

PRACTICE



FROM DRUG AND THERAPEUTICS BULLETIN

Penicillin allergy—getting the label right

Drug and Therapeutics Bulletin

Drug and Therapeutics Bulletin, Editorial Office, London WC1H 9JR, UK

Penicillin allergy is a potentially serious adverse reaction that alters and reduces the options for antibacterial treatment, and which can be life threatening.¹ It is the most commonly noted drug allergy in the UK, reported by about 10% of the population.^{2,3} It is estimated, however, that only around 20% of those reporting penicillin allergy are truly allergic.^{2,4} It is important that the term “penicillin allergy” is correctly applied to avoid adverse effects or inappropriate treatment.

Here, we discuss key features that help to distinguish patients at low or high risk of having a true penicillin allergy, summarise what is known about the risk of allergic reactions to other β lactam antibacterials in patients with penicillin allergy, and discuss the steps to consider when assessing a label of penicillin allergy.

Who is at risk of penicillin allergy?

Repeated exposure to antibacterials, for example in medical conditions that require frequent antibacterial use such as cystic fibrosis, is recognised as a clinical risk factor for penicillin allergy.¹ Female sex has been identified as a risk factor in adults for both self reported and confirmed penicillin allergy,^{5,6} possibly related to greater antibacterial use in women.⁶ The prevalence of penicillin allergy appears to increase with age and might be partly explained by higher rates of antibacterial exposure in older age groups.⁶

A family history of penicillin allergy has been found to be associated with self reported penicillin allergy, however whether there is a genetic component to penicillin allergy is not clear.^{1,7} There does not appear to be a major relationship between atopy and the incidence of penicillin allergy.^{1,7} However, the British National Formulary advises that people with atopic allergies could be at greater risk from anaphylactic reactions to penicillins.⁸

No specific risk factors have been identified in children.¹ In a study of children (average age 3.5 years, range 6 months to 14.5 years) in whom delayed onset urticarial or maculopapular rash after penicillin administration had been reported, the rash recurred in only 6.8% on rechallenge.⁹ Viral infections were detected in the majority of children with a negative rechallenge

result and it has been suggested that many rashes attributed to penicillin allergy might be viral in origin.^{9,10}

What are the different types of reaction to penicillin?

Reactions can be classified as immediate or non-immediate based on the timing of appearance of symptoms.^{1,11}

Immediate reactions have their onset in 1 to 6 hours (generally within 60 minutes) after exposure to a dose of an antibacterial, and often involve symptoms of an immunoglobulin E mediated allergic reaction, ranging from urticaria or pruritus to angioedema and anaphylaxis.^{1,12}

Non-immediate reactions, occurring more than 60 minutes (commonly several days) after exposure to penicillin, mainly result from the release of specific cytokines by activated T cell subsets. The most common non-immediate reactions are maculopapular or morbilliform and urticarial rashes.^{1,12}

Less commonly, severe reactions can occur, including Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis.

How is penicillin allergy confirmed?

For some people, the label of penicillin allergy might have few clinical consequences if their need for antibacterials is infrequent. However, a full diagnostic investigation by specialist allergy services is recommended for people with specific anticipated treatment requirements (box 1).^{1,2}

There is no single validated test to diagnose or exclude hypersensitivity to β lactam and a combination of tests is required.¹³ The protocol in the European Network for Drug Allergy (ii) guidelines (2003) includes clinical history, skin tests, in vitro testing, and, when required, drug provocation tests.¹⁴ Guidelines produced by the British Society for Allergy and Clinical Immunology omit the routine use of in vitro testing (box 2).¹

What you need to know

Penicillin allergy is the most commonly reported drug allergy

It is estimated that between <10% and up to 20% of those reporting penicillin allergy are truly allergic

Prescription of a penicillin to patients with a previous allergy-like event after penicillin treatment is common and could result in serious harm or death

The diagnostic workup for penicillin allergy includes clinical history, skin tests, in vitro testing, and drug provocation tests

Some cephalosporins with a different side chain to the reacting penicillin can be considered under specialist management for life threatening infections when non-cephalosporin antibacterial drugs would be suboptimal

Box 1: Indications for investigating people with suspected penicillin allergy (immediate or non-immediate reactions)¹

- A label of "multiple antibacterial allergy," or
- a personal history of hypersensitivity to beta lactam in people who require frequent antibacterial treatment (eg, people with cystic fibrosis, diabetes, immunodeficiencies), or
- a personal history of hypersensitivity to beta lactam in people who require treatment with a specific beta lactam, or
- a history of an anaphylactic reaction during general anaesthesia, when penicillin was one of several drugs administered.

Box 2: Guidelines for verifying suspected penicillin allergy (British Society for Allergy and Clinical Immunology)

- Detailed clinical history
- Skin tests*
- If skin tests are negative, oral provocation test*

*If results are positive, avoid penicillins in future; if both skin tests and oral provocation tests are negative, patient is regarded as tolerant

Clinical history

Although clinical history alone is an unreliable basis for diagnosing penicillin allergy, it forms an essential first step in assessing the diagnosis.^{1 2} When a patient presents with suspected penicillin allergy, the following data should be collected^{1 2}:

- name and route of administration of penicillin given, and indication
- date and time of the reaction
- time between last dose administered and onset of symptoms
- description of the reaction: nature and severity of symptoms
- resolution of symptoms

In addition, written medical and nursing records, photographs, and eye witness accounts can be helpful.¹ It is important to distinguish immediate from non-immediate reactions, based on the time of onset of symptoms in relation to the last dose of drug received, and to distinguish mild symptoms from moderate to severe reactions. Complete records might be unavailable, however, especially if the reaction occurred many years previously.

Skin testing

Skin testing provides useful diagnostic information for reactions that are immunoglobulin E and T cell mediated, and should be the first line of investigation in adults.¹ Testing should be carried out in specialist allergy centres, as experience is required to interpret the results and to manage any potential adverse systemic reactions. Testing should be performed shortly after a reaction has occurred, as positive responses are less likely after a long interval.¹⁵ Skin testing for penicillin allergy is useful in children with a history of anaphylaxis.¹ The diagnostic value of skin testing is lower in non-immediate reactions.¹⁻¹⁶ The authors of a study in children with a history of delayed onset urticarial or maculopapular rashes concluded that painful and time consuming skin tests would have predicted a positive

response in only four of 88 children, and that an oral challenge was the best diagnostic test in these children.⁹

In vitro testing

The sensitivity of bioassays for Immunoglobulin E in penicillin allergy is low.¹ Advice should be sought from a specialist.

Oral provocation testing

For people with negative skin test results, drug challenge is required to confirm or exclude both immediate or non-immediate drug allergy.¹ Oral provocation testing is not used in people with a positive skin test and is not recommended for people at high risk of delayed life threatening reactions (eg, those who have had a severe cutaneous systemic reaction) or for people with unstable asthma or those taking β blockers. Oral provocation tests should only be undertaken by specialist centres and typically involve administering incremental doses of the suspect drug under supervision.

Is there cross reactivity with other antibiotics?

Penicillin and cephalosporin cross reactivity appears to have been overestimated, in part because first generation cephalosporins were contaminated with penicillin.¹ In patients allergic to penicillin, cross reactivity between penicillin and first and early second generation cephalosporins has been reported to occur in up to 10% of patients, and between penicillin and third generation cephalosporins in 2%-3% patients.¹⁷

Cefadroxil, cefradine, cefaclor, cefalexin, and ceftaroline should be avoided in patients who have a confirmed reaction to a penicillin, as cross reactivity can result from similarities in the side chains of the molecules.^{1 8} Other second and third generation cephalosporins with a different side chain to the reacting penicillin can be considered, under specialist management, for life threatening infections when non-cephalosporin antibacterials would be suboptimal.¹⁸ Guidelines from the British Society for Allergy and Clinical Immunology for patients with a history of

penicillin allergy requiring cephalosporin treatment recommend skin tests for both penicillin and cephalosporin followed, depending on the results, by oral provocation and, if necessary, desensitisation.¹

The British National Formulary advises that patients with a history of immediate hypersensitivity to penicillin should not receive a cephalosporin.⁸

What are the antibacterial choices for people with a label of penicillin allergy?

If there is a specific or regular requirement for treatment with penicillin, people with suspected immunoglobulin E mediated allergy should be formally re-evaluated for penicillin allergy in a drug allergy clinic.¹ For patients with confirmed immunoglobulin E mediated penicillin allergy, drug desensitisation under expert supervision leads to a temporary tolerance of a single course of penicillin, but should only be carried out if this is felt to be clinically important and no alternative drug is available.¹ However, expertise in drug desensitisation is limited to a relatively small number of specialist allergy centres in the UK.

For people with allergy to a particular penicillin side chain, it might be possible to select a β lactam with a different side chain.^{1 19}

For patients in whom all β lactams are contra-indicated, alternative non- β lactam antibacterials include tetracyclines, metronidazole, macrolides, aminoglycosides, quinolones, and glycopeptides.²⁰ National antimicrobial prescribing guidelines include suggested alternatives for people with penicillin allergy.^{21 22} The British National Formulary suggests that patients with a history of a minor rash (ie, non-confluent, non-pruritic rash restricted to a small area of the body) or a rash that occurs more than 72 hours after penicillin administration are probably not allergic to penicillin.⁸ In these individuals, a penicillin should not be withheld unnecessarily for serious infections; the possibility of an allergic reaction should, however, be borne in mind. Other β lactam antibiotics (including cephalosporins) can be used in these patients.⁸

What are the risks of inappropriate labelling?

Guidelines highlight the need to check for hypersensitivity and outline treatment options for people with penicillin allergy.^{2 22} Prescription of a penicillin to patients with a previous allergy-like event following penicillin treatment is common and could result in a severe allergic reaction if there is a true penicillin allergy.^{2 23} People with suspected but unverified penicillin allergy are likely to be treated with alternative antibacterials that have a broader spectrum of activity, which might impact on microbial resistance patterns.^{24 26} In addition, alternative antibiotics might have more adverse effects and be more expensive.

In case control studies, people with a history of suspected penicillin allergy spent more time in hospital and had poorer clinical outcomes than controls without such a history.^{27 28} In a retrospective study of patients in hospital in the USA, those with a label of penicillin allergy were exposed to substantially more fluoroquinolones, clindamycin, and vancomycin ($P < 0.0001$) and had higher rates of *Clostridium difficile*, methicillin resistant *Staphylococcus aureus*, and vancomycin resistant enterococcus infections than matched controls.²⁷

Strategies aimed at reducing incorrectly labelled penicillin allergy are important given the growing concern about the emergence of multi-resistant pathogens and the importance of

antimicrobial stewardship programmes to preserve the effectiveness of antibacterials. Preliminary studies suggest that appropriate allergy testing and removal of incorrect labelling of penicillin allergy can decrease broad spectrum antibacterial use and reduce the length of inpatient stay, mortality, and treatment costs.^{29 30}

Drug allergy notification

Penicillin allergy notification is important for the prevention of further episodes. People with suspected or confirmed penicillin allergy should have their allergic status documented in their medical records and in all correspondence between primary and secondary care (and other healthcare providers).² This information should be disseminated to other healthcare professionals to reduce the risk of re-exposure. If the suspected allergy has been excluded by allergy testing, details should be added to the medical record and all interested parties informed in writing.

Competing interests: Competing interests are in line with *Drug and Therapeutics Bulletin's* policy on conflicts of interests.

- Mirakian R, Leech SC, Krishna MT, et al. Standards of Care Committee of the British Society for Allergy and Clinical Immunology. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy* 2015;45:300-27. doi:10.1111/cea.12468pmid:25623506.
- Clinical Guideline Centre. 2014. Drug allergy: diagnosis and management of drug allergy in adults, children and young people. <https://www.nice.org.uk/guidance/cg183/evidence/drug-allergy-full-guideline-193159693>
- Kerr JR. Penicillin allergy: a study of incidence as reported by patients. *Br J Clin Pract* 1994;48:5-7.pmid:8179985.
- Mota I, Gaspar A, Chambel M, Piedade S, Morais-Almeida M. Hypersensitivity to beta-lactam antibiotics: a three-year study. *Eur Ann Allergy Clin Immunol* 2016;48:212-9.pmid:27852424.
- Park MA, Matesic D, Markus PJ, Li JT. Female sex as a risk factor for penicillin allergy. *Ann Allergy Asthma Immunol* 2007;99:54-8. doi:10.1016/S1081-1206(10)60621-7pmid:17650830.
- Macy E, Poon K-Y T. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med* 2009;122:778.e1-7. doi:10.1016/j.amjmed.2009.01.034pmid:19635279.
- Apter AJ, Schelleman H, Walker A, Addya K, Rebbeck T. Clinical and genetic risk factors of self-reported penicillin allergy. *J Allergy Clin Immunol* 2008;122:152-8. doi:10.1016/j.jaci.2008.03.037pmid:18538381.
- Joint Formulary Committee. British National Formulary. Ed. 72. London: BMJ Group and Pharmaceutical Press, September 2016.
- Caubet J-C, Kaiser L, Lemaître B, Fellay B, Gervais A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol* 2011;127:218-22. doi:10.1016/j.jaci.2010.08.025pmid:21035175.
- Zambonino MA, Corzo JL, Muñoz C, et al. Diagnostic evaluation of hypersensitivity reactions to beta-lactam antibiotics in a large population of children. *Pediatr Allergy Immunol* 2014;25:80-7. doi:10.1111/pai.12155pmid:24329898.
- Torres MJ, Blanca M. The complex clinical picture of beta-lactam hypersensitivity: penicillins, cephalosporins, monobactams, carbapenems, and clavams. *Med Clin North Am* 2010;94:805-20. xii. doi:10.1016/j.mcna.2010.04.006pmid:20609864.
- Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. *Allergy* 2014;69:420-37. doi:10.1111/all.12350pmid:24697291.
- Richter AG, Nasser SM, Krishna MT. A UK national survey of investigations for beta-lactam hypersensitivity - heterogeneity in practice and a need for national guidelines - on behalf of British Society for Allergy and Clinical Immunology (BSACI). *Clin Exp Allergy* 2013;43:941-9. doi:10.1111/cea.12134pmid:23889247.
- Torres MJ, Blanca M, Fernandez J, et al. ENDA EAACI Interest Group on Drug Hypersensitivity. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003;58:961-72. doi:10.1034/j.1398-9995.2003.00280.xpmid:14510712.
- Fernández TD, Torres MJ, Blanca-López N, et al. Negativization rates of IgE radioimmunoassay and basophil activation test in immediate reactions to penicillins. *Allergy* 2009;64:242-8. doi:10.1111/j.1398-9995.2008.01713.xpmid:19178402.
- Blanca-López N, Zapatero L, Alonso E, et al. Skin testing and drug provocation in the diagnosis of nonimmediate reactions to aminopenicillins in children. *Allergy* 2009;64:229-33. doi:10.1111/j.1398-9995.2008.01903.xpmid:19178402.
- Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: a meta-analysis. *Otolaryngol Head Neck Surg* 2007;136:340-7. doi:10.1016/j.otohns.2006.10.007pmid:17321857.
- Pegler S, Healy B. In patients allergic to penicillin, consider second and third generation cephalosporins for life threatening infections. *BMJ* 2007;335:991. doi:10.1136/bmj.39372.829676.47pmid:17991982.
- Romano A, Gaeta F, Arribas Poves MF, Valluzzi RL. Cross-Reactivity among Beta-Lactams. *Curr Allergy Asthma Rep* 2016;16:24. doi:10.1007/s11882-016-0594-9pmid:26898316.
- Jethwa S. 2015. Penicillin allergy: identification and management. <http://www.pharmaceutical-journal.com/learning/learning-article/penicillin-allergy-identification-and-management/20069170.article>.
- Public Health England. 2016. Management of infection guidance for primary care for consultation and local adaptation. <https://www.gov.uk/government/uploads/system/uploads/>

Who should not receive a penicillin?

- Individuals with a history of anaphylaxis, urticaria, or rash immediately after penicillin administration—who are at risk of immediate hypersensitivity to a penicillin⁸
- People with a positive skin test¹
- People with severe non-immediate reactions to penicillin (eg, toxic epidermal necrosis or Stevens Johnson syndrome), who should be advised to avoid penicillins under all circumstances

Information for patients

People with suspected or confirmed penicillin allergy and their carers should be given verbal and written information about the allergy and the drugs and drug classes to be avoided.^{1,2} The information should be carried at all times (eg, using a MedicAlert product) and be shared with healthcare professionals. Adrenaline auto-injectors are not usually prescribed for people with a drug allergy on the basis that the likelihood of an acute severe allergic reaction occurring outside a medical setting is low.³¹

Education into practice

- Do you take a full history of previous reactions when a patient reports that they are allergic to penicillin?
- Do you refer patients to specialist allergy services if they are labelled penicillin allergic and have specific anticipated treatment requirements?
- Do you ensure that people with suspected or confirmed penicillin allergy have their allergic status documented in their medical records and in all correspondence between primary and secondary care?

This article was originally published in *Drug and Therapeutics Bulletin* doi:10.1136/dtb.2017.3.0463

Drug and Therapeutics Bulletin is a highly regarded source of unbiased, evidence based information and practical advice for healthcare professionals. It is independent of the pharmaceutical industry, government, and regulatory authorities, and is free of advertising

Drug and Therapeutics Bulletin is available online at <http://dtb.bmj.com>.

- attachment_data/file/524984/Management_of_infection_guidance_for_primary_care_for_consultation_and_local_adaptation.pdf
- 22 All Wales Medicines Strategy Group. 2015. Primary care antimicrobial guidelines. <http://www.awmsg.org/docs/awmsg/medman/Primary%20Care%20Antimicrobial%20Guidelines.pdf>
- 23 Apter AJ, Kinman JL, Bilker WB, et al. Represcription of penicillin after allergic-like events. *J Allergy Clin Immunol* 2004;113:764-70. doi:10.1016/j.jaci.2003.11.032pmid:15100685.
- 24 MacLaughlin EJ, Saseen JJ, Malone DC. Costs of beta-lactam allergies: selection and costs of antibiotics for patients with a reported beta-lactam allergy. *Arch Fam Med* 2000;9:722-6. doi:10.1001/archfam.9.8.722pmid:10927711.
- 25 Solensky R, Earl HS, Gruchalla RS. Clinical approach to penicillin-allergic patients: a survey. *Ann Allergy Asthma Immunol* 2000;84:329-33. doi:10.1016/S1081-1206(10)62782-2pmid:10752918.
- 26 Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of suspected and challenge-verified penicillin allergy in a university hospital population. *Basic Clin Pharmacol Toxicol* 2006;98:357-62. doi:10.1111/j.1742-7843.2006.pto_230.xpmid:16623858.
- 27 Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. *J Allergy Clin Immunol* 2014;133:790-6. doi:10.1016/j.jaci.2013.09.021pmid:24188976.
- 28 Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. *Pharmacotherapy* 2011;31:742-7. doi:10.1592/phco.31.8.742pmid:21923600.
- 29 Trubiano J, Phillips E. Antimicrobial stewardship's new weapon? A review of antibiotic allergy and pathways to 'de-labeling'. *Curr Opin Infect Dis* 2013;26:526-37. doi:10.1097/QCO.000000000000006pmid:24126717.
- 30 Li M, Krishna MT, Razaq S, Pillay D. A real-time prospective evaluation of clinical pharmaco-economic impact of diagnostic label of 'penicillin allergy' in a UK teaching hospital. *J Clin Pathol* 2014;67:1088-92. doi:10.1136/jclinpath-2014-202438pmid:25185139.
- 31 Jones C, Brathwaite N, Leech S, et al. Allergy UK, a national patient organisation, response to the BSACI guideline: prescribing an adrenaline auto-injector. *Clin Exp Allergy* 2016;46:1619-20. doi:10.1111/cea.12854pmid:27893939.

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://group.bmj.com/group/rights-licensing/permissions>