**BSACI guideline for the set-up of penicillin allergy de-labelling services by non-allergists working in a hospital setting**

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All members of the writing group contributed to the development of the PICO questions and the drafting of the guideline**.**

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**ABSTRACT**

The Standards of Care Committee of the British Society for Allergy and Clinical Immunology (BSACI) and a committee of experts and key stakeholders have developed this guideline for the evaluation and testing of patients with an unsubstantiated label of penicillin allergy. The guideline is intended for UK clinicians who are not trained in allergy or immunology, but who wish to develop a penicillin allergy de-labelling service for their patients. It is intended to supplement the BSACI 2015 guideline ‘Management of allergy to penicillin and other beta-lactams’ and therefore does not detail the epidemiology or aetiology of penicillin allergy, as this is covered extensively in the 2015 guideline(1). The guideline is intended for use only in patients with a label of penicillin allergy and does not apply to other beta-lactam allergies. The recommendations include a checklist to identify patients at low risk of allergy and a framework for the conduct of drug provocation testing by non-allergists. There are separate recommendations for adults and children within the guideline, in recognition of the common differences in reported allergy history and likelihood of true allergy.

Keywords: penicillin allergy, de-labelling, healthcare professional, drug provocation testing, risk stratification.

**Executive Summary**

Grades of recommendation, A-E are based on evidence graded using SIGN criteria

* All patients labelled as ‘penicillin allergic’ attending secondary or tertiary care should be considered for penicillin allergy testing (E)
* Non-allergists providing de-labelling services should be networked with a specialist allergy immunology service for advice and support. (E).
* All patients identified as low risk for true penicillin allergy should be offered direct drug provocation testing (DPT), providing no exclusion criteria are met (C)
* Non-allergists should perform DPT in low-risk patients in a setting where allergic reactions including anaphylaxis can be treated (C)
* Minor gastro-intestinal upset, nausea, headache, and a family history of penicillin allergy without a personal history are not predictors of penicillin allergy. Patients with these symptoms or history do not require allergy testing. However, if patients seek reassurance of their tolerance to penicillin, a single dose DPT may be appropriate.(Delphi consensus process)
* The penicillin involved in the index reaction should be used for the DPT. If this is not known amoxicillin should be used (C)
* Drug provocation testing requires a set of minimum safety standards (E)
* A prolonged (multiple dose) DPT should be considered when the index reaction occurred after the second or subsequent dose of a course of penicillin (or where the timing of the reaction is unknown) (D)
* Where indicated, a prolonged DPT lasting 3 days is sufficient in the majority of patients. If the index reaction is clearly remembered to have occurred after more than 3 days, advice should be sought from the local or regional allergy service as to how long to extend the DPT. (E)

**Background**

A label of penicillin allergy is carried by 5.6% of the general population, with an estimated 2.7 million people in the UK affected (2). The incidence in hospitalised patients appears to be higher (3,4). Around 95% of penicillin allergy labels are incorrect when tested (5,6). Over the past 10 years, the clinical ramifications of a label of ‘penicillin allergy’ have been clearly defined. A diagnosis of penicillin allergy increases the risk of MRSA, *C.difficile* or VRE infections and death; presumably through increased use of alternatives to beta lactam antibitoics (2,3,7). It increases the duration of hospital admissions and has significant implications for the cost of healthcare (8,9). The economic impact of penicillin allergy labels has also been elucidated in recent years, with several studies demonstrating the healthcare costs of the label and the economic benefits of removing incorrect labels (10-12).

Despite this clear association with harm, penicillin allergy testing is a scarce resource in the NHS (13). Testing is currently performed by allergists and immunologists working in specialist clinics and is consequently limited to select patient groups (NICE CG 183)(14). This model cannot meet either current or future demand and leaves the vast majority of labelled patients unable to access testing. The provision of de-labelling at scale is therefore only possible with the engagement of clinicians who are not trained in allergy or immunology, referred to throughout this document as ‘non-allergists’.

A drug provocation test (DPT) is considered the gold standard test to confirm or refute the diagnosis of allergy in individuals at low-risk of an IgE-mediated type 1 immediate hypersensitivity reaction. Current UK and international guidelines for penicillin allergy testing recommend the use of skin testing prior to DPT as a means of assessing the likelihood of a positive provocation (15). In recent years several studies have demonstrated that it is possible to identify patients who are at low risk of penicillin allergy with an allergy history alone (16-20). It appears to be safe and efficacious to offer a direct drug provocation test (DPT) without prior skin testing in such patients. The term ‘direct provocation test’ in this guideline refers to the administration of single or multiple doses of the drug without prior skin testing. In some patients, the allergy history may indicate that there is no increased risk of allergy compared to that of the baseline population risk. In this group no allergy testing is required before removing the allergy label.

In many of these studies, de-labelling has been performed by non-allergists including allied medical healthcare workers such as pharmacists, nurses and associate physicians, working under immediate or remote medical supervision. There is currently no defined pathway or governance framework in the UK to support this practice. The definition of ‘low-risk’ varies, but the proportion of patients deemed suitable for a direct DPT may be as high as 65% (4). This novel approach offers the potential for testing at-scale within the NHS as it allows a significant proportion of patients to be de-labelled in settings outside a specialist allergy clinic. It is also less costly and may be more acceptable to the patient since it is less invasive.

The aim of this guideline is to provide a framework for the set-up and delivery of penicillin allergy de-labelling services by non-allergists. The intended users are non-allergists with an interest in clarifying the penicillin allergy status of their patients. The target population is adult and children with an untested label of penicillin allergy. The guideline is intended to supplement the 2015 BSACI guideline ‘Management of allergy to penicillin and other beta-lactams’ that details the aetiology of penicillin allergy, the molecular structure of antigenic determinants, clinical patterns of penicillin hypersensitivity, cross-reactivity with cephalosporins and management of allergic reactions to penicillin (1). The guideline details appropriate patient selection, risk stratification, minimum safety standards, conduct of a drug provocation test, and the degree of oversight required from allergy or immunology specialists.

The writing group comprises members of BSACI with an interest in this topic and invited representatives of specialties identified by the BSACI as key stakeholders in this topic. All additional members have a clinical and/or research interest in penicillin allergy de-labelling and all are formally representing their respective professional body on the guideline working group (GWG). Evidence for the recommendations made in this guideline was included based on the PICO questions developed by the GWG (see Supplementary Materials). The inclusion criteria for patients suitable for a direct drug provocation test (DPT) performed by a non-allergist were determined through a Delphi consensus process run amongst adult allergists and immunologists practising drug allergy in the UK. The findings were extended to children on the advice of the paediatric allergists in the GWG. For other areas of the guideline where evidence was lacking, expert opinion amongst the GWG and wider BSACI membership was sought.

The guideline will be reviewed 5 years from original publication date.

**Methods**

The PICO (Population, Intervention, Comparator, Outcome) questions were developed and refined by the GWG (see Supplementary Material). These questions, broadly, ask whether non-allergist healthcare workers can safely identify patients who are suitable to undergo a drug provocation test (DPT) to confirm tolerance to penicillin without prior skin testing and without evaluation by an allergy specialist, as well as how this testing can be performed outside of the specialist allergy clinic setting. The literature search was conducted by the BSACI Chief Scientific Officer on 12/10/2020 using Embase and Medline, English language only and from the last 10 years. The keywords used for the search were: penicillin allergy; de-labelling; beta lactam; drug provocation test; challenge test; risk stratification. A total of 445 papers were identified. These were reviewed by two members of the GWG and after removal of abstracts and papers not directly relevant to the PICO questions a total of 35 papers remained. Each of these was graded by at least two members of the GWG, following the SIGN guidelines. A further literature search was conducted by the BSACI Scientific Officer to cover the period between October 2020 and October 2021, during which time work on the guideline was paused due to the COVID 19 pandemic. The same search critieria were employed, yielding 91 papers of which 2 were subsequently graded and included into the evidence table.

Where evidence was lacking, a consensus approach was taken by the GWG. The patient group considered suitable for direct DPT by a non-allergist was defined through a formal Delphi consensus process undertaken by consultant allergists and immunologists practising adult drug allergy in the UK. All such individuals were approached via BSACI, with 27 subsequently participating in the survey. They were asked to rate the appropriateness of several statements. A median score of 7-9 indicated that a statement was ‘appropriate’, whilst a score of 1-3 indicated ‘inappropriate’. Consensus was deemed to have been achieved if the disagreement index (DI) was < 0.5. Following the first round of the survey, statements for which consensus had not been achieved were removed or modified in light of feedback from participants. A further round was completed in which consensus was gained in all areas. See Supplementary Material for survey questions and scores and for the CREDES checklist for reporting of a Delphi process.

**Recommendations**

**Adults**

These recommendations apply to patients in a hospital setting. There is insufficient evidence to make strong recommendations about the use of drug provocation testing in primary care. However, primary care physicians can remove a label of penicillin allergy where the history suggests there is no risk of penicillin allergy.

***Risk stratification***

A detailed drug allergy history, including review of prescription records where possible, will allow the clinician to stratify the risk of allergy. Patients may report symptoms and/or signs:

1. In keeping with non-immunological side effects from penicillin antibiotics and probable non-allergic phenomena (Table 1). This group is often referred to as ‘low risk’, however, there is wide variation within this definition and the GWG preferred to consider patients as either ‘suitable’ or ‘not suitable’ for direct DPT.
2. Consistent with either type 1, (IgE-mediated) immediate hypersensitivity reactions, or, type 4 (typically T cell mediated) delayed reactions (Table 2). These patients are considered not suitable for direct DPT by non-allergists and require evaluation by an allergy specialist.
3. Entirely in keeping with side effects and other non-allergic phenomena, in whom no allergy testing in indicated (Table 1). However, such patients may require reassurance from a test as proof of tolerance and in this situation, a DPT could be considered.

There are patients in groups 1 and 2 in whom there is a clinical imperative for treatment with penicillin but a DPT is not appropriate - for example, treatment of syphilis in pregnancy. These patients must be evaluated and treated by an allergy specialist who may perform desensitisation. This is a highly specialised procedure in which temporary tolerance of pencillin is induced in the patient, but this topic falls outside the scope of the guideline.

***Conduct of DPT***

Where a patient reports a reaction to penicillin in which only symptoms from Box 1 occurred, and none of the exclusion criteria from Table 2, a direct DPT can be performed. See Table 3 for the safe conduct of DPT. A single or graded DPT may be used, depending on local preference of the allergy team supporting the set-up of the de-labelling service. Amoxicillin is the drug of choice unless the index penicillin is known to be different, in which the index penicillin should be used. Amoxicillin is widely used in routine NHS practice for DPC and has a more favourable side effect profile compared to other penicillins such as co-amoxiclav. All personnel administering a DPT should have up to date training in advanced life support and management of anaphylaxis, and immediate access to on-site resuscitation facilities including provision of critical care.

***Use of prolonged DPT***

The evidence supporting the use of prolonged DPT is too weak to mandate this practice in all patients. There are important considerations around the unintended potential risk of antimicrobial resistance when prolonged courses are used, which must be weighed against the benefits of ensuring that delayed reactions to penicillin are not missed. It is not known whether a single dose of antibiotic is sufficient to trigger a delayed hypersensitivity reaction or whether this is a problem which develops only after accumulation of the drug (see Table 4). Consultation with the local/regional allergy service providing oversight for the de-labelling service should be sought to define which patients require a prolonged DPT and how long this should be.

**Recommendations**

**Paediatrics**

True allergic reactions to penicillin are less common than in adults. Children treated with beta lactams, particularly those under 4 years of age, frequently develop urticarial or maculopapular skin rashes. These reactions are rarely reproduced with challenge testing. De-labelling provides reassurance that penicillin use is safe in the future (22). Less than 7% of children react on re-exposure (23-27). Reactions, if they develop, are usually mild-moderate and occur 3-4 days from the start of the challenge. Recommendations for children of all ages are as the same as those for adults, in terms of risk stratification and the conduct of DPT (see Tables 1-3). Doses of medication should be age adjusted. Research around the use of DPT in primary care settings, suggests that it is safe and acceptable to patients, parents and healthcare providers (28). However, more research is needed before this can become a standard of care and this guideline does not support the provision of DPT in primary care for children (see Table 4).

**Retention of de-labelled status**

Failure to retain ‘de-labelled’ status is associated with persistent and unnecessary penicillin avoidance by the patient. Failure to cascade the information robustly to all relevant healthcare providers and poor understanding of the implications of a negative test, by both patients and their healthcare providers, contribute to this problem. It is beyond the scope of this guideline to determine the most effective way to address these issues, but as a minimum the patient and their GP should be provided with clear written information about the test result and its implications for future prescribing. Some centres have successfully implemented a range of initiatives to improve retention of patients’ de-labelled status (29). Research into this problem is ongoing and may inform future iterations of this guideline (see Table 4).

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Table 1: Low risk symptoms in adults and children

* Minor gastro-intestinal symptoms (nausea, abdominal pain, diarrhoea)\*
* *Candidiasis* (thrush)\*
* Minor symptoms unrelated to any form of allergic reaction eg headache, arthralgia, strange taste in mouth\*
* Family history of penicillin allergy but without personal history of allergy\*
* Patient has taken and tolerated the same penicillin subsequent to the index reaction\*
* Patient reports ‘benign’† rash which developed more than 1 hour after the first dose of a course of penicillin
* Patient reports a childhood rash with no other history available‡
* Patient cannot remember what happened during index reaction but was told it was not serious and did not require hospital treatment

\*These patients do not require allergy testing in the form of either skin tests or DPT. However, some patients may continue avoiding penicillin if they don’t have the reassurance of a negative allergy test. In these circumstances, a DPT should be considered.

†Benign defined as non-urticarial, non-itchy, non-blistering, short-lived (less than 24 hours) and did not require treatment

‡’No other history available’ assumes that such information has been sought from patients, carers, relatives and healthcare records where possible.

Patients with symptoms listed in Table 1 but none of the exclusion criteria listed in Table 2 are suitable for direct DPT performed by a non-allergist outside an allergy clinic setting

Table 2: Exclusion criteria for adults and children

* Rash occurring within one hour of the first dose of penicillin
* Rash lasting more than 24 hours and/or affecting more than 10% of body surface.
* Rash associated with blisters, skin peeling, mucosal inflammation (eyes, mouth, genitals), purpura.
* Patients reporting any symptoms suggestive of a type 1 immediate hypersensitivity reaction to penicillin, including swelling, urticaria, angioedema, shortness of breath, wheeze, loss of consciousness, or collapse.
* Patients who required hospital treatment due to their reaction
* Patients who required treatment with adrenaline for their reaction
* Patients who cannot remember what happened during the index reaction but were told it was serious and/or required medical intervention
* Unable to give informed consent
* Severe or uncontrolled asthma
* Severe chronic obstructive airways disease
* Severe aortic stenosis
* Patients who, at the time they are being considerd for DPT, are acutely unwell or clinically unstable. This includes patients with respiratory and/or cardiac compromise
* Pregnancy
* Previous penicillin allergy testing which concluded that the patient was allergic to penicillin

Table 3: Exclusion criteria for direct DPT

Table 3. Principles for the conduct of a drug provocation test (DPT)

* Written informed consent is required
* If the index penicillin is not known, amoxicillin should be used
* Blood pressure, heart rate and oxygen saturations should be checked prior to commencing the DPT and after each dose given.
* Single or divided dose DPT may be used according to local preference
1. *Single dose DPC*
2. *Administer 100% of a full dose of amoxicillin (500mg)*
3. *Graded DPC*
4. *Administer 10% of a full dose of amoxicillin (50mg)*
5. *Observe for 30 minutes*
6. *Administer 50% of a full dose of amoxicillin (250mg)*
7. *Observe for 30 minutes*
8. *Administer remainder of a full dose of amoxicillin (200mg)*
* If an alternative penicillin is used for the DPT, follow ths same percentage dosing schedules as above
* Peak flow should be included in the observations measured, depending on local guidelines in place during the COVID-19 pandemic
* Should symptoms consistent with anaphylaxis develop during the test, treat the patient in accordance with the Resuscitation Council Guidelines for management of anaphylaxis (20)
* The patient should be observed for 1 hour after the last dose (if an in-patient, ensure this observation is conducted by a member of the de-labelling team)
* The patient should be provided with clear written instructions about what to do if symptoms develop after leaving the hospital
* If a prolonged course is required (see ‘Use of prolonged DPT’ below), this should be provided to the patient. They must be contacted at the end of the course to check for delayed reactions
* A system should be in place to inform the GP and other relevant healthcare professionals about the result of the DPT. The patient should receive clear written information about the test result and its implications

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**Table 4:** Areas for future research

**The process described in Table 3 is intended only as a guide**. Specific local protocols, including training for those delivering the service, should be developed in collaboration with the allergy/immunology service providing support for the de-labelling service.

Table 4: Areas identified for future research

* Optimal length of prolonged DPT in adults and children
* Feasibility of penicillin allergy de-labelling in primary care settings
* Optimising retention of delabelled status
* Development of educational packages for non-allergists delivering de-labelling services