



The role of a clinical pharmacist in spurious Penicillin allergy: a narrative review

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Abstract

Background A label of penicillin allergy is held by 6–10% of the general population and 15–20% of inpatients. > 90% of these labels are found to be spurious after formal allergy assessment. Carrying an unnecessary label of penicillin allergy is not benign. Such patients may receive second line, more expensive antibiotics, representing a significant impediment to antimicrobial stewardship. **Aim of the review** To (a) Explain the burden of spurious penicillin allergy, and evaluate the safety of direct oral penicillin challenge in ‘low risk’ patients (b) appraise the place for a clinical pharmacist-led penicillin allergy de-labelling programme. **Method** Narrative review. Search engines: PubMed, Google Scholar and Cochrane reviews. Search criteria: English language; search terms: penicillin allergy, antimicrobial stewardship, antimicrobial resistance, clostridium difficile, vancomycin resistant enterococci, risk stratification, clinical pharmacist and direct oral provocation test **Results** Penicillin allergy labels are associated with: longer hospital stay, higher readmission rates, enhanced risk of surgical site infections, risk of *Clostridioides difficile* infection and Methicillin resistant *Staphylococcus aureus* infection, a delay in the first dose of an antibiotic in sepsis and higher healthcare costs. A direct oral penicillin challenge in ‘low risk’ patients has proven to be safe. **Discussion** Recent studies including those led by a clinical pharmacist have demonstrated safety of a direct oral penicillin challenge in ‘low risk’ patients. This intervention needs validation within individual health services. **Conclusion** Direct oral penicillin challenge reduces the adverse impact of spurious penicillin allergy. A pharmacist-led penicillin allergy de-labelling program needs further validation in prospective multi-centre studies.

Keywords Antimicrobial stewardship · Clinical pharmacist · Direct oral amoxicillin challenge · Penicillin allergy

Impacts on practice

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- Patients with spurious penicillin allergy labels receive alternative non-beta-lactam antibiotics, contributing to suboptimal antimicrobial stewardship, antimicrobial resistance and higher healthcare costs.
- There is emerging evidence for the safety of a direct oral penicillin challenge procedure as a means to de-label ‘low risk’ patients with spurious penicillin allergy following a process of systematic clinical risk stratification.
- Clinical Pharmacists are ideally placed in secondary care to deliver a direct oral penicillin challenge procedure. By providing this service pharmacists will broaden the breadth of services they can offer as well as support the unmet need for allergy specialists in delivering this service.

- Recent studies support the role for a clinical pharmacist-led penicillin allergy de-labelling program that is supported by a multidisciplinary team and with robust governance measures in place. This service will allow patients with a spurious penicillin allergy to access first-line empirical beta-lactam antibiotics, thereby improving antimicrobial stewardship, reducing hospital stay and reducing overall healthcare costs.

Introduction

Spurious penicillin allergy (PenA) and its impact on antimicrobial resistance (AMR) has been a key target for antimicrobial champions, leading antimicrobial stewardship (AMS) strategies [1–5]. Patients with a PenA label pose clinical challenges with respect to timely choice of an alternative antibiotic, especially if admitted under a sepsis pathway. Antibiotic allergy labels have consequences for patients that are both ecological and economic [5].

AMR is recognised as a global public health problem and causes approximately 700,000 deaths a year globally owing to untreatable infections [1]. The UK five-year plans (2019–2024) for tackling AMR reflect and align with the global AMR action plan to promote and embed good AMS practices worldwide [1].

Beta lactam antibiotics include penicillins, cephalosporins, monobactams and carbapenems. Penicillins are often recommended as empirical treatment choices for a wide spectrum of infections, including sepsis of unknown source.

‘Spurious’ PenA labels describe a situation where the patient is in fact clinically tolerant to penicillins. A spurious PenA label may be related to a mislabelled adverse reaction in childhood, an ‘indeterminate’ (or vague) clinical history or incomplete information of an index episode. However, in some cases, patients may be reporting a ‘true’ allergy that may be clinically characterized [6, 7]. In the vast majority of cases, a label of PenA is a contraindication to receiving penicillins. These patients are prescribed alternative less preferable, expensive antibiotics, including fluoroquinolones, glycopeptides, daptomycin, linezolid, macrolides, chloramphenicol and in some instances cephalosporins [3, 8, 9] often leading to adverse clinical outcomes. From a health economic viewpoint, PenA labels lead to higher healthcare costs in the order of several million US dollars each year [5, 10, 11].

PenA labels may be broadly categorised as immunological and non-immunological reactions [7], the former also termed as hypersensitivity reactions (HSRs). In 1968, Gell and Coombs classified HSRs into 4 categories, Type I to Type IV reactions [12].

In clinical practice, ‘true’ PenA’s are usually either ‘immediate (IgE mediated) HSR or ‘non-immediate HSR’

(independent of IgE, mediated by T cells) [7]. Immediate HSRs usually occur within an hour of exposure to penicillin, however non-immediate/delayed HSRs occur > 1 h after exposure, usually during a course of treatment.

Type I (IgE mediated) HSRs usually manifest with one or more of the following: urticaria (or ‘hives’), angioedema (soft tissue swelling), bronchospasm (wheeze), rhinoconjunctivitis (hay fever type symptoms) and in severe cases, as anaphylaxis (severe allergic reaction with cardio-respiratory compromise involving low blood pressure). Type II and III HSRs are extremely rare and may manifest as haemolysis, vasculitis, or acute renal failure. Delayed (non-immediate) or type IV HSRs are most common and manifest as a maculopapular rash. Other rare and severe systemic forms of non-immediate HSRs include Steven-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis and drug rash with eosinophilia and systemic symptoms syndrome.

Aim of the study

The aim of this narrative review is to: (a) describe the burden and impact of PenA labels on AMS and critically appraise processes for rapid PenA de-labelling following appropriate risk stratification of patients (b) consider the role for a clinical pharmacist in leading PenA de-labelling programmes supported by a multidisciplinary team in hospital based care environments.

Method

A narrative review of international literature was conducted in accordance with the project aims. Review databases searched were PubMed, Google Scholar and Cochrane reviews. The following search criteria were devised by consensual discussion between RB, TK and JM and were refined according to each database key terms: “penicillin allergy”, “antimicrobial stewardship”, “antimicrobial resistance”, “Clostridium difficile”, “vancomycin resistant enterococci”, “risk stratification”, “clinical pharmacist” and “direct oral provocation test”. The searches considered outputs between 2010 and 2020 and were limited to those in English language. A total of 42 outputs were found addressing elements of the project aims when reviewed by RB and ratified by co-authors. A further 17 outputs were identified, reviewed and included from references listed in these publications.

Results

It is estimated that 6–10% of the population and nearly 15–20% of inpatients carry a PenA label [9, 13–17]. However, a ‘true’ allergy can be confirmed only in 5–10% of

these patients [9, 13–17]. A vast majority of patients with PenA labels give a history that is not consistent with an immunologically mediated response e.g. headache, diarrhoea, ‘benign rash’ (see Table 1). A significant proportion of patients report a non-life-threatening childhood episode of an indeterminate nature. Some patients report an ‘allergy’ on the basis of a family history, despite no exposure to penicillin. We and others have also reported that, despite 20–30% of patients with a PenA label having received penicillins without an adverse consequence subsequent to their documented index event, their allergy record was not updated [6, 8, 11, 17, 18]. These patients constitute ‘spurious’ PenA labels.

PenA testing involves specialist review comprising a comprehensive assessment including a systematic clinical history, review of previous clinical/prescription records, skin tests and (if negative) a supervised oral penicillin challenge.

This process is onerous, time consuming and resource dependent. In most countries, PenA tests are not routinely available.

Emerging evidence from the UK, USA, Canada, New Zealand and Australia strengthens the case for a ‘Direct Oral Penicillin Challenge’ (DPC) in PenA de-labelling [11, 18–24]. This describes administration of a supervised oral dose of a penicillin in a patient with a PenA label without undertaking allergy tests. DPC requires a risk stratification process that involves obtaining a standardised, focused clinical history of the index reaction to allow categorisation to ‘low risk’ or ‘high risk’ (see Table 1). ‘Low risk’ patients represent those with a history inconsistent with an immune-based reaction, making it highly unlikely that they are ‘truly allergic’ and may be appropriate for a DPC. Studies involving DPC have been reported (see Table 2) to be safe. These

Table 1 Risk stratification of a penicillin allergy label [6, 28, 40, 43, 44]

	Penicillin allergy label risk stratification		
	Low	Medium	High*
Symptoms from allergy history	<i>Non-immunological reactions</i> Headache Gastrointestinal disturbances ‘Benign’ rash Pruritis with no description of a rash Family history of penicillin allergy only, i.e., with no history of reaction <5 years elapsed since reaction (score 2) >10 year elapsed, history of non-IgE mediated reactions Tolerated penicillin/s since index episode Treatment given for reaction (score 1)	<i>Mild-moderate with symptoms in keeping with an IgE mediated reaction but not anaphylaxis:</i> Cardio-respiratory: mild symptoms such as chest tightness, wheezing, shortness of breath or bronchospasm, presyncope/syncope Cutaneous: pruritis with rash, flushing, urticaria, mild angio-oedema Treatment given for reaction (score 1) <5 years elapsed since reaction (score 2)	Anaphylaxis (score 2) Severe cutaneous skin reaction (score 2) Positive allergy skin tests Treatment given for reaction (score 1) <5 years elapsed since reaction (score 2)
PEN-FAST score	0–2	3	4–5
Patients’ clinical status	No significant co-morbidities stable haemodynamic and respiratory status Not pregnant	Co-morbidities such as significant haemodynamic or respiratory compromise e.g. Unstable angina, asthma, COPD etc Pregnant	
Management	Seek patient consent Clinical pharmacist led Direct oral Penicillin Challenge as per protocol with medical cover in a safe clinical environment with immediate access to treatment of anaphylaxis	Allergist / immunologist referral: Skin testing DPC, if negative skin tests Microbiologist / ID consultant input for rationalisation of infection management options	Allergist / immunologist referral: Consider desensitisation Microbiologist / ID consultant input for rationalisation of infection management options
Communicate outcome with primary care and update patient’s allergy status in both primary and secondary care records			
Counsel patient/patient representative about outcome and changes to allergy status			

IgE Immunoglobulin E, *COPD* Chronic obstructive pulmonary disease, *DPC* Direct oral penicillin challenge, *ID* Infectious diseases physician, *TENS* Toxic epidermal necrolysis, *DRESS* Drug reaction with eosinophilia and systemic symptoms

*Exclusions for consideration of beta-lactam antibiotic exposure include: severe cutaneous reactions e.g. Steven Johnson’s syndrome, TENS, DRESS, haemolytic anaemia, serum sickness or a reaction involving organ damage e.g.: acute interstitial nephritis or acute renal failure

studies involved both allergy specialists and non-allergy specialists, in both inpatient and outpatient settings; a few studies involved clinical pharmacist-led multidisciplinary teams.

There are international consensus statements supporting the use of DPC in a clinically safe and controlled environment for ‘low risk’ patients with a PenA label [23, 24]. This approach is well established in Partners Healthcare Systems, Boston, USA where approximately 1000 challenge procedures are carried out annually [23]. Their projected cost saving is \$8.3–13.4 m USD *per annum* [11]. We reported an excess spend of 250–500 k GBP *per annum* on alternative antibiotics in patients with PenA labels in a single large National Health Service (NHS) hospital in Birmingham, UK [17].

The pre-requisites for a DPC are summarised in Fig. 1. Implementation of DPC depends on multiple factors including favourable uptake by patients, healthcare professionals, a robust fit for purpose clinical governance framework, training of relevant personnel and appropriate audit tools. Further studies in different countries and healthcare systems are warranted to ascertain the attitudes of healthcare professionals and patients towards DPC. Understanding the facilitators and barriers in implementing DPC would be a key determinant for the success of this approach [25].

The UK 5 years strategy (2019–2024) outlines key priorities in tackling AMR [1]. The 2020/21 NHS contract requires hospitals to reduce overall antibiotic usage year on year within the contractual agreement [4]. Hospitals in the UK aim to meet these contractual requirements within recommendations from National Institute for Health and Care Excellence (NICE) [26] and the national Start smart then focus for good AMS [2].

The key principles of AMS [2, 26] include starting empirical antibiotic therapy within one hour for patients on the sepsis pathway, after obtaining a drug allergy history. Relevant microbiological cultures must be taken at this stage. After 48–72 h, antimicrobials must be reviewed to (1) de-escalate to narrower spectrum agents (2) change an antibiotic if needed owing to resistant organisms (3) encourage early switch from intravenous (IV) to oral antibiotics or (4) if no evidence for a bacterial infection, stop all antibiotics [2].

We have recently reported that the time to administration of the first dose of antibiotics in sepsis is delayed in patients with a PenA label, resulting in inferior emergency care on admission [27]. Patients with a PenA label received more expensive or inferior non beta-lactam antibiotics and had higher antibiotic usage in comparison to non-PenA patients [5, 27, 28]. Another study involving a retrospective medication chart review showed that the time to first dose of antibiotic treatment when admitted via emergency department is delayed by approximately 50 min in patients with a PenA label compared to non-PenA patients [29]. Although this finding did not adversely affect the overall clinical

outcomes of patients, for each hour of delay in the first dose of antibiotic treatment for patients with acute sepsis or septic shock, there is a proven increase in mortality [2, 30]. This study also showed that PenA patients were more likely to receive fluoroquinolones, cephalosporins, ‘other antibiotics’ and carbapenems [29]. Macy and co-workers showed similar antibiotic prescribing in PenA patients with the addition of vancomycin, clindamycin and aminoglycosides [10]. PenA patients were also 18% less likely to be de-escalated from broad to narrow spectrum antibiotics. In practice this encourages multi-drug resistant infections and poorer clinical outcomes for patients.

A retrospective matched cohort study evaluated the impact of a PenA label on antibiotic treatment for community onset gram negative bloodstream infections (GNBSI) before and after AMS interventions [31]. This study showed that patients with a PenA label are more likely to be prescribed carbapenems empirically for GNBSI. However, in the post-intervention phase, the median time to de-escalation of carbapenems was much shorter [31]. Carbapenems are often referred to as life-saving antibiotics and are recommended as treatment options in patients who have a PenA label or multi-drug resistant organisms such as an extended spectrum beta-lactamases. The widespread empirical use of carbapenems in patients with spurious PenA labels can enhance the risk of colonisation with carbapenemase producing enterobacteriaceae (CPE) organisms or further increase the risk of infections with resistant organisms. CPEs are an iatrogenic infection which pose a major threat to healthcare systems owing to an increase in morbidity, mortality and associated healthcare costs. There is a global increase in CPE isolates [32].

A recent UK population-based cohort study [33] examined the relationship between a confirmed diagnosis of *Clostridioides difficile* infection (CDI) or Methicillin resistant *Staphylococcus aureus* infection (MRSA) in patients with a PenA label compared to those without a PenA label. Patients with a PenA label received alternate inferior antibiotics such as macrolides, clindamycin or fluoroquinolones and had a 55% and 35% enhanced risk of MRSA and CDI respectively. Macy and co-workers [10] also reported in a matched cohort study of patients with and without a PenA label, that there was an enhanced incidence of CDI, MRSA and VRE in the PenA group.

Surgical patients with an inaccurate PenA label can have adverse clinical outcomes post-operatively. A retrospective study examined the risk of a surgical site infection (SSI) in patients with and without PenA labels who had undergone hip arthroplasty, knee arthroplasty, hysterectomy, colon surgery and coronary artery bypass grafting [34]. They reported that a PenA label can enhance the odds of a SSI by 50% [34]. Patients received clindamycin, vancomycin and gentamicin instead of penicillins for surgical prophylaxis [34]. A recent

Table 2 Literature review for direct oral penicillin (DPC) challenges

Publication	Country	Clinical setting	Patient population	Specialist or non-specialist	Mean age in years with SD/range	Clinical outcome with comments
Blumenthal et al. 8	USA	Inpatient	Two patient populations: 21 months pre-guideline phase n = 49 12 months post-guideline phase n = 183 A guideline was implemented to support antibiotic prescribing for patients with a penicillin allergy and encourage beta-lactam test doses without an allergy or infection specialist	Non-specialist	Pre-guideline phase: 58.7 Post-guideline phase: 59.9	A standardised guideline encouraged an increase in beta-lactam test doses for empiric treatment Beta-lactam test doses were prescribed a median of 2 days into the patient's hospital stay after the guideline was implemented in comparison to a median of 4 days into the patient's hospital stay In the post guideline phase, there was a significant increase in penicillin (79% of these patients had a primary penicillin allergy) and cephalosporin prescriptions (generation 1, 3 and 4). Fewer patients were on vancomycin, aminoglycosides, aztreonam and fluoroquinolones No significant difference in the adverse drug reaction rate in the pre- and post-guideline phase
Bourke et al. 45	Australia	Outpatient	N = 401 Patients with a penicillin allergy label underwent skin prick testing, intradermal testing and if negative an oral challenge to assess the efficacy and safety of these allergy tests and to devise a risk stratification protocol. Patient adherence to the allergy label modification was used as a marker for effectiveness of testing	Specialist	47.4 (15–85 years)	From 401 patients recruited, 151 patients had an immediate penicillin-related index reaction and 250 patients had a non-immediate index reaction 355 patients had an oral challenge with penicillin VK. 3 patients with an immediate index penicillin allergy history had a positive oral challenge (NPV 99.2%) Positive oral challenges were higher in patients who were given amoxicillin (4/64 6.25%) and cephalexin (13/91 14.3%) Oral challenges with co-amoxiclav and flucloxacillin were all negative Positive oral challenge reactions were all mild skin or subjective reactions and were noted within 45 min of the challenge

Table 2 (continued)

Publication	Country	Clinical setting	Patient population	Specialist or non-specialist	Mean age in years with SD/range	Clinical outcome with comments
Mill C et al. 46	Canada	Outpatient	N=818 A graded provocation challenge was offered to all children referred to the allergy clinic for a possible amoxicillin allergy	specialist	1.7 years	770 patients were tolerant to a graded oral provocation challenge 17 patients suffered an immediate reaction. Reactions were non-severe and the most common reaction was hives. 5 patients reacted within 20 min with 10% of the dose 31 patients suffered a non-immediate reaction. Reactions were non-severe and the most common reactions were macular / papular rash or angioedema. 9 children had a reaction > 24 h after the graded oral provocation 250 patients responded to an annual follow up. 55 patients received amoxicillin treatment, from these 6 patients had a delayed skin reaction The graded provocation test had a specificity of 100%, a negative predictive value of 89.1% and a positive predictive value of 100%
Tucker et al. 47	US	Outpatient	N=402 N=74: skin testing and oral amoxicillin challenge N=328: direct oral amoxicillin challenge A retrospective chart review of a direct oral amoxicillin challenge for marine recruits, who reported a non-severe penicillin allergy	Specialist	18–25 years	No reaction was seen in the 74 patients who underwent skin testing and oral amoxicillin challenge 5 (1.5%) patients reacted to an oral challenge of amoxicillin. No anaphylaxis, 3 patients suffered from hives or a rash and in 2 patients the reaction was unknown

Table 2 (continued)

Publication	Country	Clinical setting	Patient population	Specialist or non-specialist	Mean age in years with SD/range	Clinical outcome with comments
Confino-cohen et al. 48	Israel	Outpatient	N=642 (Children < 18 = 435 and adults > 18 = 207) Patients with history of non-immEDIATE reactions to beta-lactams were offered a graded oral penicillin challenge and then discharged with 4 days of the penicillin treatment. This is independent of the skin test result	Specialist	Children: 5.2 ± 4.6 Adults 48.4 ± 18	25 patients did not consent to an oral challenge due to anxiety or lack of an on-going infection On day 1, immediate mild rashes were seen in 9 patients after the higher dose of the graded oral challenge. Late onset mild rashes were seen in 24 patients 93 patients refused to persevere with a 5 day oral challenge -5 day oral challenge was well tolerated in 417 patients and 30 patients experienced mild rash, pruritus or abdominal discomfort
Savic et al. 19	UK	Outpatient	N=74 Surgical pre-assessment patients who required penicillin for surgery and described 'low risk' symptoms after taking a penicillin	Non-specialist	Not stated	56 patients in total underwent a direct oral amoxicillin challenge No immediate or serious delayed reactions were seen 1 patient stopped taking amoxicillin after the second dose due to urticaria. Upon questioning, this was similar to the index reaction which wasn't declared by the patient at the start of the study 4 patients experienced nausea, sore throat and an exacerbation of arthralgia. There were a high number of ineligible patients (n = 145). In 50% of these patients, this was due to not consenting to a direct oral challenge The most common reason for refusing testing was 'would never take penicillin whatever the result'

Table 2 (continued)

Publication	Country	Clinical setting	Patient population	Specialist or non-specialist	Mean age in years with SD/range	Clinical outcome with comments
Ibanez et al. 49	Spain	Outpatient	N=732 The primary objective was a comparison of the results of commonly used diagnostic protocols to investigate penicillin allergy (clinical history, skin prick test, intradermal test, serum specific IgE to aminopenicillins and its determinants) to the results of a direct oral drug provocation test	Specialist	5.5 (± 3.8)	All patients with an immediate index reaction to penicillin's (classified as a reaction occurring in the first hour after taking the first dose of a penicillin) did not have a reaction to a direct oral drug provocation test The first drug provocation test was positive in 34 patients. 5 of these patients had a second drug provocation test, from which only 3 patients had a positive result After the first drug provocation test 6 patients had immediate reactions and 28 patients had non-immediate reactions. There were no severe reactions. Treatment of the reactions included oral antihistamines, oral corticosteroids and intramuscular corticosteroids. One patient received intramuscular adrenaline and salbutamol 6.2% of patients would have been misdiagnosed as having a true penicillin allergy if a direct oral drug provocation test had not been used in addition to clinical history, skin prick test, intradermal test and serum specific IgE test

Table 2 (continued)

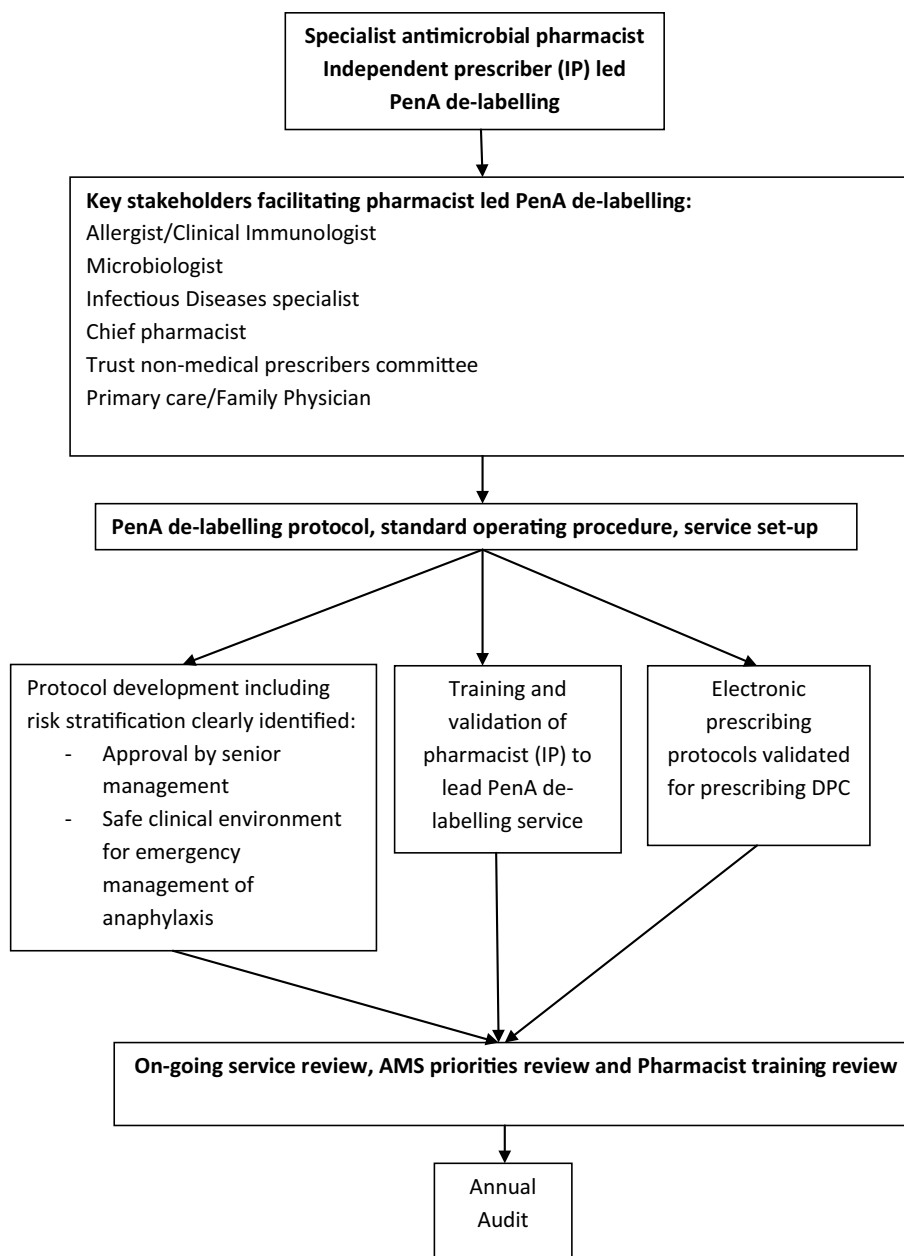
Publication	Country	Clinical setting	Patient population	Specialist or non-specialist	Mean age in years with SD/range	Clinical outcome with comments
Labrosse et al. 50	Canada	Outpatient	N=130 Paediatric patients with a noted allergy to amoxicillin or co-amoxiclav were referred for a direct oral challenge, followed by an ongoing 4 day course of amoxicillin if the initial oral challenge result was negative	Specialist	5.1 (0.7 – 17.0)	3/130 (2.3%) of patients had mild immediate reactions within an hour of taking oral amoxicillin. The mild reactions included urticaria and pruritis 127 patients had a prolonged 4 day course of oral amoxicillin. 3 patients had non-immediate maculopapular or papular rashes. 3 patients experienced an equivocal reaction, these patients were re-assessed and found to be negative After 2 years 114 patients were followed up. 67 patients had used amoxicillin and 8 patients received non-beta lactam antibiotics and amongst these patients, 1 patient refused to receive penicillin's due to fear of a repeat allergy reaction Most patients with a negative 5 day oral challenge of amoxicillin tolerated subsequent amoxicillin doses. However, 3 patients experienced mild delayed skin reactions
Iammatteo M et al. 51	USA	Outpatient	N=155 Patients who did not have a life-threatening reaction to penicillin's were offered placebo followed by a graded direct oral challenge	specialist	No reaction group: 51.8 ± 1.85 Non allergic reactions group: 48.3 ± 3 Allergic reactions group: 54.3 ± 13.3	120 patients had no reaction 15 patients reported non-allergic reactions after amoxicillin challenge 16 patients reported non-allergic reactions to placebo 4 patients reported pruritis and non-immediate rash within 24hours of the oral challenge

Table 2 (continued)

Publication	Country	Clinical setting	Patient population	Specialist or non-specialist	Mean age in years with SD/range	Clinical outcome with comments
Mustafa et al. 20	US	Outpatient	N=185 A prospective randomised controlled trial comparing 2 arms: penicillin skin testing followed by an amoxicillin challenge vs a 2 step direct oral amoxicillin challenge in 'low risk' penicillin allergic patients who did not undergo prior penicillin skin testing Patients excluded from the randomised cohort (n=159): 13 children under 5 years of age underwent direct oral challenge and 13 patients with a high risk IgE mediated penicillin allergy history underwent penicillin skin testing followed by oral amoxicillin challenge	Specialist	Randomised cohort: Penicillin skin testing and amoxicillin challenge group n=80, mean age 39.6±24.8 2 step direct oral amoxicillin challenge group n=79, mean age 36.8±25.2	The most common reported penicillin allergy reaction history included rash, urticaria and intolerance to penicillin Non randomised cohort: 13/185 patients <5 years old had a direct oral amoxicillin challenge. 100% were de-labelled for penicillin allergy 13/185 patients >5 years had penicillin skin testing. Only 2/13 patients had a positive penicillin skin test and 11/13 patients had a negative penicillin skin test Randomised cohort: A higher number of positive penicillin allergy tests were seen in patients randomised for penicillin skin testing (not statistically significant): 10/80 patients had a positive skin test compared to 3/79 patients who had a positive direct oral amoxicillin challenge. No systemic reactions were noted with penicillin skin testing. Cutaneous reactions were seen in patients who had the direct oral amoxicillin challenge, these were treated with oral antihistamines 76/79 patients had a negative direct oral amoxicillin challenge and 70/80 patients had a negative penicillin skin test A cost analysis showed that direct oral amoxicillin challenges in 'low risk' patients cost less than a penicillin skin test

SD standard deviation, USA United States of America, UK United Kingdom, Penicillin VK phenoxymethylpenicillin, NPV negative predicted value, IgE Immunoglobulin E

Fig. 1 A Proposal for Framework for Clinical Pharmacist led DPC for 'low risk' PenA patient Figure 1 is for the following manuscript: The role of a Clinical Pharmacist in Spurious Penicillin Allergy: A Narrative review. *DPC* direct oral penicillin challenge, *PenA* penicillin allergy, *IP* independent prescriber, *AMS* antimicrobial stewardship



National Audit Project-6 (NAP6) conducted by The Royal College of Anaesthetists of the UK reported that patients with PenA label are more likely to receive teicoplanin peri-operatively, which carries a higher relative risk of peri-operative anaphylaxis [35].

A recent alert from the UK Medicines and Healthcare products Regulatory Agency warned that use of fluoroquinolones may be associated with a small but enhanced risk of aortic aneurysm and dissection [36]. Other antibiotics such as clindamycin may increase the risk of acquiring CDI infection and vancomycin requires therapeutic drug level monitoring which cannot be offered as an outpatient, thus increasing the length of hospital stay.

Patients with a PenA label usually receive alternative inferior antibiotics that can lead to adverse clinical outcomes and increase healthcare costs in the order of several million US dollars annually.

In the UK, specialist senior clinical pharmacists have been embedded into the delivery of AMS across primary and secondary care [37–39]. Roles and responsibilities include: (1) intensive bedside review of antimicrobial treatment, (2) antimicrobial guideline development, (3) antimicrobial formulary development, (4) facilitating outpatient antimicrobial treatment for home services, (5) educating healthcare professionals on safe and appropriate use of antimicrobials, (6) public engagement and increasing

awareness of the global threat of AMR, (7) specialist roles such as independent prescribing for antimicrobials, (8) antimicrobial governance across the whole health economy and (9) monitoring antimicrobial usage in line with local and national antimicrobial surveillance.

Clinical Pharmacists have been recognised as key members of AMS ward rounds within a multidisciplinary team including infectious diseases specialists, microbiologists and infection prevention and control nurses. Therefore, can we empower clinical pharmacists with appropriate training to de-label 'low risk' PenA patients?

Safe PenA de-labelling includes a robust risk stratification process, standardised informed consent procedures, a safe and controlled clinical environment to undertake a DPC with appropriate medical cover in the unlikely event of an adverse reaction, a 'fit for purpose' information technology (IT) system, counselling of the patient/carer following completion of DPC and communication of the outcome in writing to the family physician to update records in primary care.

Clinical pharmacists are well placed in a secondary care setting to facilitate and lead PenA de-labelling. Risk stratification could be standardised on a proforma, preferably in an electronic format, so that data can interface with electronic patient records to maintain an audit trail. The proforma should allow capture of key information relating to PenA and comorbidities facilitating stratification of patients into 'low', 'medium' and high risk' categories (Table 1). The former could then undergo a DPC in accordance with a standardised protocol. In a recent study, a PEN-FAST risk stratification protocol was validated to facilitate a robust point of care scoring test [40]. The test was found to have a high negative predictive value of 96.3% [40] and therefore should be considered for risk stratification of patients.

In the UK, amoxicillin seems an appropriate target for DPC, as it is the most commonly prescribed penicillin antibiotic and factors in the possibility of 'side chain reactivity' [41]. A single dose of 500 mg can be administered orally after checking baseline vital parameters including heart rate, blood pressure and peak expiratory flow rate. The patient is monitored for an hour post-DPC and the outcome is clearly documented. In those reporting an indeterminate history or when temporal association of the index episode is unclear, a relatively prolonged course of 250 mg twice daily for 2–3 days is prescribed. Patients are followed up on day 5 to ascertain clinical tolerance and exclude a non-immediate HSR [6, 18]. Those stratified as 'medium or high risk' are treated with alternative choice of antibiotics and referred to an allergy specialist for further assessment.

A standard operating procedure and a multidisciplinary team (internist, microbiologist, infectious diseases physician and allergist) with individual roles and responsibilities clearly laid out in a terms of reference document are

imperative so that clinical pharmacists are medico-legally covered to undertake risk stratification and DPC (see Fig. 1).

Whilst this approach is promising and seemingly a logical way forward with emerging evidence from several countries [11, 18–24], further research is warranted in prospective multi-centre studies involving larger sample sizes.

Discussion

The core skills of a pharmacist including drug history taking, prescribing and counselling are paramount for PenA de-labelling. Pharmacist independent prescribers (IPs) have a recognised operating framework from the pharmacist professional governing body in the UK [42]. In secondary care, pharmacist IP roles are well established and embedded into clinical services. At a national level, pharmacists are recognised as key stakeholders for AMS with established roles in consultant pharmacist-led or independent pharmacist-led antimicrobial ward rounds in secondary care.

The operational framework outlined in Fig. 1 allows for accountability and pharmacist oversight by clinical specialists. This provides medico-legal oversight for pharmacist's activities within a PenA de-labelling service. For the service to be delivered robustly and safely, a clinical governance framework should be built around three key components. Firstly, all members of the team should have their competencies reviewed at regular intervals by the senior management team. Secondly, audit data should be collected using a standard proforma to allow comparison between predefined time points. Thirdly, the hospitals drugs and therapeutic committee (or equivalent decision-making body) should regularly review outcome data and have oversight of the patient pathways. This will ensure that corrective actions can be implemented in a timely fashion.

In the UK, the main barriers for a pharmacist-led PenA de-labelling service include dedicated funding and time management. Ideally, a team of trained IP pharmacists are required to ensure PenA de-labelling is offered as an ongoing service and if taken forward, such training should commence and be embedded into the curriculum for undergraduate pharmacists.

Strengths and limitations of this review

The present narrative review has been conducted from a broad perspective but is directed to the study research questions and aims. The burden of spurious PenA use and its adverse impact on clinical care, specifically with respect to AMS and excess healthcare costs, are placed in perspective. Whilst recent studies make a strong case for a DPC in de-labelling 'low risk' patients with PenA labels, data were

generated mostly from retrospective observational studies involving relatively small sample sizes and exhibiting heterogeneity with respect to healthcare frame works and governance policies. Unfortunately funding constraints limited the review to outputs published in English, however this was unlikely to have impacted on findings significantly.

Conclusion

A pharmacist-led PenA de-labelling service should be considered as an integral part of an AMS strategy in secondary care. De-labelling ‘low risk’ patients with PenA enhances use of penicillins and reduces the need for inferior second line antibiotics. This approach is likely to improve clinical outcomes, reduce the risk of iatrogenic infections, improve AMS and the management of multi-drug resistant infections and drive down healthcare costs. Further studies are required to optimise and validate DPC in individual countries to ensure that this approach is acceptable and conducive to their healthcare service and governance framework. Patient safety should be at the core of this intervention.

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