

Is direct oral amoxicillin challenge a viable approach for 'low-risk' patients labelled with penicillin allergy?

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Spurious penicillin allergy (PenA) is a major public health problem. Up to 10% of the population and 20% of inpatients are labelled with PenA, but only <5%–10% have a proven allergy following comprehensive investigations. PenA tests are labour intensive and require specialist input, which may not be readily available due to limited allergy services. Therefore, patients with PenA receive alternative antibiotics that are associated with higher rates of iatrogenic infections, antimicrobial resistance and a longer hospital stay with consequent increased costs. Recent evidence suggests that a supervised 'direct' oral amoxicillin challenge (without performing allergy tests) is a safe option in low-risk patients (those least likely to be allergic based on history). Patient selection for this procedure is based on a careful guideline-based risk stratification process. Further research is needed to validate this intervention in routine clinical practice and explore potential facilitators and barriers to implementation in different healthcare settings.

Introduction

Patients labelled with penicillin allergy (PenA) present a major challenge to antimicrobial stewardship.^{1,2} Approximately 10% of the population and 20% of inpatients carry a label of PenA.^{3–5} However, only <5%–10% of them have a confirmed allergy following comprehensive investigations involving skin tests and a challenge procedure.^{6–8} Whilst skin tests have a high negative predictive value (NPV), a supervised challenge procedure is the 'gold standard' in establishing clinical tolerance.^{9–11} PenA tests are labour intensive, time consuming and require an allergy specialist.⁹ There is a high demand for allergy services and PenA testing is not routinely available for inpatients even in major centres (usually performed electively as a day case by an allergist).^{12–14} Consequently, patients with a PenA label receive alternative antibiotics such as carbapenems, fluoroquinolones, vancomycin, clindamycin and teicoplanin for the treatment of common and serious infections and for pre-surgical prophylaxis.^{15,16} The additional cost of alternative antibiotics *per se* (drug costs only) has been reported at £250 000–500 000 GBP per annum in a single NHS trust in the UK.¹⁶ Macy and Contreras¹⁵ estimated a projected excess cost of \$64 million USD in healthcare expenditure for PenA patients in Kaiser Permanente group, CA, USA over a 3 year period. Patients with PenA had longer hospital stays and higher rates of infections with *Clostridioides* (*Clostridium*) *difficile*, VRE and MRSA in comparison with non-PenA controls.¹⁵ In a UK population-based

cohort study employing 'The Health Improvement Network' (THIN) primary care database, PenA was associated with an enhanced risk of *C. difficile* and MRSA, due to the use of non- β -lactams.¹⁷ Also, a recent National Audit Project conducted under the auspices of The Royal College of Anaesthetists, UK, reported a high risk for teicoplanin-induced perioperative anaphylaxis (relative rate 17.4) in patients with a label of PenA.¹⁸ Thus, PenA is a major public health problem and there is an urgent need to put in place safer strategies for delivery of robust antimicrobial stewardship. Antimicrobial resistance was declared as a high priority area by the United Nations (2016 resolution) and the UK Chief Medical Officer has put this item on the national risk register.

What can be done?

Patients with a PenA label can be stratified into low risk {e.g. those with a history of non-specific (non-allergic) symptoms, pruritus only, 'benign rash' or an indeterminate history [>10 years with a previous history not suggestive of an IgE-mediated hypersensitivity reaction (HSR)]} and high risk [those where the history is suggestive of an IgE-mediated (type I) or a delayed (type IV) HSR or those at an increased risk due to comorbidities, e.g. uncontrolled/severe asthma or COPD or those in heart failure] based on clinical history and comorbidities.^{2,10,19,20} We reported that 40%–60% of PenA cases were low risk.^{7,16} We have also shown that 30% of patients with a PenA label in our cohort had tolerated penicillin(s)

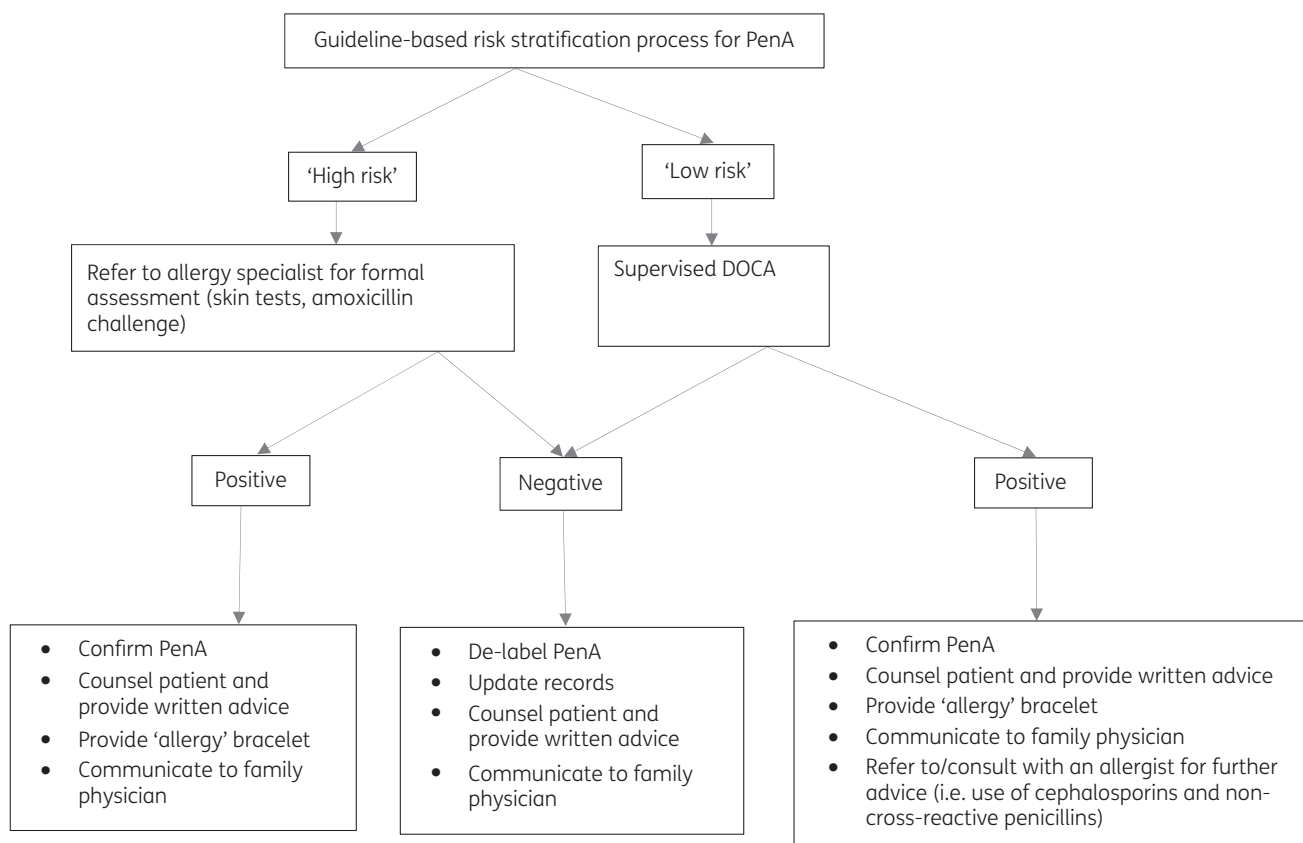


Figure 1. Proposed multidisciplinary coordinated approach for a supervised DOCA. This service model should include a supportive framework: a ‘fit-for-purpose’ governance policy; a multidisciplinary steering committee [an allergist (lead), senior nurse, microbiologist, infectious diseases physician, internist, pharmacist and IT personnel]; an appropriate IT system; and a clear *modus operandi* including accountability, roles and responsibilities of respective personnel that is ratified by senior management. This model should also include mandatory training of all relevant personnel involved in the PenA-delabelling programme, a standardized prospective method of electronic documentation of adverse drug reactions by clinicians, audits and a prompt mechanism to analyse any serious adverse events or ‘near-miss’ episodes.

since they were first labelled, but their records had not been amended.¹⁶

Recent studies have reported that a supervised direct (without carrying out allergy tests) oral challenge with amoxicillin (DOCA) is safe in low-risk patients. Amoxicillin rather than phenoxymethylpenicillin or benzylpenicillin is recommended for a challenge test as it includes a potentially antigenic side chain and accounts for the majority of penicillin-class antibiotic usage. Tolerance of amoxicillin, therefore, not only excludes selective amoxicillin allergy due to side-chain reactivity, but also provides reassurance of tolerance to the wider penicillin family.^{2,10} A single- or two/three-step DOCA is performed under medical supervision with a cumulative dose of 500 mg.^{2,10} A further course for 3–5 days may be prescribed to those reporting an indeterminate history or a non-immediate adverse reaction in order to exclude both immediate and non-immediate HSR.^{2,10} Patient selection for a DOCA is based on a guideline-based risk stratification process (Figure 1).^{2,20} Patients stratified as high risk are referred to an allergy specialist for further evaluation.^{2,20}

We proposed a computerized decision support system (CDSS) to facilitate risk stratification by non-allergy specialist healthcare professionals (HCPs).² The risk stratification algorithm was

validated in a cohort of patients who had undergone elective delabelling using standard-of-care tests (i.e. skin tests and amoxicillin challenge), demonstrating a high NPV (94% for the low-risk group and 83% for the high-risk group), thereby strengthening the case for a supervised DOCA in low-risk patients.⁷ Blumenthal *et al.*^{21,22} reported that a guideline-based supervised direct challenge procedure with β -lactams (penicillins and cephalosporins) was not only safe in low-risk inpatients, but it also enhanced overall β -lactam prescriptions by 7-fold. Implementation of a computerized guideline for PenA delabelling in the Harvard group of hospitals alone has been estimated to produce a cost saving of \$8.9–13.7 million USD in the first year.¹

Table 1 summarizes studies^{19,21–26} reporting outcomes of a supervised DOCA in low-risk patients.

Next steps

Whilst a supervised DOCA is a promising option to address the spurious PenA epidemic, larger multicentre studies in different patient groups and health service frameworks, focusing on safety, operational service issues, institutional factors and health economic outcomes, are warranted. Raising awareness amongst

Table 1. Recent studies highlighting safety of a supervised 'direct' oral amoxicillin (penicillin/cephalosporin) challenge in 'low-risk' patients with PenA

Reference, country	Patient group: n, adults/children, age (years) history/selection	Setting	Observations/outcome	Safe procedure (yes/no)
Mill <i>et al.</i> , ²³ Canada	$n = 818$, children, median age = 1.7 years (IQR 1.0–3.9) - history of suspected skin allergic reactions to amoxicillin, those with serious delayed reactions excluded	outpatient based, elective testing	770 (94%) tolerated; 17 (2%) mild immediate reactions; and 31 (3.8%) non-immediate reactions - specificity 100%, NPV 89%	yes
Iammatteo <i>et al.</i> , ²⁴ USA	$n = 155$, adults, mean age = 51 years - history of non-life-threatening reactions to penicillin	- outpatient based, elective testing - underwent single blind placebo-controlled challenge with amoxicillin	120 no reaction; 16 and 19 (4 allergic—non-immediate rash, pruritis—and 15 non-allergic) reacted to placebo and amoxicillin, respectively	yes
Tucker <i>et al.</i> , ²⁵ USA	$n = 328$, adults, marine recruits, age = NS - non-life-threatening reaction history to penicillin/s	- outpatient based, elective testing - DOCA without skin tests	5 (1.5%) reacted, isolated cutaneous reactions only	yes
Confino-Cohen <i>et al.</i> , ²⁶ Israel	$n = 642$, 435 children [median age = 4 years (range 0.1–17)] and 207 adults [median age = 48 years (range 18–83)] - history of non-immediate non-life-threatening reactions	outpatient based, patients were skin tested but underwent 5 day oral amoxicillin challenge ($n = 617$) disregarding results of skin tests	34 positive skin tests, 208 equivocal skin tests and 400 negative skin tests; 9 patients had immediate reactions, 24 had late reactions on first day and 30 had reactions during home challenge; all reactions classed as mild only	yes
Blumenthal <i>et al.</i> , ²² USA	$n = 94$, adults, age = NS - low-risk group identified with a computerized guideline, multi-disciplinary group approach to service delivery, direct penicillin or cephalosporin challenge under supervision	inpatients	no adverse reactions	yes
Blumenthal <i>et al.</i> , ²¹ USA	- adults, mean $\pm$ SD age = 59.9 ± 20 years - guideline-based selection of low-risk patients; 183 test doses involving cephalosporins (139), penicillins (36) and carbapenems (8)	inpatients	- seven adverse reactions (six immediate and one delayed and five out of seven considered to be immunologically mediated grade 1 and grade 2, i.e. mild cutaneous manifestations) - guideline-based test doses led to significant reduction in the time to administration of β-lactams	yes
Savic <i>et al.</i> , ¹⁹ UK	- adults >18 years old, age = NS - pre-surgical patients, $n = 219$ screened and risk-stratified, 90 deemed high risk, 10 declined to give details and 56 stratified as low risk	- during pre-surgical review for anaesthetic assessment - incremental amoxicillin (500 mg) challenge, followed by 3 day course	55 delabelled, no serious adverse reaction; 1 patient reported urticaria in hands after second dose, but it later transpired that they did not disclose the index history of generalized urticaria following first dose, which would not have made them eligible to be included in the study - patient feedback: 81% of patients reported little or no anxiety, 85% thought it was a 'smooth process', patients preferred formal delabelling process via a challenge procedure	yes

NS, not stated.

This table focuses on direct oral challenge for delabelling; rechallenges are not included.

HCPs, as well as exploring behavioural aspects in patients and HCPs for accepting this intervention would help in the design of studies. There is some evidence that HCPs are open to considering newer methods for PenA delabelling and there is patient acceptance for a supervised DOCA.^{19,27}

Barriers to the implementation of a supervised DOCA may relate to anxiety surrounding potential harm to patients and possible downstream medicolegal consequences, workforce requirement, accuracy of the risk stratification process, concerns about resensitization etc. Previous studies have highlighted significant knowledge gaps in allergy amongst HCPs and poor training in allergy in medical schools, which may at least in part have contributed to mislabelling and poor documentation of adverse reactions.^{28–30}

Supervised DOCA to delabel low-risk patients presents a promising option, but needs validation in larger prospective studies in different healthcare settings. The success of a PenA-delabelling programme and antimicrobial stewardship also depends on quantification of the clinical burden relating to the high-risk group and developing robust drug allergy referral pathways. It requires a coordinated effort from a multidisciplinary group of HCPs from General Medicine, Infectious Diseases, Microbiology, Pharmacy and Allergy/Immunology to establish a safe framework of service delivery. This service model also requires a robust governance framework including a *modus operandi* with roles and responsibilities of individual HCPs clearly defined and ratified by the senior management. A recent study reported a successful pharmacist-led PenA-delabelling programme in a district hospital.³¹ Whilst PenA delabelling should be available to all patients, priority should be given to those at a higher risk of infections (e.g. immunosuppressed, immunodeficient, bronchiectasis etc.). Taremi et al.³² highlighted the benefits of a PenA-delabelling process in immunocompromised cancer patients. We believe that adoption of this delabelling strategy will enhance delivery of antimicrobial stewardship.

Transparency declarations

None to declare.

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