

Penicillin allergy: a practical approach to assessment and prescribing

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Keywords

beta-lactams,
cephalosporins,
hypersensitivity

Aust Prescr 2019;42:192–9
<https://doi.org/10.18773/austprescr.2019.065>

SUMMARY

Penicillin allergies are not always lifelong. Approximately 50% are lost over five years.

A reaction to penicillin during a childhood infection is unlikely to be a true allergy.

Only 1–2% of patients with a confirmed penicillin allergy have an allergy to cephalosporins. In patients with a low risk of severe allergic reactions, cephalosporins are a relatively safe treatment option.

Patients with a history of delayed non-severe reactions, such as mild childhood rashes that occurred over 10 years ago, may be suitable for an oral rechallenge with low-dose penicillin. This should be done in a supervised hospital environment.

In many cases, with appropriate assessment and allergy testing, it may be possible to remove the penicillin allergy label.

Introduction

Most patients who say they have a penicillin allergy are not allergic to penicillins. While 10% of the population will report a penicillin allergy, less than 1% will be truly allergic.^{1,2} They have been erroneously labelled as penicillin-allergic.

In the USA, penicillin allergies are the most commonly documented drug allergy, with up to 20% of hospitalised patients having a recorded penicillin allergy.^{3,4} In Australian hospitals, national point prevalence data (2013–14) show that 8.9% of patients have a penicillin allergy label on their medical record.⁵ A high proportion of these labels are likely to be incorrect. The patient may have had a non-immune-mediated reaction such as nausea and vomiting, an exanthema (e.g. after taking amoxicillin during an Epstein-Barr virus infection) or an injection-site reaction.^{6,7}

Impact of allergy labels

Patient-reported penicillin allergies alter antibiotic management and may result in the use of suboptimal or broader spectrum drugs such as fluoroquinolones, macrolides, glycopeptides and cephalosporins.^{6,8–11} Having a penicillin allergy label has been associated with an increased risk of *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci infections and colonisation.³ The increased use of broad-spectrum drugs in hospitalised patients with penicillin allergies also contributes to the growing global problem of antimicrobial resistance.^{6,9,12,13} Antibiotic allergy labels are correlated with increases in length of hospital

stay,³ hospital readmission rates,¹⁰ surgical site infections,¹⁴ and admissions to intensive care units.¹⁵ Similarly in general practice, penicillin allergy labels are associated with an increased risk of death and MRSA infection or colonisation.¹⁶

Impermanent allergy

It has been demonstrated that more than 90% of patients labelled as having a penicillin allergy would be able to tolerate penicillins following appropriate assessment and allergy testing.^{17–19} Even penicillin allergies confirmed by skin tests can wane over time. Half the patients who have a positive skin test for penicillins will lose that reactivity after five years.^{13,20} There is therefore interest in penicillin allergy ‘de-labelling’. This is the removal of the allergy label following either allergy history reconciliation or testing (oral provocation or skin testing).

What is true penicillin allergy?

The classification of a patient-reported penicillin allergy label is the first important step in appropriate care (Table 1). Before prescribing, ask patients about their allergies, as not all allergies may have been documented in their medical records. Conversely, some reactions labelled as allergic may be other types of adverse events. Ask about the clinical features of suspected reactions.

Allergic cross-reactivity

The beta-lactam antibiotics include penicillins, cephalosporins, carbapenems and monobactams. Previously it was thought that patients with penicillin

Table 1 Antibiotic allergy classifications

Type	Mechanism	Clinical examples	Common antibiotic examples	Antibiotic recommendation
Type A adverse drug reactions - non-immune-mediated				
Non-severe	Pharmacologically predictable reactions	Nausea, vomiting, diarrhoea, pruritis (without rash), headache	Beta-lactams	Use all antibiotics
Severe		Encephalitis, renal impairment, tendinopathy	Cefepime, aminoglycosides, fluoroquinolones	Only avoid the implicated drug or dose
Type B adverse drug reactions - immune-mediated				
1	IgE-mediated	Urticaria, angioedema, bronchospasm, anaphylaxis	Penicillins, cephalosporins	
2	Antibody (usually IgG)-mediated cell destruction	Haemolytic anaemia, thrombocytopenia, vasculitis	Penicillins, cephalosporins	Avoid implicated drug. Caution with drugs in the same class and structurally related drugs
3	IgG or IgM and complement	Fever, rash, arthralgia	Penicillin, amoxicillin, cefaclor	
4	T-cell mediated	Maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis	Beta-lactams, glycopeptides, sulfonamides	Avoid implicated drug, drugs in the same class and structurally related drugs
Anaphylactoid reactions - non-immune-mediated				
Non-IgE-mediated	Direct mast-cell stimulation or basophil activation	Flushing, itching, urticaria, angioedema	Vancomycin, macrolides, fluoroquinolones	Manage the reaction, either by slowing the infusion or premedication (with antihistamines or corticosteroids)

allergies had a 10% risk of cross-reactivity with cephalosporins and carbapenems.²¹ However, reviews have reported that the risk of cross-reactivity between cephalosporins, carbapenems and penicillins may be as low as 1%.²¹⁻²⁴

The cross-reactivity between beta-lactam antibiotics may be due to the beta-lactam ring itself, an adjacent thiazolidine or dihydrothiazine ring, or from the side chains (R1 in penicillins or R1 and R2 in cephalosporins) – see Fig. 1. True cross-reactivity is largely due to the R1 side chains, with the highest risk being in beta-lactams with identical side chains.

Cross-reactivity is particularly seen with aminopenicillins (amoxicillin, ampicillin) and aminocephalosporins (cefalexin, cefaclor, cefadroxil, ceftazidime).²⁴ The rate of cross-reactivity between aminopenicillins and aminocephalosporins has been reported to be as high as 30–40% in predominately European studies.^{23,25-27} At the antibiotic allergy testing centres of Austin Health and the Peter MacCallum Cancer Centre in Melbourne, out of 15

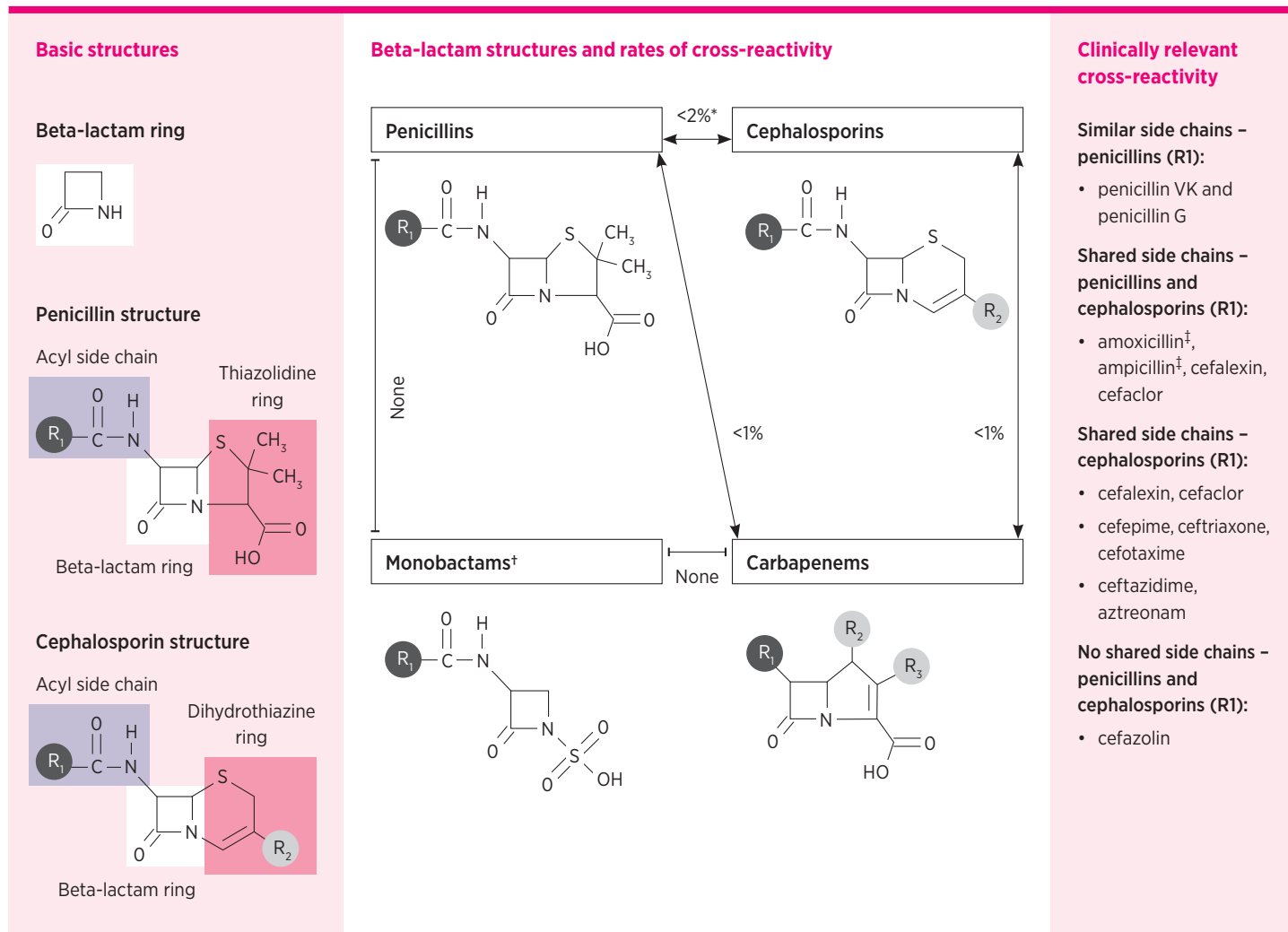
patients reporting a severe-immediate cefalexin hypersensitivity, intradermal tests determined that six (40%) would not be able to tolerate ampicillin.^{5,28}

While the data regarding cross-reactivity have primarily been about immediate hypersensitivities, similar patterns have been reported in non-severe delayed penicillin allergies.^{29,30} There are limited data regarding cross-reactivity in severe delayed reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis. For these severe delayed reactions, information regarding cross-reactivity is not a reliable guide for empirical prescribing.

Assessing penicillin allergies

The key to both prescribing and de-labelling for patients with a history of penicillin allergy is an accurate assessment. This involves an understanding of the allergy particularly the severity, timing and tolerance. *Therapeutic Guidelines: Antibiotic* contains a guide for this assessment (Fig. 2).³¹

Fig. 1 Rates of cross-reactivity between beta-lactam antibiotics



Beta-lactam antibiotics include penicillins, cephalosporins, carbapenems and monobactams.

The left panel shows basic structures of beta-lactam antibiotics. Cross-reactivity is possible through the core beta-lactam ring, adjacent thiazolidine (penicillin) or dihydrothiazine (cephalosporin) ring, and also from a side chain (R1 or R2). Cephalosporins have both R1 and R2 side chains while penicillins only have R1. Despite varied mechanisms, true cross-reactivity is largely based on R1 side chains. Identical side chains in patients with IgE-mediated allergy pose the highest risk. However, cross-reactivity from side chains that are similar, but not identical, and from R2 side chain similarity, is possible and reported.

The centre panel demonstrates the structure and rates of cross-reactivity between penicillins, cephalosporins, carbapenems and monobactams. The right panel details the most clinically important cross-reactivity considerations.

* Except for shared group aminopenicillins and cephalosporins.

† Monobactams have no shared cross-reactivity with other beta-lactams, with the exception for aztreonam and ceftazidime, which share an identical R1.

‡ Amoxicillin and ampicillin are structurally similar aminopenicillins and should be considered clinically cross-reactive with each other and the respective cephalosporins with shared R1 side chains listed in the figure. Similar considerations exist for the aminocephalosporins.

Source: Adapted from Blumenthal et al. (with permission)²²

Severity

An understanding of the severity of an allergy includes obtaining a description of its 'type'. Information can be obtained by asking about how the reaction was managed, for example, was the patient hospitalised? What treatments were given for the reaction (e.g. adrenaline (epinephrine), antihistamine, systemic steroids or no therapy)? Simply asking the patient if the reaction was 'severe' is unlikely to gather accurate information.

Timing

The timing of the reaction is important to determine if it was delayed (e.g. T-cell mediated reaction) or immediate (e.g. IgE-mediated reaction). Immediate reactions typically occur within a 'few hours' of the first or second dose of the antibiotic. A delayed reaction usually occurs after 'days' of taking the antibiotic and the reaction can be accelerated if the antibiotic is given again.

Fig. 2 Penicillin allergy assessment guide

Penicillin allergy assessment guide

NEW UNDERSTANDINGS IN PENICILLIN ALLERGY

- 1 Penicillin allergy often wanes over time**
50% of people will no longer be allergic at 5 years.
- 2 Many reported penicillin allergies are not true allergies**
Over 90% of reported penicillin allergies can be excluded by skin testing and oral provocation.
- 3 Cross-reactivity between penicillins and cephalosporins is less common than previously thought**
Overall, only 1 to 2% of patients with a confirmed penicillin allergy have a cephalosporin allergy. (However, a reaction to cefalexin or cefaclor is more likely if the patient had a recent amoxicillin or ampicillin allergy, because these drugs have a similar side-chain structure.)

ASSESSING PENICILLIN ALLERGY

Appropriate antibiotic prescribing in a patient reporting a penicillin allergy requires an understanding of allergy SEVERITY (severe vs nonsevere) and TIMING (immediate vs delayed), and antibiotics tolerated since the reaction.

Questions to ask in a penicillin allergy assessment

SEVERITY—severe or nonsevere	<ol style="list-style-type: none"> 1. Do you remember the details of the reaction? 2. How was the reaction managed? Did it require treatment or hospitalisation?
TIMING—immediate (onset within hours of first or second dose) or delayed (onset after days); recent or distant past	<ol style="list-style-type: none"> 3. How long after taking the antibiotic did the reaction occur? 4. How many years ago did the reaction occur?
ANTIBIOTICS TOLERATED SINCE REACTION	<ol style="list-style-type: none"> 5. Since the reaction, have you taken any other antibiotics without problems? Having tolerated an antibiotic before an allergic reaction does not mean you will tolerate it after the reaction.

If the patient cannot recall the details of the reaction, use the time since reaction (childhood vs recent) and treatment (eg no treatment vs hospitalisation) to gauge the likely severity. Many people who report allergy to a penicillin in childhood are able to tolerate the drug as an adult.

Examples of penicillin allergy, classified by severity and timing

	Severe	Nonsevere
Immediate	anaphylaxis, compromised airway, angioedema, extensive urticaria, hypotension, collapse	mild urticaria or mild immediate rash
Delayed	severe cutaneous adverse drug reactions (eg DRESS, SJS/TEN), or significant internal organ involvement (eg acute interstitial nephritis)	benign childhood rash or maculopapular rash

DRESS = drug rash with eosinophilia and systemic symptoms; SJS/TEN = Stevens–Johnson syndrome / toxic epidermal necrolysis

PRESCRIBING FOR PATIENTS WITH PENICILLIN ALLERGY

If the patient reporting a penicillin allergy cannot recall the details of the reaction, use the information available to assess the level of risk, and weigh up the benefits and harms of prescribing a particular antibiotic. For less severe infections, consider whether an antibiotic is really needed.

While prescribing a non-beta-lactam antibiotic may seem the simplest option, in many cases this is not the optimal treatment for the infection, and it can be associated with a greater risk of adverse reactions and antimicrobial resistance.

Consult eTG complete for treatment recommendations and further information:

- antibiotic recommendations for specific infections, based on four categories of penicillin allergy: severe immediate / severe delayed / nonsevere immediate / nonsevere delayed
- a flowchart summarising the management of patients reporting hypersensitivity to penicillins in whom a beta-lactam antibiotic is the preferred drug
- information on beta lactam cross-reactivity. An understanding of penicillins and cephalosporins that share similar side-chain structures is helpful to predict cross-reactivity.



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Ask how many years ago the reaction occurred. This is important for assessing the likelihood that the penicillin allergy has persisted. In patients with true immediate penicillin allergies, the response wanes over time, with 80% of patients becoming tolerant to penicillins after 10 years.³²

Tolerance

The patient should be questioned about antibiotics that they have tolerated since the reaction, particularly oral penicillins or cephalosporins. Antibiotics that have been tolerated following the reaction should be considered first. Being able to tolerate a specific antibiotic before the reaction does not predict tolerance following the reaction.

Risk assessment

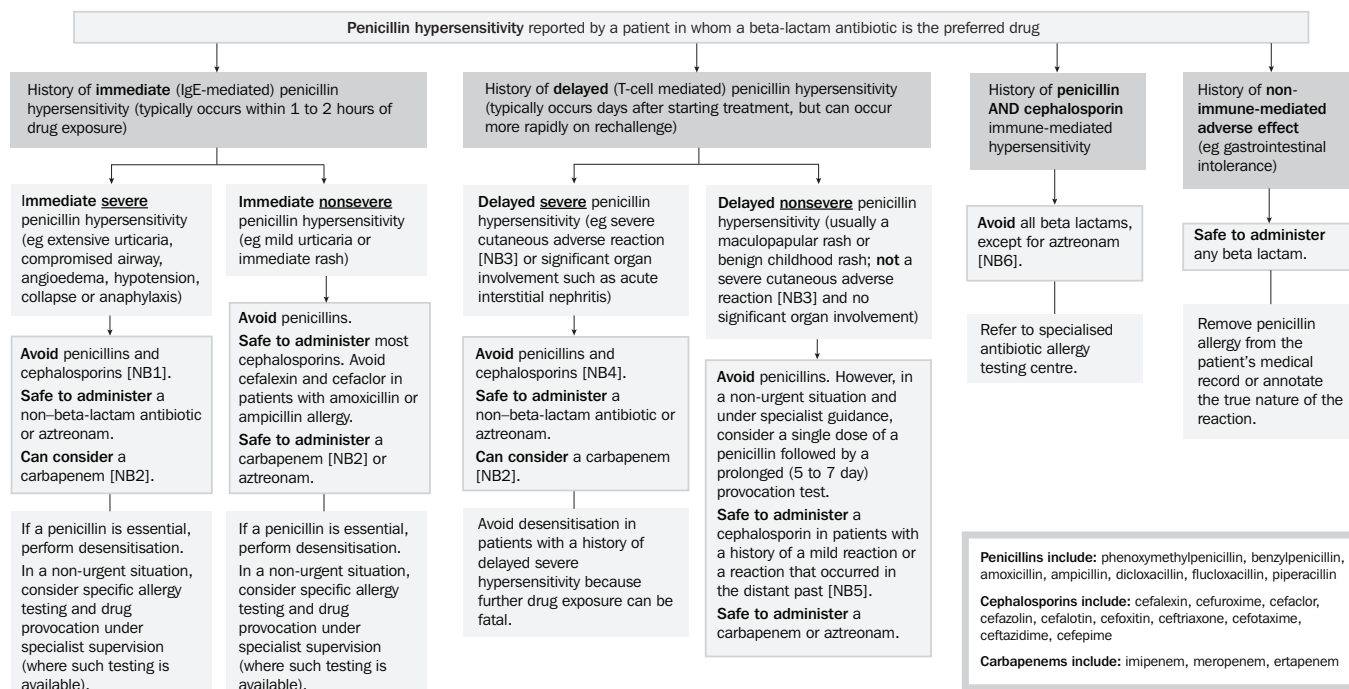
The assessment of penicillin allergy enables classification of phenotypes as either severe versus non-severe and immediate versus delayed. This is helpful in stratifying the risk of using alternative beta-lactam antibiotics. Recommendations for prescribing based on the phenotypes appear in the Therapeutic Guidelines: Antibiotic (Fig. 3).³¹

There are tools that can be used to aid in the assessment of penicillin allergies.³²⁻³⁴ An example is the Antibiotic Allergy Assessment Tool.³⁴ This underwent multidisciplinary validation by nursing staff, pharmacists, junior and senior medical staff with no training in allergy. It has subsequently been used

Fig. 3 Suggested management of patients reporting hypersensitivity to penicillins in whom a beta-lactam antibiotic is the preferred drug

Therapeutic Guidelines

Suggested management of patients reporting hypersensitivity to penicillins in whom a beta-lactam antibiotic is the preferred drug



NB1: In a critical situation, a cephalosporin can be considered in this group after undertaking a risk-benefit analysis and assessment of potential side-chain cross-reactivity. Seek expert advice.

NB2: In patients with penicillin hypersensitivity, the rate of immune-mediated cross-reactivity with carbapenems is approximately 1%; therefore, carbapenems can be considered in supervised settings. However, in patients with a history of a severe cutaneous adverse reaction (eg drug rash with eosinophilia and systemic symptoms [DRESS], Stevens-Johnson syndrome / toxic epidermal necrolysis [SJS/TEN], acute generalised exanthematous pustulosis [AGEP]), consider a carbapenem only in a critical situation when there are limited treatment options.

NB3: For example DRESS, SJS/TEN, AGEP.

NB4: There is limited evidence on the safety of cephalosporins in patients with a history of penicillin-associated acute interstitial nephritis (AIN). In a critical situation, directed therapy with a cephalosporin can be considered.

NB5: In patients who have had a recent reaction, consider avoiding cephalosporins with the same or similar R1 side-chain as the implicated penicillin.

NB6: However, avoid aztreonam in patients hypersensitive to ceftazidime; these drugs have the same R1 side-chain, so there is a risk of cross-reactivity.

by hospital pharmacists and nurses to assess beta-lactam allergy labels.³⁵ This tool classifies penicillin allergies into colour-coded risk groups and suggests an appropriate method for de-labelling:^{34,36}

- no risk – direct ‘de-label’
- low risk – potential direct oral rechallenge
- moderate risk – formal skin testing required before oral rechallenge
- high risk – formal allergy assessment (may include skin testing).

Table 2 shows an extract of the Antibiotic Allergy Assessment Tool.

De-labelling

Non-immune-mediated adverse drug reactions (type A) are not true allergic reactions. Common examples are gastrointestinal symptoms, such as nausea, vomiting and diarrhoea. If a patient has been labelled as penicillin-allergic because of a type A reaction, this should not stop the prescribing of beta-lactam antibiotics and patients do not need to undergo allergy testing. These labels should

be directly removed from the patients’ medical records after a discussion about the nature of these reactions and the potential for treatment failure and adverse events if these antibiotics are avoided.

In severe type A reactions, the implicated drug should be avoided. However, it may be possible to use other drugs in the same class.

Sometimes allergies are reported reflecting the history of a family member rather than the patient. These spurious cases of allergy can usually be de-labelled.

Oral rechallenge

If there was a delayed, non-severe reaction (such as mild childhood rashes or a maculopapular rash that occurred over 10 years ago) an oral rechallenge with low-dose penicillin can be considered.

Increasing evidence supports this in patients with a low risk of severe reactions, but the rechallenge should be in a supervised hospital environment.^{37,38}

At present, there is limited evidence for trying an oral rechallenge in general practice.

Table 2 Extract from the Antibiotic Allergy Assessment Tool

Clinical manifestation	Recommendation and resultant allergy type
Dermatological	
Childhood exanthem (unspecified)	Unlikely to be significant (non-severe)
Details of rash timing unknown and no severe features or hospitalisation	Unlikely to be significant (non-severe)
Diffuse rash or localised rash with no other symptoms developing >24 hours after starting antibiotic, over 10 years ago	Delayed hypersensitivity (non-severe, low-risk)
Liver	
Hepatic enzyme derangement (does not meet criteria for liver failure or severe injury)	Unlikely to be immune-mediated (non-severe, low-risk)
Neurological or gastrointestinal	
Gastrointestinal symptoms (nausea, vomiting, diarrhoea)	Unlikely to be immune-mediated (non-severe, low-risk)
Neurological or central nervous system manifestation (headache, optic neuritis, confusion, depression, mood disorder, low mood, psychosis)	Unlikely to be immune-mediated (non-severe, low-risk)
Renal	
Renal impairment (does not meet criteria for renal failure or severe injury)	Unlikely to be immune-mediated (non-severe, low-risk)
Unknown reaction	
Unknown reaction >10 years ago or family history of penicillin allergy only	Unlikely to be significant (non-severe, low-risk)

 Appropriate for supervised direct oral rechallenge  Appropriate for direct de-labelling – removal of allergy label without testing (oral rechallenge if required)

Note: This extract of the tool does not include clinical manifestations such as angioedema and haematological adverse reactions, which require further investigation.
Source: Reference 34

Considering which penicillin to use in an oral rechallenge is important as patients can retain hypersensitivity to one penicillin (e.g. amoxicillin) while tolerating another (e.g. penicillin VK) due to variations in the antibiotic R1 side chains. Before the widespread use of amoxicillin, most 'penicillin allergies' would be secondary to penicillin VK or G. This should guide the drug to be used for the rechallenge if the 'penicillin' is unspecified. For example, if the patient's allergy dated back to the 1960s, it would be appropriate to use penicillin VK in the rechallenge.

Prescribing for patients with penicillin allergies

Treatment options for patients with a penicillin allergy can be difficult. Prescribing should be guided by the information obtained from a thorough allergy assessment. Detailed advice regarding the use of cephalosporins and carbapenems is given in the Therapeutic Guidelines: Antibiotic (Fig. 3).³¹

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Conclusion

While penicillin allergies can be life-threatening, it is important to ensure that all patients with a recorded penicillin allergy label undergo a thorough antibiotic allergy assessment. These labels should be removed if the patient did not have a true immune-mediated reaction. An assessment of the severity, timing and tolerance of allergic reactions will lead to more 'de-labelling' and improved prescribing.

If there has been a presumed immune-mediated reaction, formal antibiotic allergy testing should be considered. While the management of patients with a penicillin allergy can be challenging, the cross-reactivity between penicillins and other beta-lactams is lower than initially reported. In patients with a low risk of severe allergic reactions, cephalosporins can be considered as an appropriate treatment option to penicillins. ◀

Conflicts of interest: none declared

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FURTHER READING

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