study selection flow chart presented according to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines.[19]

Methodological quality

The results of the critical appraisal of included studies are presented in Tables 1 and 2. Twelve observational studies and one randomized clinical trial (RCT) were critically appraised and included in the review. Overall median quality score was 6/8 (range 4–8) for observational studies and 6/13 for the RCT.

Description of studies

A summary of included studies ($n = 13$) is presented in Table 3. This systematic review included one RCT,[20] nine prospective observational studies[21–29] and three retrospective observational studies,[30–32] with a total of 1202 participants. There was considerable variation in the number of participants in individual studies, with a median of 47 participants (range 7–328). Studies investigated the safety and effectiveness of direct oral challenge with culprit penicillin or amoxicillin in participants with a documented penicillin allergy label. The RCT compared skin prick test plus OC versus OC only.[20] The clinical settings for included studies were outpatient clinics ($n = 5$),[20,22,27,31,32] inpatient facilities ($n = 7$),[21,23–26,28,29] and a Marine recruit assessment centre.[30] Studies were conducted in the US ($n = 6$),[20,22,25,26,30,31] Australia ($n = 5$),[21,23,28,29,32] the Netherlands ($n = 1$),[24] and the UK ($n = 1$).[27]

The study in a Marine recruit assessment centre included only male participants aged typically between 18 and 25 years,[30] the

Table 1. Critical appraisal of observational studies

Question	Savic 2019[27]	Devchand 2019[21]	Ramsey 2020[26]	Iammatteo 2019[22]	du Plessis 2019[25]	Trubiano 2018[28]	Li 2019[23]	Stevenson 2020[32]	Lin 2020[24]	Tucker 2017[30]	Kuruvilla 2019[31]	Chua 2020[29]
1. Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y	Y	Y	Y	UC	Y	Y	Y	Y	Y
2. Were the study subjects and the setting described in detail?	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
3. Was the exposure measured in a valid and reliable way?	Y	UC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Were objective, standard criteria used for measurement of the condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Were confounding factors stated?	NA	NA	NA	UC	NA	NA	NA	Y	NA	NA	NA	NA
6. Were strategies to deal with confounding factors stated?	NA	NA	NA	N	NA	NA	NA	Y	NA	NA	NA	NA
7. Were outcomes measure in a valid and reliable way?	Y	Y	Y	Y	UC	Y	Y	Y	Y	Y	Y	Y
8. Was appropriate statistical analysis used?	UC	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y

Legend: Y, yes; N, no; NA, not applicable; UC, unclear.
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Table 2. Critical appraisal of randomized clinical trials

Question	Mustafa 2019[20]
1. Was true randomization used for assignment of participants to treatment groups?	N
2. Was allocation to treatment groups concealed?	N
3. Were treatment groups similar at baseline?	Y
4. Were participants blind to treatment assignment?	N
5. Were those delivering treatment blind to treatment assignment?	N
6. Were outcomes assessors blind to treatment assignment?	N
7. Were treatment groups treated identically other than the intervention of interest?	UC
8. Was follow-up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	Y
9. Were participants analysed in the groups to which they were randomized?	Y
10. Were outcomes measured in the same way for treatment groups?	Y
11. Were outcomes measured in a reliable way?	Y
12. Was appropriate statistical analysis used?	Y
13. Was the trial design appropriate, and any deviations from the standard RCT designed account for in the conduct and analysis of the trial?	N

Legend: Y, yes; N, no; NA, not applicable; UC, unclear.
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remaining studies reported a higher proportion of female patients ranging from 51.4%–77.4%. The mean age of study participants ranged from 35.3–70.4 years. Two studies had inclusion criteria that allowed for participation of children[20,22] and two studies allowed for patients aged 16 years or older.[23,32] One study provided no patient characteristics in the study report[27] and the Marine recruits study reported only a typical age range.[30]

All studies reported that patients' history related to penicillin allergy was assessed, 11 used a structured questionnaire or algorithm to determine the risk of true allergy. Three studies reported that a validated tool was used;[21,28,29] other tools had been developed from previously published work or specifically for the study. Two studies reported review of clinical history only, however these studies were conducted by allergy specialists.[23,30] Studies reported that only those assessed as low risk were offered a direct OC. There was some variation in definition of low risk between studies (see Table 3), however most definitions included mild cutaneous reactions, delayed reactions, unknown/cannot remember reaction and those that occurred >1 year previously. The purpose of one study was to assess criteria used to determine low allergy risk to ascertain the optimal definition.[32] Patients were screened and assessed by a variety of healthcare professionals including medically trained allergists,[20,22,23,26,30,31] specially trained nurses or pharmacists[21,25,27–29] or the treating physician.[24] One study did not report who screened or assessed patients.[32] The type of direct OC included a single dose of the culprit penicillin or amoxicillin ($n = 5$),[24,28–31] a two- or three-step incremental dose of amoxicillin ($n = 4$),[23,26,27,32] an initial challenge with placebo followed by a two-step challenge with amoxicillin ($n = 2$),[22,25] and comparison of a two-step OC with a group receiving SPT plus OC with amoxicillin.[20] One study did not report the dose(s) or type of penicillin administered.[21]

Studies reported that participants were monitored for at least 30 min between doses in multi-step oral challenges[20,22,23,25–27,32] and for between 1 and 2 h after administration of a full single dose.[24,28,29,31] Patients were contacted by the research team, usually within 1–4 weeks of the oral challenge, or instructed to make contact if a delayed reaction to the challenge drug occurred.[22,26–28,32] Longer-term follow-up at 90 days[28] and 1 year[21,24] was reported in three studies to determine subsequent use of penicillin-based antibiotics. Researchers contacted patients' general practitioners in two studies to confirm that medical records were updated to reflect the patient's updated allergy status.[23,27]

Findings of the review

Primary outcome: response to direct oral challenge

The main clinical outcome reported in included studies was the ability to remove the penicillin allergy label from the medical records of patients who had no reaction to direct OC with culprit penicillin or amoxicillin. Figure 2 shows the percentage of patients in individual studies who reacted to direct OC along with the population weighted mean for all studies.

Overall, 1202 patients were assessed as low risk and proceeded to a supervised oral challenge with penicillin. One study reported that 20% of patients experienced a non-allergic reaction to the placebo or amoxicillin.[22] Of the 1202 patients challenged, a total of 41 patients (3.41%) experienced a reaction to direct OC, of which 17 (41%) reactions were immediate and 24 (59%) were delayed reactions to direct OC. All reactions were reported as mild or intermediate. Three studies reported treatment for reactions; Immatteo *et al.*[22] reported that one patient who required treatment with antihistamines for a non-immediate rash had resolution within 24 h and one patient with intractable pruritus determined to be an allergy had resolution within 1 h of antihistamine treatment, Ramsay *et al.*[26] reported that one patient with mild swelling and redness under the eyes was treated with oral diphenhydramine while Tucker *et al.*[30] reported treating four isolated cutaneous reactions and one globus reaction with oral antihistamine—participants were also given a single intramuscular dose of epinephrine to avoid reaction progression. There were no reported cases of serious adverse reactions or anaphylaxis in any study and 96.5% of challenged patients could be de-labelled. The proportion of patients who experienced a reaction to direct OC in individual studies ranged between 0% and 15%. The population-weighted mean proportion of patients across all 13 studies who had an immediate or delayed reaction following direct OC was 3.41%, (95% CI: 2.38%–4.43%) (Figure 2).

The patients randomized to receive direct OC in the RCT were included in the pooled analysis as an outpatient cohort.[20] In the RCT, 3/79 (3.8%) patients randomized to direct OC had a reaction, compared with 10/80 (12.5%) patients randomized to SPT plus OC who reported a positive SPT. Participants in the direct OC

Table 3. Included studies

Study	Clinical setting/ country	Sample size	Low risk criteria/assessment tool used	Type of challenge	Length of observation/follow-up	Staff involved	Results
Savic *et al.* (2019)[27] Prospective single-centre non-randomized clinical trial	Dedicated de-labelling clinic UK	56	Low risk symptoms (nausea, vomiting, diarrhoea, non-itchy rash, thrush, not admitted to hospital, do not know/cannot remember) Reaction occurred >15 years ago Screening questionnaire	Amoxicillin 500 mg in incremental doses 10%, 50% and 100% 3 day course of antibiotics to complete at home	20 min intervals between doses and 1 h after full dose in clinic Phone call at end of course (5–7 days after clinic)	Screened by nurses trained to undertake screening	One patient developed urticaria in hands after 2nd dose and stopped. 4 patients mild non-allergic symptoms during prolonged course (sore throat, cough, worsening arthralgia and mild nausea in 2) 17/19 had penicillin-based SAP. Correct allergy status confirmed by GP for 47/55 patients
Devchand *et al.* (2019)[21] Prospective single-centre audit	General wards Australia	20	Childhood exanthem, details of rash timing unknown and no severe features or hospitalization Delayed hypersensitivity rash >10 years ago Unknown reaction or family history of penicillin allergy only Validated assessment tool used	Inpatient DOC administered by trained allergy nurse Dose and type of drug not reported	Not reported	Screened by AMS pharmacist Reviewed on ward round by ID consultant, allergy nurse and AMS pharmacist Administered by allergy nurse	1/20 experienced delayed rash post-discharge. Label reapplied 18/20 patients prescribed penicillin during current admission. 10/20 (50%) prescribed restricted antibiotic before challenge vs 4/20 (20%) after ($P = 0.0958$)
Ramsey *et al.* (2020)[26] Prospective single centre single-blind clinical trial	Medical wards US	48	Cutaneous-only reaction (non-specific rash, itching, or urticaria) Unknown reaction history of >20 years ago No need for medical attention Algorithm developed from previously published work	3 step direct challenge 1/100th full dose, 1/10th full dose, full dose	30 min separation between doses Follow-up call 2 weeks later	Screened by ID PharmD Evaluated by allergist Administered by nurse in usual ward	1/48 immediate mild reaction after step 2 2/48 (4.2%) experienced delayed reaction.
Iammatteo *et al.* (2019)[22] Prospective single-centre single-blind clinical trial	Outpatient drug allergy clinic US	155	Non-life threatening reactions Decision support tool	Patients challenged with placebo followed by a 2-step oral graded	30 min observation following placebo + 30 min observation following 1st dose + 60 min observation	Screened by allergy clinic staff Administered by allergy clinic staffed	16 non allergic reaction to placebo 15 non allergic reaction to amoxicillin.

Continued

Table 3. *Continued*

Study	Clinical setting/ country	Sample size	Low risk criteria/assessment tool used	Type of challenge	Length of observation/follow-up	Staff involved	Results
with historical controls				challenge to amoxicillin	following therapeutic dose. Phone call follow-up within 1 month of amoxicillin challenge		4 (2.6%) developed allergic reaction (non-life threatening) 19 patients completed subsequent course of amoxicillin—5 reported mild delayed symptoms that self-resolved
Kuruvilla *et al.* (2019)[31] Retrospective single-centre chart review	Outpatient allergy clinic US	20	History of benign rash, benign somatic symptoms or unknown history associated with last penicillin exposure >12 months ago Standardized algorithm	Amoxicillin 500 mg single dose	Monitored for 60 min after challenge. Vital signs at baseline and every 30 min. Advised to call if delayed reaction occurred.	Assessed by allergist	3/20 self-limited subjective symptoms
Mustafa *et al.* (2019)[20] Single-centre RCT comparing skin test + OC vs OC only	Outpatient allergy practice US	159	Cutaneous-only reaction >10 years ago Algorithm developed for study	80 SPT followed by oral amoxicillin challenge 79 2-step DOC 1/10th dose amoxicillin followed by full dose	Monitored for 30 min following 1st dose and 30 min following 2nd dose	Assessed by allergist	10/80 had positive skin test 3/79 had positive DOC—no systemic reactions in either group 8.7% fewer positive evaluations compared with skin test $P = 0.079$
du Plessis *et al.* (2019)[25] Prospective single-centre interventional study	General wards New Zealand	34	Delayed onset rash >5 years ago Standardized questionnaire	Placebo, Placebo, amoxicillin 5 mg, 50 mg then 500 mg	Patients observed for 30 min between doses Followed up 1 month and 1 year	Screening, assessment and challenge conducted by specially trained pharmacist	3 (3.8%) positive reaction within 72 h. no hypersensitivity reaction
Trubiano *et al.* (2018)[28] Prospective multi-centre study	Hospital inpatients and outpatients Australia	46	Unknown reaction >10 years ago or date cannot be recalled Type A adverse reaction Maculopapular exanthem >10 years ago or isolated non-urticarial rash or benign childhood rash Validated assessment tool	Penicillin VK 250 mg or amoxicillin 250 mg based on implicated drug Patients with history of delayed hypersensitivity were given 5-day challenge with same drug	Patients observed for 2 h following administration of drug.	Screened by antibiotic allergy nurse or ID physician Allergy service Nurse supervised challenge	No adverse reactions reported

Li *et al.* (2019)[23] Prospective single-centre clinical case series with retrospective control group	General wards Australia	7	Type A reaction (nausea, abdominal pain, vomiting, diarrhoea) Clinical history review	3 day course of amoxicillin	30 min observation after each dose until final dose then 2 h observation.	Assessed by allergist and allergy nurse Allergy nurse or registrar	No adverse reactions reported
Stevenson *et al.* (2020)[32] Retrospective multi-centre cohort study	7 Hospital immunology outpatient clinics Australia	167	Benign immediate or delayed rash (without mucosal involvement) >1 year ago identified as optimal definition of low risk Assessment of methods used to determine low risk	1 or 2 doses e.g. 1/10, full dose amoxicillin or culprit drug if known	Minimum 30 min observation between doses and 1 h after the final dose. Telephone follow-up 3 to 7 days	Challenge administered by staff trained to manage anaphylaxis	3 immediate reactions 3 reacted later on day of testing No life-threatening reactions
Lin *et al.* (2020)[24] Prospective single-centre cohort study	General wards Netherlands	42	Delayed onset of Rash, rhinitis, gastrointestinal symptoms >12 months ago OR ≤2 symptoms considered moderate risk (e.g. urticaria, oedema, mild dyspnoea, fever, indication for hospitalization) >10 years ago Risk assessment tool developed from published work	DOC 500 mg amoxicillin or 500 mg/125 mg amoxicillin-clavulanic acid depending on preferred treatment.	60 min observation following administration	Screened by treatment physician or pharmacist assistant. Medical supervision of challenge	2 non-severe skin reactions
Tucker *et al.* (2017)[30] Retrospective chart review	Marine recruit depot US	328	Low risk not defined. Exclusion criteria defined as serious cutaneous reactions Risk assessment based on history—no structured tool	250 mg amoxicillin	Not reported	Assessed and challenged by allergist/medical centre staff	5 (1.5%) acute objective challenge reactions –4 isolated cutaneous reactions 1 included globus. All treated with oral antihistamine and single dose of IM epinephrine—no anaphylaxis
Chua *et al.* (2020)[29] Prospective 2 centre study	General and cancer wards Australia	200	Unknown reaction >10 years ago Type A adverse drug reaction (where direct delabelling not accepted by patient)	250 mg penicillin VK or 250 mg amoxicillin	2 h	Screened and assessed by trained nurses, pharmacist or medical staff	3 non-immune mediated reactions No immune-mediated reactions during 2 h challenge.

Continued

Table 3. *Continued*

Study	Clinical setting/ country	Sample size	Low risk criteria/assessment tool used	Type of challenge	Length of observation/follow-up	Staff involved	Results
			History of unspecified childhood rash, localized injection site reaction (only), or maculopapular exanthem >10 years ago Validated assessment tool				3 patients reported probably T cell mediated reaction occurring between 5–7 days after OC

Abbreviations: RCT, randomized controlled trial; OC, oral challenge; DOC, direct oral challenge; ID, infectious diseases; EMR, electronic medical record; SPT, skin prick test; IM, intramuscular; IV, intravenous; SAP, surgical antibiotic prophylaxis; GP, general practitioner.

group experienced 8.7% fewer positive results than those randomized to the SPT plus OC group ($P = 0.079$). In addition, four studies reported that patients assessed as very low risk were directly delabelled.[21,22,25,29]

In seven studies, inpatients who required antibiotics for surgical prophylaxis or treatment of an infection where penicillin was the preferred option were switched to penicillin immediately or prescribed penicillin after the direct oral challenge.[21,24–29] Three studies reported that patients who had subsequently completed treatment with penicillin sometime after the challenge experienced either no adverse effects or only mild, delayed symptoms that self-resolved and did not preclude the completion of treatment.[22,28,30] The penicillin allergy label was reported as removed from patients' electronic medical record.[21,30] In one study participants' GPs confirmed that 47/55 (85%) patients had the correct revised allergy status recorded on their medical files,[27] however in another study only 33% of patient medical records had been updated to reflect the correct allergy status.[23]

Discussion

The aim of this review was to investigate the safety and efficacy of direct OC for the removal of an unverified penicillin allergy label. Analysis of the studies included in the review demonstrates that in patients assessed as having a low risk of true allergy to penicillin, based on their allergy history, direct oral challenge can be carried out safely and is effective for de-labelling patients with unverified allergy labels. Two earlier reviews support the need for non-specialist evaluation of penicillin allergy and the safety of direct OC in low-risk individuals.[2,15]

Use of a structured process or algorithm to standardize how an allergy history was taken was a key component of assessment by both allergists and non-specialists in most of the included studies. Clear guidelines, validated tools and training of generalist care providers in accurately assessing patients' allergy history is essential to ensure patient safety during direct OC.[33] It should be noted that only patients who were assessed as low risk according to individual study criteria were offered direct OC. Those who reported a recent allergy reaction and those reporting serious symptoms associated with IgE-mediated hypersensitivity were deemed high risk and direct OC was not offered. This group of patients were advised to continue to avoid using penicillin or referred for specialist allergy assessment. In addition to reducing the need for specialist input, using direct OC to remove an unverified penicillin allergy label requires less staff and patient time, and less equipment, than SPT or IDT, making it less expensive overall.[26,34] Studies in this review have also demonstrated that with the correct training in assessment and administration processes, direct OC could be delivered in non-specialist settings. Given that four studies reported that very low-risk patients were de-labelled based on history alone,[21] it may be prudent to include training on direct de-labelling for non-specialists.

Multiple benefits are derived from removal of an inappropriate penicillin allergy label. The most commonly reported clinical benefit is a change of antibiotic therapy,[21,24–29,35] thus where a β-lactam is the preferred treatment patients are more likely to receive the most appropriate therapy,[33,36,37] which in turn reduces inappropriate use of antibiotics classified as Watch or Reserve by the World Health Organisation.[38]

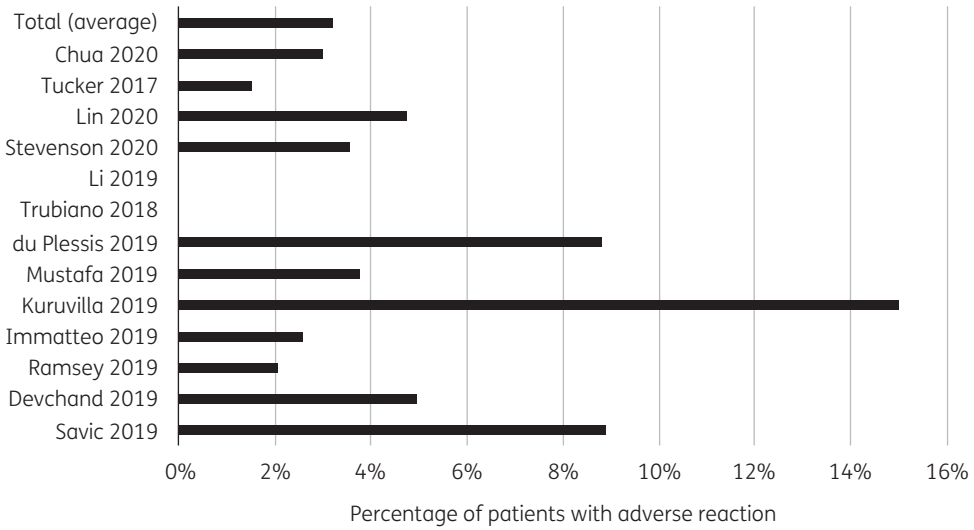

Figure 2. Percentage of patients with adverse reaction to direct OC.

Decreased use of broad-spectrum non-penicillin antibiotics reduces direct drug costs[25,26,37,39] and length of hospital stay, with an associated reduction in healthcare costs.[11,25] A recent study in the UK estimated that de-labelling 50% of patients with a self-reported penicillin allergy would save £5501 in antibiotic drug costs and £503 932 in reduced excess bed days annually in one large hospital.[13] Long-term follow-up to determine accurate update of patient records and patient understanding of de-labelling is also important to ensure patients continue to receive optimal antibiotic treatment.[40]

Eleven of the studies in this review used a standardized questionnaire or screening tool to assess the patients' history to determine risk of true allergy. The two studies that assessed patients on clinical history alone were carried out by allergy specialists. While elements of the tools were similar across the studies, only three were reported as validated. Devchand *et al.*[41] recently validated a tool designed to be used by non-specialist clinicians to assign an accurate phenotype and management strategy for patients reporting penicillin allergy. Adoption of a validated tool and provision of appropriate training could increase the confidence of non-specialist clinicians in assessing, testing and de-labelling patients with unverified penicillin allergy, which will contribute to antimicrobial stewardship.

The inclusion of only one RCT could be considered a limitation of this review, therefore further RCTs are required to demonstrate the safety of de-labelling with direct OC in low-risk patients. The majority of included studies were single-arm observational studies, which prevented assessment of the comparative safety of direct OC for de-labelling penicillin allergy. Six of the included studies were conducted by allergists, thus perhaps limiting replication of these results by non-allergy specialist clinicians, therefore future studies with direct OC conducted by non-specialists should be considered. Additional limitations concerning the review process include the language restriction to papers in English, the validity of pooling studies conducted in different settings and patient groups, or using different methods of direct oral challenge and combining subjective and objective measures of reactions.

Further longitudinal studies should be carried out to address the effects of de-labelling on subsequent use of antibiotics, allergy status documentation, hospital admissions and associated costs.

Conclusions

Patients with an unverified penicillin allergy should be investigated, especially those who require (or are likely to require) treatment with an antibiotic. Following careful screening using a standardized approach by trained (non-allergy specialist) clinicians, patients deemed at low risk of true allergy to penicillin can safely be offered direct OC and effectively de-labelled if appropriate. Non-specialist clinicians should be empowered to safely undertake the assessment of patients to risk stratify those for whom direct OC is appropriate. These measures will support antimicrobial stewardship, facilitate optimal infection management, and support other efforts to reduce antimicrobial resistance.

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Transparency declarations

None to declare.

Supplementary data

The search strategy is available as Supplementary data at *JAC-AMR* Online.

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