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BSACI GUIDELINE

Management of allergy to penicillins and other beta-lactams

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Clinical & Experimental Allergy

Summary

The Standards of Care Committee of the British Society for Allergy and Clinical Immunology (BSACI) and an expert panel have prepared this guidance for the management of immediate and non-immediate allergic reactions to penicillins and other beta-lactams. The guideline is intended for UK specialists in both adult and paediatric allergy and for other clinicians practising allergy in secondary and tertiary care. The recommendations are evidence based, but where evidence is lacking, the panel reached consensus. During the development of the guideline, all BSACI members were consulted using a Web-based process and all comments carefully considered. Included in the guideline are epidemiology of allergic reactions to beta-lactams, molecular structure, formulations available in the UK and a description of known beta-lactam antigenic determinants. Sections on the value and limitations of clinical history, skin testing and laboratory investigations for both penicillins and cephalosporins are included. Cross-reactivity between penicillins and cephalosporins is discussed in detail. Recommendations on oral provocation and desensitization procedures have been made. Guidance for beta-lactam allergy in children is given in a separate section. An algorithm to help the clinician in the diagnosis of patients with a history of penicillin allergy has also been included.

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Glossary AGEP, Acute generalized exanthematous pustulosis; BP, Benzylpenicillin; CF, Cystic fibrosis; CMV, Cytomegalovirus; DHS, Drug Hypersensitivity Syndrome; DRESS, Drug rash with eosinophilia and systemic symptoms; EBV, Epstein–Barr virus; HHV, Human herpes virus; HIV, Human immunodeficiency virus; RAST, Radioallergosorbent test; SJS, Stevens–Johnson syndrome; TEN, Toxic epidermal necrolysis.

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Executive summary (grades of recommendation see [1])

- This guideline addresses immediate and non-immediate allergic reactions to beta-lactams.
- Up to 20% of drug-related anaphylaxis deaths in Europe and up to 75% in the United States are caused by penicillin. (C)
- Repeated courses are more sensitizing than a single prolonged course. (C)
- Investigation of allergic reactions requires a detailed knowledge of beta-lactam structural chemistry. (B)
- Investigation of an IgE-mediated reaction to penicillin involves skin prick testing, and if negative, intradermal testing. (B)
- Delayed reading of intradermal skin tests or patch tests is used to detect T-cell-mediated reactions to beta-lactams. (C)

- Skin tests are not positive in IgG, IgM or immune complex-mediated reactions. (B)
- Immunoassays are less useful than skin testing for the diagnosis of IgE-mediated sensitivity to penicillin. (C)
- Patch tests are likely to be safe and are useful in testing patients with severe cutaneous reactions such as SJS/TEN, DRESS and AGEP. Intradermal testing can be considered in selected cases but only in specialized units following careful 'risk assessment'. (D)
- Patients with a family history but no personal history of penicillin allergy do not require investigation. (D)
- Skin tests should be undertaken with commercially available major and minor penicillin determinants, benzylpenicillin and amoxicillin and also include the index beta-lactam. (B)
- IgE can be directed to the central ring and/or to the side chain of the beta-lactam molecule. Immunological side chain recognition is particularly relevant for cephalosporin and amoxicillin reactions. (C)
- The negative predictive value of skin tests to penicillin determinants is lower than previously believed. (B) Therefore, if skin tests are negative, a controlled challenge is required. (B)
- The positive predictive value of skin test to penicillin is estimated to be approximately 50%. (B)
- Desensitization should be considered if there is an absolute requirement for a specific beta-lactam in the presence of positive skin or challenge tests. (B)
- Individuals with a positive skin test to an aminopenicillin but negative skin tests to penicillin determinants are likely to be sensitized to the aminopenicillin side chain. (B) In this situation, a cautious challenge to benzyl or phenoxymethyl penicillin can be considered to ascertain whether the patient has a selective penicillin allergy. (D)
- If a cephalosporin is required in a patient with a clinical history of penicillin allergy and positive skin tests – the patient should undergo skin testing using a cephalosporin with a different side chain and, if negative, provocation testing should be undertaken to exclude allergy to the specific cephalosporin. (D)
- If penicillin is required in a patient with a clinical history of cephalosporin allergy, skin testing should be undertaken with penicillins and, if negative, provocation testing to exclude allergy to penicillin. (B) If skin tests are positive, then penicillin avoidance or desensitization can be considered. (B)
- If a cephalosporin is required by a patient with a previous reaction, skin testing to penicillins and the required cephalosporin should be carried out to establish whether sensitization is to the beta-lactam core or side chain. (B) This should be followed by either provocation testing to exclude allergy or desensitization if the patient is allergic. (D)

Introduction and aim of the guideline

'Allergic' or immune-mediated reactions in the form of urticaria and serum sickness began to emerge in the early 1940s when penicillin was introduced as a useful therapeutic agent. The first report is attributed to Lyons [2] who found that 5.7% of US army personnel treated with penicillin for surgical infections suffered from urticaria. The first review on allergic reactions to penicillin was published in 1946 [3]. These 'allergic' or immune-mediated reactions are currently termed 'hypersensitivity' reactions according to the Coombs and Gell classification [4].

Immunological responses to penicillin and other beta-lactam antibiotics can be broadly classified as 'immediate' and 'non-immediate' based on the temporal association of onset of symptoms following drug administration. While 'immediate' responses are IgE-mediated and generally occur within minutes to 1 h following exposure to the last dose, 'non-immediate' reactions are non-IgE-mediated and manifest generally more than 60 min to several days after last dose administration [5]. The latter group is heterogeneous with respect to clinical manifestations and underlying immunological mechanisms. An extended classification of non-immediate drug-induced type IV reactions was introduced by Pichler and colleagues [6, 7]. The longer the interval between the onset of reaction and time of drug intake, the less probable the reaction is IgE-induced, reviewed in [8]. In some cases, however, it is not possible to classify the reaction according only to this time frame.

Investigating immediate and non-immediate reactions to beta-lactams remains challenging particularly when skin tests are negative in the presence of a good clinical history or when there is a selective immunological response to a side chain epitope requiring selection of an alternative beta-lactam.

A recent UK survey on the investigation and management of beta-lactam hypersensitivity revealed an 'alarming' heterogeneity among clinical practices and highlighted the urgent requirement for evidence-based national guidelines [9].

The aim of this guideline was to provide a framework for UK specialist allergists in the investigation, diagnosis and management of the most commonly encountered hypersensitivity reactions to beta-lactams.

Evidence for the recommendations was obtained from systematic literature searches of MEDLINE/PubMed/EMBASE, NICE and the Cochrane library (from 1946 to the cut-off date July 2014) using the following keywords: penicillin, beta-lactam, cephalosporin, monobactam, carbapenem, epidemiology, incidence, prevalence, death, mortality, allergy, hypersensitivity, cross-reactivity, drug provocation test, skin test, basophil activation

test, serum-specific IgE, oral challenge, desensitization, resensitization, risk factor, anaphylaxis, paediatrics and children. Knowledge of the literature and hand searches as well as papers suggested by the panel consulted during the development stage were also used. Where evidence was lacking, a consensus was reached among the panel. The strength of evidence was documented in evidence tables using the grading of recommendations as in a previous BSACI guideline [1]. Conflict of interests was recorded by the BSACI. None jeopardized unbiased guideline development. During the development of the guideline, all BSACI members were consulted using a Web-based system and their comments carefully considered by the Standards of Care Committee (SOCC).

Epidemiology in adults

Beta-lactams are recognized as one of the most frequent causes of immediate and non-immediate drug reactions [10–12]. The prevalence of penicillin hypersensitivity in the general population is unknown as there are no prospective studies evaluating sensitization rates during treatment [13]. Self-reported beta-lactam 'allergy' is common (up to 20% of hospitalized patients), reviewed in [13, 14], but only 1–10% of these patients have evidence of type I hypersensitivity on testing [15, 16]. Adverse reactions to penicillin have been reported in 0.2% per course of treatment in a large unselected cohort [17] and between 3.3% and 5% in a large drug surveillance programme [18, 19]. From data extracted from the electronic health medical records of patients who had at least one outpatient visit, the prevalence of penicillin 'allergy' was 9% and for cephalosporin 1.3%. Women have higher reported 'allergy' prevalence rates for all classes of antibiotics including penicillins in most decades of life in comparison with men [14, 19, 20]. In a retrospective study of 1740 children and young adults who received monthly intramuscular injections of penicillin G for an average of 3.4 years, 3.2% had an 'allergic reaction' with 0.2% developing anaphylaxis [21].

Primary occupational sensitization among medical/laboratory personnel exposed to beta-lactams at work through skin contact or airborne exposure has been reported [22, 23].

Amoxicillin and ampicillin are associated with delayed maculopapular rashes in 5–10% of patients particularly in the presence of a viral infection [24–27]. The overall rate of cephalosporin reactions is 10 times lower than that of penicillin [28].

Epidemiology of skin testing

Skin testing is critical because 'risk assessment' based on clinical history alone is unreliable. For example, the reaction may have occurred in childhood, the patient may not recall the sequence of events, and the reaction may have been related to either the underlying infection or due to side effects of the drug.

Testing is relatively straightforward but undertaken infrequently, potentially resulting in enhanced drug costs due to the prescription of alternative antibiotics especially in patients requiring prophylactic antibiotic treatment for planned procedures [29, 30]. In a matched cohort of hospitalized patients, those with a history of penicillin 'allergy' had 0.59 more hospital days during 20 months follow-up compared with controls [31]. These patients were 23.4% more likely to have C. difficile and 30.1% more likely to have vancomycin-resistant Enterococcus than controls which likely resulted from the use of alternative antibiotics such as clindamycin, quinolones and vancomycin [31]. Mean antibiotic costs in hospital patients labelled as allergic to penicillin were estimated to be 63 times greater than for those not allergic to penicillin [32, 33]. It has been calculated that if 95% of patients with a penicillin 'allergy' history had negative skin test responses and 50% of the additional hospital days could be avoided in the patients with negative skin tests, this would still save about four times the cost of undertaking penicillin tests at admission in those with a penicillin 'allergy' history [31]. In a 6-month UK survey of inpatients with a history of penicillin allergy, the additional cost per patient was £89.29 [34]. These studies emphasize the high level of vigilance required in prescribing non-penicillin-based antibiotics.

There have been American reports of a decreasing rate of positive skin tests in the last two decades [35–37]. This may be partially the result of a decreased topical and parenteral use of penicillins, larger weal size requirement for a positive result implemented by American centres, changes in prescribing and different concentrations of amoxicillin used for skin tests in comparison with European studies.

Older patients and a long time interval since the reaction are independent factors for low rates of positive penicillin tests [19, 37]. The issue over a higher female prevalence of positive skin tests remains unresolved [19, 37–39].

Anaphylaxis

Penicillin is estimated to cause between 0.7% and 10% of all cases of anaphylaxis [40, 41]. With each course of penicillin, the rate of anaphylaxis is estimated to be between 0.015% and 0.004% [32, 41]. Anaphylaxis after prophylaxis with a single dose of benzathine penicillin was 2.17/10 000 healthy military recruits [42].

Anaphylaxis to penicillin occurs most commonly in adults aged between 20 and 49 years with a lower frequency in other age groups [43]. The incidence of anaphylaxis to cephalosporin is not known but is at least

one order of magnitude lower than to penicillin [28] with an estimated risk range between 0.0001% and 0.1% for each treatment course. In Europe, allergy to benzylpenicillin has been gradually replaced by aminopenicillins and cephalosporins because of changes in prescribing habits [44].

Death from penicillin anaphylaxis

The risk of fatal anaphylaxis with penicillin has been estimated at 0.0015% to 0.002% of treated patients [41, 45]. In a study of 151 fatalities, 70% had received penicillin previously and 1/3 had already experienced rapid-onset allergic reactions. Death occurred within 15 min [41]. Up to 20% of drug-related anaphylaxis deaths in Europe and up to 75% of deaths for all drug-related anaphylaxis in the USA are caused by penicillin [40, 46, 47]. In the US, this corresponds to 500–1000 deaths/year [40].

A UK study of drug-induced fatal anaphylaxis between 1992 and 1997 reported 12 deaths due to antibiotics, of which six were due to the first dose of a cephalosporin. Three were known to be allergic to amoxicillin and one had a history of penicillin allergy [48]. Eight fatal cases of anaphylaxis to amoxicillin, of which five had received an intravenous dose, were reported to MHRA between February 1972 and May 2007. Only one case of fatal anaphylaxis after oral amoxicillin was reported [49].

The 'risk factors' for immediate hypersensitivity reactions and for reaction severity are not fully understood. However, one of the most important risk factors relates to the chemistry and metabolism of the drug once administered. Beta-lactams act as haptens and covalently conjugate body proteins, thereby becoming immunogenic molecules.

Other risk factors relate to the host. Based on limited evidence, these are summarized in Box 1.

Box 1. Risk factors for immediate responses to penicillin related to the host

History of previous 'allergic' reaction to penicillin
- A clinical history of penicillin allergy in the more distant past (>15 years) is associated with only a very low risk (0.4%) of reacting on drug challenge [50].
- A clinical history of penicillin allergy does not necessarily predict a positive skin test result [51] reviewed in [52].

Female gender
- Women are more likely to report a history of drug allergy including penicillin 'allergy' than men (11.0% vs. 6.5%) [19, 38, 39] possibly because of the higher number of antibiotic prescriptions for women.

Route of exposure and frequency of administration
- Topically applied penicillin is highly immunogenic and is therefore no longer used [53]. This practice has been endorsed recently by the WAO [54].
- There is limited evidence that the oral route is less likely to cause reactions than other routes [55].
- Frequent courses are more likely to sensitize, for example in patients with cystic fibrosis receiving frequent intravenous antibiotics [56–59]. In these patients, reactions are most commonly caused by penicillin and less commonly by cephalosporins [57, 60, 61].

Age
- Early studies showed that most reactions occur between 20 and 49 years of age [62]. More recent studies report increasing antibiotic allergy with increasing age with 20% of those over 80 years old reporting penicillin allergy [19].
- Older age is also more likely to predispose to a fatal outcome because of cardiovascular or respiratory comorbidity or the use of beta-blockers [43].

Concurrent infections
- Some systemic non-immediate hypersensitivity reactions are associated with reactivation of herpes viruses (EBV, HHV, CMV) [63]. The high occurrence of morbilliform eruptions with aminopenicillins results from hyperstimulation of T cells caused by specific virus exposure [64].
- Amoxicillin is reported to induce a flare up of DRESS by inducing replication of HHV6 [65].
- Rashes are reported in HIV patients treated with co-amoxiclav [66].

Possible risk factors for penicillin allergy

Atopy

Atopy does not predispose to the development of allergic reactions to penicillin [13], but asthma can be a risk factor for life-threatening reactions [13].

Genetic predisposition

The issue of genetics and family history remains unresolved with a family history of adverse reactions to beta-lactams likely more relevant in non-immediate rather than in immediate hypersensitivity reactions [67–70]. The emerging studies indicating a role for genetic predisposition [71, 72] have been relatively small, largely investigating subsets of candidate genes, and have not been confirmed.

In patients with positive penicillin IgE, there is limited evidence for polymorphisms in immunomodulatory genes (i.e. IL4, IL4R, IL10, IL13 and related genes) [71, 73, 74].

Polymorphism in the beta-lactamase gene was found weakly associated with penicillin allergy. The lactamase enzyme is important in the breakdown of penicillin to penicilloate, and this metabolite influences penicillin allergenicity [71].

In a Chinese study, polymorphism in the signal transducer and activator of transcription 6 (STAT6) has been found associated with penicillin allergy but not with IgE levels of patients with penicillin allergy [75]. STAT6 signalling pathway is required for IL4 function.

An association with *HLA A2 DRw52* haplotype has been reported in a cohort of Italian patients with history of delayed hypersensitivity reaction to aminopenicillins [70].

An association of flucloxacillin-induced liver injury has been reported with *HLA-B*5701* in Caucasians [67].

Co-amoxiclav-induced liver injury in Caucasians has been associated with the *HLA-DRB1*1501-DRB5 0101-DQB1*0602* haplotype [69]. High-resolution HLA genotyping showed an association with *HLA-A*0201* and confirmed an association with *HLADQB1*0602* [76]. This study used genomewide genotyping technology.

Molecular structure

Benzylpenicillin belongs to the broad class of antibiotics whose bactericidal activity is mediated by the inhibition of synthesis of the peptidoglycan layer of bacterial cell walls. The first beta-lactams were only active against gram positive bacteria, but later generations displayed activity against a broad spectrum of infectious agents including gram negative bacteria (Table 1).

Table 1. Classification of beta-lactams and their formulation available in the UK

Group	Compound	Activity	Formulation
Penicillins			
Natural penicillins	Penicillin G and V	Gram positive	G: parenteral; V:oral
Penicillinase resistant	Flucloxacillin, temocillin	Mainly for Staphylococcus (but narrower spectrum)	Fluclox: oral and parenteral Temocillin: parenteral
Aminopenicillins ± beta-lactamase inhibitor	Amoxicillin, Ampicillin Co-amoxiclav Co-fluampicil	Gram positive and some gram negative	Oral and parenteral
Mecillinams	Pivmecillinam	Gram negative, but not pseudomonas or enterococci	Oral
Extended penicillin spectrum (in the UK combined with beta-lactamase inhibitor):			
Carboxypenicillin	Ticarcillin and clavulanic acid	Gram positive and gram negative and anaerobes	Parenteral
Acylaminopenicillin	Piperacillin and tazobactam	Wider range of gram negative > Pseudomonas	Parenteral
Cephalosporins			
1st generation	Cefalexin, cefadroxil	Gram positive only	Oral
	Cefradine		Oral
2nd generation	Cefaclor	Moderate gram positive and some gram negative	Oral
	Cefuroxime		Oral and parenteral
3rd generation	Cefixime	Longer duration than the others	Oral
	Cefpodoxime		Oral
	Cefotaxime, ceftriaxone, ceftazidime	Gram negative > gram positive	Parenteral
Carbapenems	Doripenem, ertapenem, meropenem Imipenem and cilastatin	Broad gram positive and gram negative and anaerobes	Parenteral
Monobactam	Aztreonam	Gram negative, not active against gram positive	Parenteral

Penicillins share a core four-member beta-lactam ring structure required for bactericidal activity and an adjacent five-member thiazolidine ring (= sulphur containing) which confers resistance to beta-lactamases. The side chain at position six distinguishes the different penicillins and is an important site of immunological recognition and hence allergic cross-reactivity [11, 13, 77] (Fig. 1).

The cephalosporin family consists of four generations containing a large number of compounds with varied bactericidal activity. Cephalosporins share a beta-lactam ring with penicillins but have a 6-member sulphur-containing dihydrothiazine ring instead of the 5-member thiazolidine ring (Fig. 1). While penicillins have only one side chain (at position 6), cephalosporins have two, one in position 7 and one at position 3. Variations in the chemistry of the position 3 side chain affects drug metabolism, and the side chain at position 7 alters resistance to beta-lactamases and broadens anti-bacterial activity. Carbapenems contain a carbon double bond in place of sulphur in the 5-member thiazolidine ring, while monobactams comprise the β-lactam ring without an attached 5- or 6-membered sulphur ring (Fig. 1).

Antigenic determinants. The beta-lactam ring, the thiazolidine/dihydrothiazine rings and the side group are all potentially immunogenic. Penicillins are too small to be full antigens but develop immunogenicity by acting as haptens covalently binding tissue or serum proteins. Once administered, penicillin undergoes spontaneous degradation because of a chemically unstable β-lactam ring, forming reactive intermediate products which can bind to lysine residue aminogroups on soluble or cell-bound proteins [13, 78, 79]. This results in the formation of benzyl penicilloyl, the major antigenic determinant of penicillin against which the majority of allergic patients react [80, 81].

Following identification, the penicilloyl determinant was conjugated with a polylysine carrier-forming penicilloyl-poly-L-lysine (PPL), which is available as a commercial product used for skin testing in the UK. The remaining part of the penicillin molecule degrades to a range of derivatives which can also act as haptens. These are 'minor determinants' accounting for allergic reactions in approximately 15–16% of patients. Half of these patients react to potassium benzylpenicillin G with the remaining reacting to its alkaline hydrolysis metabolites (sodium benzylpenicilloate and benzylpenicilloate) and its acid hydrolysis product benzyl-N-propylamine. The minor determinants do not cross-react with each other and are known to provoke severe anaphylactic reactions [11, 13, 82].

In addition to the beta-lactam ring, the side chains can also trigger allergic reactions [77, 83–85].

The degradation process for cephalosporins leads to fragmentation of the beta-lactam ring as well as the thiazinic group causing larger degradation products, and this process is more rapid than the fragmentation of penicillin. The exact nature of these intermediate products has not been characterized [86, 87], but the haptenization mechanism appears slower and possibly more complex than with penicillins [88, 89]. Our knowledge of the immunological relevance of cephalosporin hapten-carrier conjugates remains incomplete.

Because of these differences in degradation processes between penicillins and cephalosporins, immune-medi-

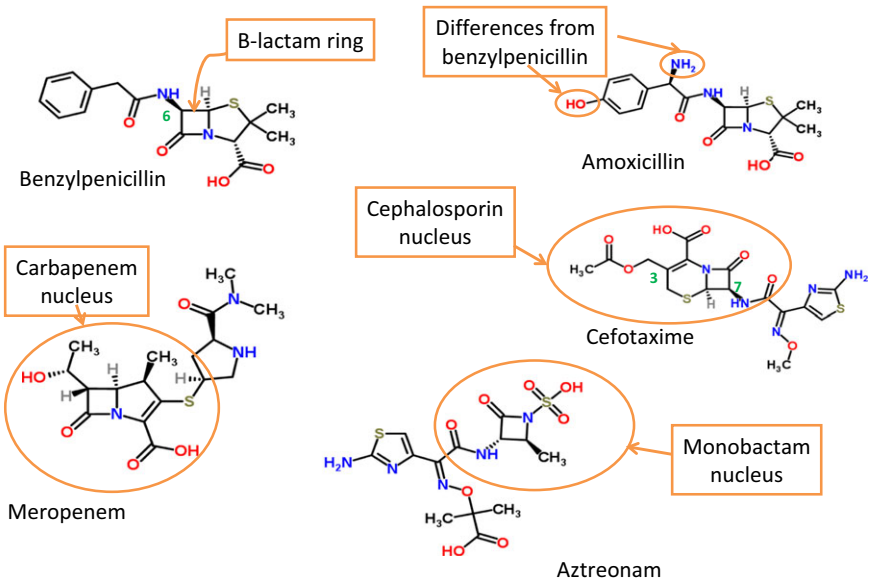

Fig. 1. Beta-lactams – molecular structure.

ated reactions to penicillin can be investigated by detection of specific IgE to major and minor penicillin determinants as well as to the whole molecule. Conversely, cephalosporin allergy can only be studied by the detection of IgE against the native molecule.

Clinical patterns

There is considerable overlap of clinical presentation within the range of Gell and Coombs hypersensitivity reactions to beta-lactams particularly within the non-immediate reactions. Most of them affect the skin, but any organ of the body can be affected. Table 2 shows the classification of allergic reactions.

Diagnosis

Clinical history. As already highlighted by the BSACI drug allergy Guideline [97], a detailed and accurate clinical history is required as the first step to a correct diagnosis. This should include details of the drug, the nature, the time of onset and resolution of the symptoms. These details are particularly important when several drugs are implicated. In addition, written medical and nursing records as well as photographs and eye witness accounts should be sought.

However, despite best efforts, the clinical documentation is often incomplete or inaccurate as the reaction may have taken place many years previously and the patient may have lost his/her sensitivity to the drug. Specialist diagnostic algorithms are available [44, 97, 98].

Skin testing

Clinical expertise is necessary to undertake skin tests and interpret the results with the consequences of misdiagnosis potentially serious. Therefore, investigation for antibiotic allergy should be carried out in specialized drug allergy centres.

Skin testing to beta-lactams provides useful diagnostic information for both type I and type IV hypersensitivity reactions and should be the first line of investigation [99], reviewed in [100, 101]. Indications for skin tests are reported in Boxes 2 and 3. When positive, skin tests reduce the requirement for drug challenge [102, 103]. Testing should be carried out shortly after the reaction has occurred because a long interval between the reaction and skin testing reduces the likelihood of a positive response [104]. Only 20–30% of patients positive on a penicillin skin test remain positive after 10 years [104]. Five years after a positive skin test, 100% of amoxicillin-allergic patients lost skin test reactivity compared to 40% of patients who reacted to a beta-lactam determinant [105]. Approximately one-third of those with a selective positive skin test for cephalosporins maintain skin test reactivity after 5 years follow-up [106]. Conversely, more than half of patients with both penicillin- and cephalosporin-positive allergy tests (non-selective reactors) remain positive after 5 years [106]. It is not known whether the loss of skin test reactivity corresponds to a loss of allergy [8]. It is common practice to wait for 6 weeks from the time of the reaction before undertaking skin testing to avoid a possible lack of response resulting from a refractory period. However, there is little evidence to support this practice, and skin testing may be carried out earlier if clinically indicated although, if negative, repeat testing at a later time is recommended.

Skin testing as a routine screen for beta-lactam hypersensitivity in the absence of a clinical history does not have clinical merit and is not recommended [107]. In the last two decades, there is evidence for a decline in the proportion of skin positive skin tests, which could be in part due to the decreased use of parenteral penicillin [37].

Safety of skin tests

Skin tests are generally safe, but systemic reactions can occur. Therefore, testing should be undertaken in a specialist setting by healthcare professionals with the knowledge, experience and training to interpret test results and the ability and facilities to deal with severe allergic reactions. Facilities for resuscitation and treatment of anaphylaxis must be available, and all patients should have baseline measurements of peak expiratory flow rate, pulse and blood pressure before skin testing [108, 109].

Systemic reactions have been reported in 0.7% to 11% of those with positive skin test results [8, 20, 82, 110], reviewed in [52, 109]. In a cohort of 998 patients with suspected allergy to beta-lactams, 8.8% of skin test-positive patients experienced a systemic reaction with five cases occurring after prick tests [109]. Ten of thirteen reactions were classed as anaphylaxis, and no difference was found between atopic and non-atopic patients. In another cohort of 29 patients skin-tested to penicillin, one patient experienced anaphylaxis during intradermal testing [111]. Occasional fatalities during skin testing have also been reported [112–114].

Procedure. The procedure for skin testing follows the general principles laid out in the BSACI drug allergy guidelines [97]. Histamine as a positive control and relevant negative controls (usually the diluent) must be included. Unlike certain macrolides and quinolones, beta-lactams have not been shown to provoke irritant reactions. Testing for beta-lactams must include major and minor penicillin-allergenic metabolites which are commercially available (Diater™, Madrid, Spain), benzylpenicillin [8, 11, 99, 115], amoxicillin and the specific beta-lactam under test. Ampicillin which has a

Table 2. Types of allergic reactions to beta-lactams

Type	Common name	Mechanism	Characteristics of clinical reaction	Characteristics of patients/applications	Severity/comments
I	Immediate	IgE	Up to 6 h after the last drug administration		Can be life threatening, can cause anaphylaxis or mild forms of urticaria, angioedema or bronchospasm
	Accelerated/ immediate	Can be mediated by IgE	Up to 4 days into drug course, but within 1–6 h from last dose		Urticaria/angioedema and/or wheezing, laryngeal oedema
II	Cytotoxic reactions	IgG lyses the leucocytes, platelets or red blood cells in the presence of complement	Blood disorders (i.e. agranulocytosis, thrombocytopenia and haemolytic anaemia)	Patients with prolonged courses of penicillin [90]	
III	Immune complex reactions	IgG, IgM or immune complexes Or non-immune-dependent clinical manifestation triggered by certain cephalosporins such as cephaclor	3–4 weeks after treatment start [91]. Serum sickness with fever, urticarial rash, arthralgias and lymphadenopathy		
IV	Non-immediate/ delayed reactions	T cell mediated resulting from the stimulation of distinct T-cell subsets. Relation between clinical manifestations and immune mechanism [6, 7, 64]	>3–4 days from the first administration or >1–2 h from the last administration [11, 92, 93]. Very heterogeneous; generally cutaneous. Onset of rash can occur up to 2–4 weeks after starting the antibiotic or soon after discontinuation of the drug		
IVa	Classical contact-induced hypersensitivity reaction	T cells stimulate IFN gamma-activated macrophages/monocytes	Eczema/dermatitis	Topical use of penicillin (abandoned in the UK because frequently sensitizing) [52, 53] Health professionals or workers in the manufacturing industry	
IVb		Mediated > by Th2 cells producing IL4 and IL5 causing in turn IgE release and eosinophil recruitment.	Morbilliform or maculopapular rashes. Occasionally: DRESS.	- In up to 10% of patients taking ampicillin and amoxicillin [24]*. - In up to 70–90% of patients infected with EBV or HPV viruses taking aminopenicillins* [25]. - Flare up of DRESS caused by other drugs with amoxicillin - HIV [66] and CMV -positive patients [94, 95, 96]	Mild to severe

Table 2. continued

Type	Common name	Mechanism	Characteristics of clinical reaction	Characteristics of patients/applications	Severity/comments
IVc		CD4 and CD8 cytotoxic T-cell activation producing massive keratinocyte apoptosis particularly in TEN.	Bullous exanthems: SJS and TEN.		Severe systemic. Re-administration of the culprit drug must be avoided
IVd		Neutrophil activation and recruitment via the production of IL8.	(AGEP).	Aminopenicillins – responsible drug [6]	

*A proportion of patients (but not all) tolerate re-administration of the aminopenicillin without any reaction [96]

Box 2. Indications for the investigation of patients with immediate or non-immediate* reaction/s to penicillin/s and cephalosporin/s [98]

- Patients with a label of 'multiple antibiotic allergy'
- Patients with a history of immediate or non-immediate* reaction to penicillin/s and/or cephalosporin/s with a requirement for frequent antibiotics, for example patients with bronchiectasis, CF, diabetes, primary and secondary immunodeficiencies or with asplenia/hyposplenism.
- Patients with a history of immediate or non-immediate* reaction to penicillin/s and/or cephalosporin/s requiring specific treatment with a beta-lactam.
- Anaphylaxis during general anaesthesia when penicillin was administered alongside multiple other agents.

*Delayed-onset urticaria, maculopapular and morbilliform exanthemata.

Box 3. Skin testing not required, unhelpful or contraindicated

- Patients who have suffered from symptoms consistent with IgG or IgM-mediated reactions. These patients should not receive penicillin again.
- Patients with a family history but no personal history of allergy to penicillin [14].
- Patients with a history of beta-lactam allergy but who subsequently tolerated the same penicillin.
- There are only limited data on the safety of intradermal testing in patients with severe cutaneous allergic reactions such as TENS, SJS and AGEP, but patch tests are likely to be safe and helpful. Intradermal testing should be considered only in selected cases following careful 'risk assessment'.

different side chain structure (C6) to amoxicillin may also be included particularly when investigating allergy to some cephalosporins with which it shares a side chain, e.g. cefadroxil (C7), [116], Fig. 1. Caution should be exercised in patients at risk of anaphylaxis and taking beta-blockers or ACEI as they may require larger doses of adrenaline in the event of an allergic reaction. In many patients, it is possible to temporarily withdraw beta-blockers for 24–48 h after consulting with the GP/cardiologist.

Skin testing for immediate hypersensitivity reactions

Skin Prick testing. Skin tests provide evidence of sensitization to beta-lactams, but must always be interpreted within the appropriate clinical context and not used to screen for drug allergy. Testing should be carried out with the drug in a parenteral form or with the drug in a liquid preparation. Non-irritant skin prick test concentrations have been recently reviewed in a position paper [117] Appendix Table A1. Weals tend to be smaller than those obtained with inhalants/food allergens; therefore, a weal diameter of at least 3 mm greater than the negative control is considered positive. The coexistence of a flare and itch supports a positive result. A larger weal, of 5 mm size, has been adopted by some American centres to increase specificity [35, 37], but the BSACI recommends a 3-mm cut-off in line with European guidelines [8, 93, 118].

Intradermal skin testing. If the skin prick test is negative, intradermal testing should be undertaken by injecting 0.02–0.04 mL into the volar aspect of the arm to raise a 4- to 6-mm bleb. In cases with a history of severe reactions, intradermal testing can start with a dilution of 1/100 of the therapeutic drug concentration increasing 10-fold until a non-irritant concentration is reached. Non-irritant concentrations for beta-lactam intradermal

tests have been identified in a European position paper [117] Appendix table A1. An increase in weal size of more than 3 mm from the initial bleb with flare is considered positive. In our experience, however, when the clinical history strongly supports IgE-mediated allergy, persistence of a smaller weal after 20 min if accompanied by a flare and itch may indicate a positive result.

Skin test reagents

The only commercially available penicillin skin testing kit in Europe is from Diater. The major determinant is conjugated to polylysine to obtain a complete antigen (benzylpenicilloyl-poly-L-lysine) (PPL). The formulation for the minor determinant mixture (MDM) has changed and no longer contains a mixture of benzylpenicillin, benzyl penicilloic acid and sodium benzylpenicilloate, reagent renamed MD, but now only comprises benzylpenicilloate. Therefore, the performance characteristics of the test are no longer validated as previously reported [119–121].

Skin testing to penicillin G, an important minor determinant, should be undertaken separately as the Diater kit does not contain benzylpenicillin. Despite its limitations, this kit has been routinely used and has been found useful in the UK [122]. Early studies estimated that omitting penicillin G, penicilloic acid and penicilloyl-poly-L-lysine would lead to non-detection of 13.4% of positive cases [104]. Furthermore, an early study by Macy and colleagues [80] found that up to 20% of patients were only positive to minor determinants (penilloate and penicilloate). The importance of including both PPL and MDM determinants has been confirmed in two series of patients with hypersensitivity reactions to beta-lactams [81, 123]. In this retrospective series which included reactions to aminopenicillins, penicillin V, cephalosporins, etc., if PPL or MDM had been omitted from testing, 14.7% and 47%, respectively, of beta-lactam allergic patients would have been missed. The sensitivity of skin testing is up to 70% if PPL, MDM, amoxicillin and ampicillin are used [8].

By contrast, in an American study of 500 sequential patients with a history of suspected penicillin allergy, skin tests performed using PPL, benzylpenicillin and amoxicillin were positive in only 0.8% patients [35], but no amoxicillin skin test-positive patient was detected. All patients negative on skin test underwent oral challenge with amoxicillin, and this was positive in only 0.8% patients confirming that only eight patients of 500 were allergic to a penicillin. Different cohorts of patients (only 2.8% with anaphylaxis), a longer time interval from the original reaction, unavailability of MDM and change to a larger weal diameter for a positive result (5 vs.3 mm) may have accounted for the small number found to be allergic. However, these results also indicate the requirement for large prospective studies on patients with a well-documented history of penicillin allergy and the availability of the full set of commercial penicillin determinants to detect IgE-mediated penicillin allergy. Currently, it is not possible to calculate the specificity of skin testing because provocation in patients with positive skin tests cannot be used as a gold standard.

By contrast, in European studies, 43% of a cohort of 290 skin-tested patients were positive to amoxicillin, hence the importance of including amoxicillin in skin testing [116, 124, 125]. The addition of minor determinants of amoxicillin does not, however, increase the detection rate [126]. The higher use of amoxicillin in Europe is a likely explanation for the different findings.

A positive test to MDM is associated with a fourfold increase in the likelihood of a positive skin test to at least one cephalosporin [127]. Selective sensitization to clavulanic acid has been described despite its low immunogenicity [128, 129]. In one reported case, specific sensitization to penicillin V was reported [130].

Skin testing for cephalosporins. Skin testing with non-penicillin beta-lactams is less validated [131] because allergenic epitopes of cephalosporin degradation products are not fully identified. Therefore, the negative predictive value of skin testing remains uncertain.

For intradermal testing, all cephalosporins are non-irritant at concentrations of 2–3 mg/mL, see Appendix, Table A1 [13, 117]. A 10-fold dilution has also been reported as non-irritant for cephalosporins [132, 133]. For patients with a history of severe reactions, a lower starting concentration for intradermal testing should be considered.

Skin tests for non-immediate hypersensitivity reactions

Non-immediate immune reactions to beta-lactams mainly affect the skin but can also target specific organs causing nephritis, hepatitis, vasculitis or multiple organ systems such as in DRESS/DHS. The clinical presentation of these reactions results from the release of specific cytokines by activated T-cell subsets. This release is responsible for the broad spectrum of syndromes ranging from morbilliform/maculopapular and urticarial rashes, which are most common to the less common but severe reactions such as AGEP, DRESS and SJS/TEN. The diagnosis of non-immediate reactions can be challenging because clinically, they can mimic autoimmune or infectious diseases and can occur in association with viral infections [44]. A subclassification of Gell and Coombs type IV delayed reactions has been proposed to show a relationship between clinical syndromes and specific cytokine release from distinct T-cell subsets (Table 2) [6].

For non-immediate reactions, skin tests are not as standardized as for immediate reactions, and their sensitivity is not fully validated. Negative skin tests with delayed reactions may occur if the reaction was not immune-mediated, or because of poor penetration of the drug into the skin or because of the absence of cofactors present at the time of the reaction. Both patch tests and delayed reading of intradermal tests can be used to diagnose T-cell-dependent reactions to beta-lactams [134–138]. The addition of penicillin determinants in evaluating non-immediate reactions is of only very limited diagnostic value [139].

By convention, patch tests are undertaken on the upper back on unaffected and untreated skin using commercial chambers [140, 141]. Topical steroids should have been avoided for at least 2 weeks prior to the test and oral steroids/immunosuppressive drugs discontinued for 3–4 weeks. A scoring system has been conventionally established by the International Contact Dermatitis Research Group as follows: 1+ (erythema, infiltration and possibly papules), 2+ (erythema, infiltration, papules, vesicles) and 3+ (intense erythema, infiltration, coalescing/confluent vesicles).

In the UK, patch testing is mainly used within a dermatological setting by specialists with an interest in drug allergy. Patch tests are necessary when the drug is only available in tablet or topical formulation. For beta-lactam patch tests, a concentration of 5–10% in petrolatum is generally considered suitable [134]. Although recent consensus recommends that the drug is diluted in petrolatum [117] Appendix table A1, if saline is used to dilute the beta-lactam for patch testing, then a 10% concentration is necessary to increase sensitivity [136]. Liquid beta-lactam preparations should be diluted at 30% in water [142]. Non-irritant concentrations and amounts of active ingredients in drug patch tests have been reported recently [143]. Drugs such as some cephalosporins not available in parenteral form can be ground down in a mortar, weighed and either diluted in saline or added to petrolatum [93].

Reading and interpretation of patch tests. If the clinical history is unclear or indicates an earlier reaction, compatible with an IgE-mediated mechanism, then the patch test should be read initially at 20 min. Further readings are taken at 48–72 and 96 h. Additional reading of the test should be considered up to 6–7 days from testing as occasionally a reaction develops at a later stage, or if sensitization is suspected to trigger a late cutaneous reaction [144].

Delayed reading and interpretation of intradermal tests. In the UK, allergists are more familiar with the practice and interpretation of intradermal rather than patch tests. With delayed reading of intradermal tests, the change in weal size from injection of the initial bleb is read after 20 min and again after 24, 48 and 72 h. Intradermal tests have been reported to provoke a relapse of the original drug reaction [109].

Systemic reactions after testing. Although both patch and intradermal testing can provoke systemic reactions, systemic reactions to patch tests are quite rare [145, 146]. Thus, patch tests have been proposed as first-line investigations in severe systemic cutaneous reactions [146, 147]. The same precautions as for drug challenge should be employed when skin testing for delayed hypersensitivity.

Sensitivity of skin testing in non-immediate reactions. In patients with mild skin reactions to beta-lactams, a sensitivity of only 9% was reported with patch testing. This may be due to poor penetration of some reagents into the skin [92]. Late reading of intradermal tests for beta-lactams appears to be more sensitive than patch testing [136] possibly because with intradermals, the drug is injected into an immunologically rich skin compartment. In a study of 241 patients with late-onset reactions to penicillins, patch tests were positive in 7.5% with benzylpenicillin and 37.3% with aminopenicillins, as opposed to IDTs which were positive in 12% for benzylpenicillin and 39% for aminopenicillins [134]. These results were consistent with those reported subsequently [148]. Patch tests may be more specific than late-reading intradermal tests as some patients who were positive by delayed intradermal tests but negative with patch tests were also negative on challenge [134].

When investigating non-immediate reactions to penicillins, patch or intradermal tests with PPL and MDM are only of limited use [139]. Patch testing has been shown to be particularly useful in the diagnosis of AGEP. Positive responses were obtained in 7/14 patients with AGEP in comparison with only 2/22 patients with SJS/TEN [149]. There is evidence that non-immediate sensitization particularly to aminopenicillins is long-lasting [134].

In summary, delayed reading of IDTs is likely more sensitive but less specific than patch tests; systemic reactions to patch tests may be less likely than with intradermal tests, and PPL and MDM are of only limited use in the diagnosis of non-immediate reactions.

Skin tests for patients with a history of unknown time interval between the last drug dose and the onset of urticaria/angioedema

Skin testing to detect both immediate and delayed reactions is undertaken for this group. Although a 7-day challenge has been shown to yield more positive reactions than shorter challenges [150], in the UK, it is

common practice to undertake a 3- to 5-day drug challenge.

Predictive value of skin tests for penicillin

The negative predictive value of skin tests for penicillin is not as high as originally reported by early American studies at a time when narrow-spectrum penicillins were prescribed [20, 82, 151–153].

More recent European studies reported that between 8.4% [154] and 30.7%, skin test-negative patients reacted on drug challenge only. In the study by Messaad and colleagues [154], only 23% were positive for major and minor determinants and 46.3% skin test positive to the specific beta-lactam (but not PPL/MDM), indicating that only 69.3% were diagnosed by skin testing and 30.7% diagnosed following drug provocation [155]. Therefore, approximately one-third of patients with penicillin allergy have negative skin tests [125, 156] and all patients with negative skin tests require oral challenge to exclude allergy. The positive predictive value of skin testing is based on very limited challenges of skin test-positive patients and estimated to range from 40% to 100% [20, 152, 157].

The negative predictive value for patch and delayed reading intradermal tests in patients with non-immediate reactions to beta-lactams has not yet been fully established as the total cohort of patients tested has been small. In one study, only 1/64 patients negative to patch/intradermal skin tests reacted on provocation [134, 146]. In a further study, only 2/22 patients positive on provocation test (maculopapular exanthema or urticaria) were positive on delayed intradermal testing, suggesting that the sensitivity of skin testing for non-immediate reactions may be lower than previously reported [92, 158]. The positive predictive value has not been evaluated.

Resensitization following investigation

One early study reported re-sensitization after high-dose parenteral penicillin with a conversion rate of 16% (3/18) [159]. Larger, more recent studies have established that patients with a previous history of penicillin allergy have a low risk of resensitization following assessment by skin testing and an oral course of penicillin [160, 161]. Oral provocation testing with beta-lactams has a negative predictive value of 94% [162] with none of the false-negative patients experiencing subsequent life-threatening reactions. This also indicates that oral challenge results in a low conversion rate. Therefore, there is no need to repeat skin tests before each course of treatment in patients who have tolerated oral penicillin. However, the International Consensus on Drug Allergy [163] has suggested that retesting should be considered in those individuals who suffered a particularly severe reaction to a beta-lactam even if they had tolerated therapeutic administration of the drug during testing.

Laboratory investigations

IgE tests for beta-lactams although specific are not sensitive. The ImmunoCAP system (Phadia AB, Uppsala) is the most widely used assay for beta-lactams, but for cephalosporins, this assay is limited to cefaclor. The specific beta-lactam is covalently coupled to ImmunoCap and interacts with specific IgE in the patient's serum and detected via fluorescence. Using the commercially available ImmunoCAP system, the sensitivity of IgE testing to amoxicillin- and/or benzylpenicillin-derived agents in 48 skin test-positive patients was estimated at 54%, while specificity was up to 95% [164]. Comparison between ImmunoCAP and an in-house RAST showed lower sensitivity for ImmunoCAP ranging from 0% to 25%, while the specificity of ImmunoCAP for beta-lactams ranged from 83.3% to 100%. The sensitivity of ImmunoCAP was found to be higher in cases where the patient's allergic reaction was anaphylaxis, while the sensitivity of a non-commercial RAST assay was highest in patients who had anaphylactic shock with hypotension [165]. Positive and negative predictive values were estimated at 45% and 77.1% with ImmunoCap and 18.5% and 81.5% with RAST. Differences in sensitivity and specificity among specific IgE testing reagents have been summarized [166]. An attempt to increase the sensitivity by lowering the detection limit for IgE to 0.1 KU/L did not significantly improve the diagnostic performance of the test as the specificity dropped from 80% to 54% [167].

Reports from relatively small Spanish cohorts with well-documented histories of immediate beta-lactam allergy showed positive IgE tests but negative skin tests for beta-lactams, indicating that serological IgE detection may have a role in diagnosis [44, 86, 125, 164]. In this Spanish cohort of 290 patients with immediate reaction to a penicillin derivative, 40 patients were skin test negative and RAST positive and 24/40 skin test-negative patients had the RAST diagnosis confirmed by provocation [168]. Conversely, in a more recent prospective study of 150 patients with a history of penicillin allergy, none of the patients positive on oral challenge were positive by ImmunoCap [169]. Furthermore, positive specific IgE immunoassays for benzylpenicillin were reported from a series of amoxicillin-selective reactors who tolerated benzylpenicillin [85].

In summary, as the sensitivity of laboratory IgE testing is low, IgE testing should be considered only in selected patients undergoing specialist investigation in

conjunction with skin tests [98]. IgE tests may have a place in cases with severe anaphylaxis to limit drug provocation, particularly if skin tests are unexpectedly negative.

Basophil activation test

Basophil activation test (BAT) has been proposed as a possible functional assay for the diagnosis of allergy to beta-lactam [170, 171]. Basophils sensitized with IgE become activated and express certain markers at increased density. Activation of basophils in these patients' blood can be measured by flow cytometry targeting the specific basophil markers CD63 or CD203c. Despite specificity of 93.3%, the sensitivity of BAT is only 50% although may be higher for cephalosporins [136, 172, 173]. In a cohort of 41 amoxicillin-allergic patients, followed up over a 4-year period with both BAT and RAST tests every 6 months, the disappearance of IgE-specific antibody was earlier with BAT than with RAST. However, the difference was only significant when amoxicillin and not benzylpenicillin was used as the hapten [174]. The clinical utility of BAT, however, remains limited by the requirement for fresh blood, specialized laboratory equipment and technician time and therefore remains largely a research tool until its role can be fully defined.

In vitro detection of beta-lactam specific T cells

An IFNγ ELISPOT sensitive assay. An IFNγ ELISPOT sensitive assay has been developed in a research setting for the detection of cross-reactivity among beta-lactams in patients with maculopapular exanthemata due to amoxicillin [175]. Interestingly, amoxicillin-specific T cells were still detectable several years after the allergic reaction occurred even after strict drug avoidance. The ELISPOT assay has the potential for clinical use in the future, but only after validation in larger numbers of allergic and non-allergic patients.

Lymphocyte transformation test (LTT). Specifically sensitized lymphocytes proliferate when exposed to the sensitizing drug, and LTT has been used to evaluate non-immediate reactions to beta-lactams [176]. This test is currently used in research settings as its precise sensitivity and specificity have not been sufficiently validated for routine clinical use [11].

Cross-reactivity among beta-lactams

Cross-reactivity among beta-lactams occurs not only through the central beta-lactam ring but particularly because of side chain homology with details listed in Tables 3 and 4.

Cross-reactivity with monobactams

Aztreonam is a monobactam with a single beta-lactam ring without the bicyclic ring structure characteristic of other beta-lactams. It is less immunogenic than penicillins or cephalosporins. Patients with proven immediate and delayed sensitivity to beta-lactams have been shown to tolerate challenge with aztreonam [177–179] including two patients with evidence of specific IgE to aztreonam [180]. Of 45 patients with a clinical history of immediate beta-lactam, mainly penicillin allergy and positive skin or IgE tests, none had a positive intradermal test for aztreonam and all tolerated a graded intramuscular challenge [178].

In a cohort of 78 patients with non-immediate allergy to beta-lactams, again mainly penicillins, and positive patch and/or delayed intradermal tests for at least one beta-lactam, none tested positive to aztreonam, and all 65 patients who underwent challenge tolerated intramuscular aztreonam [179]. However, a single case of cross-reactivity between penicillins and aztreonam has been reported in which a patient with confirmed anaphylaxis to penicillin developed anaphylaxis immediately following the administration of aztreonam [181]. It was not clear whether this was true cross-reactivity to common epitopes or due to dual allergic sensitization.

Cross-reactivity between aztreonam and ceftazidime occurs because of side chain homology [182], but the incidence of allergy in these patients is lower than would be predicted from their molecular structure alone. In a series of 11 patients with a known ceftazidime allergy, only one had a positive skin test to aztreonam [183].

Therefore, aztreonam is generally tolerated by patients with confirmed immediate and non-immediate sensitivity to beta-lactams although rarely cross-sensitization is observed with ceftazidime.

Cross-reactivity with carbapenems

On the basis of their molecular structure, one would expect cross-reactivity between penicillins and carbapenems. Early studies reported that up to 50% of patients with positive penicillin skin tests and history of penicillin allergy were also positive to imipenem reagents on skin testing indicating cross-sensitization [184]. However, more recent retrospective studies have reported clinical cross-reactivity between carbapenems and penicillins of between 9.2% and 11% compared to carbapenem allergy of 2.7–3.9% in those without peni-

Table 3. (a) Side chain homology of cephalosporins (C7 position)*, (b) side chain homology of cephalosporins (C7 position) compared to penicillins (C6 position)

	Cefaclor	Cefadroxil	Cefalexin	Cefixime	Cefotaxime	Cefpodoxime	Cefradine	Ceftazidime	Ceftriaxone	Cefuroxime
(a)										
Cefaclor		Similar	Same	Δ	Δ	Δ	Same	Δ	Δ	Δ
Cefadroxil	Similar		Similar	Δ	Δ	Δ	Similar	Δ	Δ	Δ
Cefalexin	Same	Similar		Δ	Δ	Δ	Same	Δ	Δ	Δ
Cefixime	Δ	Δ	Δ		Similar	Similar	Δ	Similar	Similar	Δ
Cefotaxime	Δ	Δ	Δ	Similar		Same	Δ	Similar	Same	Δ
Cefpodoxime	Δ	Δ	Δ	Similar	Same		Δ	Similar	Same	Δ
Cefradine	Same	Similar	Same	Δ	Δ	Δ		Δ	Δ	Δ
Ceftazidime	Δ	Δ	Δ	Similar	Similar	Similar	Δ		Similar	Δ
Ceftriaxone	Δ	Δ	Δ	Similar	Same	Same	Δ	Similar		Δ
Cefuroxime	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	

	Penicillin G	Ampicillin	Amoxicillin	Aztreonam
(b)				
Cefaclor	Similar	Same	Similar	Δ
Cefadroxil	Similar	Similar	Same	Δ
Cefalexin	Similar	Same	Similar	Δ
Cefixime	Δ	Δ	Δ	Similar
Cefotaxime	Δ	Δ	Δ	Similar
Cefpodoxime	Δ	Δ	Δ	Similar
Cefradine	Similar	Same	Similar	Δ
Ceftazidime	Δ	Δ	Δ	Same
Ceftriaxone	Δ	Δ	Δ	Similar
Cefuroxime	Δ	Δ	Δ	Δ

Δ, different (side chain)

*Side chain structure does not strictly correlate with the recognized anti-bacterial classification of cephalosporins such as 1st, 2nd, 3rd, etc. generation. 'Same' denominates an identical side chain; 'similar' indicates close resemblance (e.g. benzene ring similar to phenol side chain but different to azole ring).

cillin allergy. No difference in the rate of allergic-type reactions was observed between imipenem and meropenem, and no skin tests were performed in these studies [185–187].

Low rates of cross-reactivity on skin testing were also documented in a prospective study between meropenem and penicillin as well as imipenem/cilastatin and penicillin with a prevalence of only 0.9% [188, 189]. Importantly, all patients with negative skin tests to carbapenems tolerated graded challenges. In another prospective study, meropenem was safely administered to 110 patients self-reporting an allergy to penicillin although penicillin allergy was not confirmed by skin testing in any of the cases [190].

In patients with a proven non-immediate reaction to beta-lactams (mainly penicillin/aminopenicillin), the prevalence of cross-reactivity on patch testing to imipenem–cilastatin was 5.5% with a negative predictive value of 100% [191]. More recently, however, absence of cross-reactivity to carbapenems was reported in 204 patients with non-immediate reactions to penicillins and positive patch and/or delayed intradermal skin tests to at least one penicillin reagent. All patients were negative to carbapenems on patch and/or delayed reading intradermal tests, and all had negative challenges with imipenem/cilastatin and meropenem [192].

In summary, cross-reactivity between carbapenems and penicillin is not as high as initially reported, and skin testing for carbapenem for both immediate and non-immediate sensitization although not yet validated appears reliable.

Cross-reactivity between cephalosporins and penicillins

Evaluation of cephalosporin sensitivity in patients allergic to penicillin. The degradation processes for penicillins and cephalosporins are fundamentally different; thus, cross-reactivity between these two beta-lactam classes is likely to be clinically less relevant than previously assumed.

Much of the evidence on cross-reactivity comes from retrospective studies [193–197], some of which report on small cohorts undergoing skin testing or are based only on 'clinical history'. Conclusions based only on skin tests may overestimate cross-reactivity because the positive predictive value of skin tests remains undetermined. It is now also known that first-generation ceph-

Table 4. (a) Side chain homology of cephalosporins (C3 position), (b) side chain homology of cephalosporins compared to penicillins (C3 position)

	Cefaclor	Cefadroxil	Cefalexin	Cefixime	Cefotaxime	Cefpodoxime	Cefradine	Ceftazidime	Ceftriaxone	Cefuroxime
(a)										
Cefaclor		Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ
Cefadroxil	Δ		Same	Δ	Δ	Δ	Same	Δ	Δ	Δ
Cefalexin	Δ	Same		Δ	Δ	Δ	Same	Δ	Δ	Δ
Cefixime	Δ	Δ	Δ		Δ	Δ	Δ	Δ	Δ	Δ
Cefotaxime	Δ	Δ	Δ	Δ		Δ	Δ	Δ	Δ	Similar
Cefpodoxime	Δ	Δ	Δ	Δ	Δ		Δ	Δ	Δ	Δ
Cefradine	Δ	Same	Same	Δ	Δ	Δ		Δ	Δ	Δ
Ceftazidime	Δ	Δ	Δ	Δ	Δ	Δ	Δ		Δ	Δ
Ceftriaxone	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ		Δ
Cefuroxime	Δ	Δ	Δ	Δ	Similar	Δ	Δ	Δ	Δ	

	Penicillin G	Ampicillin	Amoxicillin	Aztreonam
(b)				
Cefaclor	Δ	Δ	Δ	n/a
Cefadroxil	Δ	Δ	Δ	n/a
Cefalexin	Δ	Δ	Δ	n/a
Cefixime	Δ	Δ	Δ	n/a
Cefotaxime	Δ	Δ	Δ	n/a
Cefpodoxime	Δ	Δ	Δ	n/a
Cefradine	Δ	Δ	Δ	n/a
Ceftazidime	Δ	Δ	Δ	n/a
Ceftriaxone	Δ	Δ	Δ	n/a
Cefuroxime	Δ	Δ	Δ	n/a
Penicillin		Same	Same	n/a
Ampicillin	Same		Same	n/a
Amoxicillin	Same	Same		n/a

'Same' denominates an identical side chain; 'similar' indicates close resemblance (i.e. acetyloxy methyl on cefotaxime and [(aminocarbonyl)-oxy] methyl on cefuroxime).

alosporins, when initially manufactured, contained traces of penicillins.

There is some evidence to suggest that patients with a history of penicillin allergy who react to cephalosporins tend to react with more severe allergic reactions, including anaphylaxis [48, 197]. Cross-reactivity between penicillin and first and early (introduced before 1980) second-generation cephalosporins has been reported to occur in up to 10% and for third generation in 2–3% penicillin-allergic patients, reviewed in [198]. Cross-reactivity with fourth-generation cephalosporins which are not available in the UK has not been reported. A meta-analysis on safe selection of cephalosporins in penicillin-allergic patients reported an increase in allergic reactions to first-generation cephalosporins but no increase with second- or third-generation cephalosporins [199].

Lack of cross-reactivity was found in 41 penicillin-allergic patients challenged with three different cephalosporins (cefazolin – 1st generation; cefuroxime – 2nd generation; ceftriaxone – 3rd generation) each with a side chain distinct from that found in penicillin [200].

Cross-reactivity as a result of antibody recognition is more closely related to side chain homology (and possibly the small beta-lactam fragment linked to the carrier protein during cephalosporin conjugation) rather than the central beta-lactam ring [86–88]. Therefore, cefadroxil, cefradine, cefaclor and cefalexin have significant cross-reactivity in patients with a previous history of allergic reaction to ampicillin/amoxicillin because of similarities in side chain structure (table 3a,b) [89]. Amoxicillin and cefadroxil have a reported cross-reactivity as high as 38% [201, 202]. In a prospective study [127] of 128 patients allergic to penicillin, 10.9% (14/128) were skin test positive for at least one cephalosporin; of these, 64% (9/14) reacted with a cephalosporin displaying the same side chain as the penicillin (cefamandole, cephalothin), but 36% (5/14) were sensitized to a cephalosporin with a different side chain. Thus, factors other than side chain homology are also important in determining allergic cross-reactivity between penicillins and cephalosporins.

Less is known about cross-reactivity between penicillins and cephalosporins in non-immediate hypersensitivity reactions which are less common but likely longer lasting than IgE-mediated reactions. Both the core structure of the beta-lactam and side chain can be recognized by T cells [44], although recognition of

the amino-benzyl side chain appears more important. In a study of 71 patients with delayed reactions, 68 had at least one positive patch or intradermal skin test to an aminopenicillin, and 69/71 tolerated oral challenge with at least one cephalosporin without an aminobenzyl side chain such as cefpodoxime or cefixime. The remaining two subjects developed exanthema during the challenge.

All 51 patients who were skin test negative to benzyl or phenoxymethyl penicillin also tolerated oral challenge with phenoxymethyl penicillin [203].

In summary, the majority of cross-reactivity between penicillins and cephalosporins is due to side chain homology although shared epitopes from other parts of the molecule also account for cross-reactivity.

Penicillin sensitivity in patients sensitive to cephalosporin. In a prospective study of 98 patients with immediate reactions to cephalosporins, 2% reacted on skin testing to penicillin, 3% to aztreonam, 2% to imipenem and 1% to meropenem. The most common cephalosporins causing a reaction were ceftriaxone, ceftazidime, cefaclor and cefotaxime. A reaction to a cephalosporin with a side chain similar or identical to a penicillin increased the risk of skin test cross-reactivity by threefold (55.5% vs. 18.7%) [183].

In a prospective study of 105 patients with a history of non-immediate reactions to cephalosporins, all subjects were tested by both patch and delayed intradermals using a panel of penicillins and the suspected cephalosporin. Drug challenge was undertaken in those negative to both skin tests. 5/105 (= 4.7%) patients were positive to the suspected cephalosporin (three with both patch and delayed intradermal tests and two only on delayed intradermal reading). In two patients, cephalexin displayed skin test cross-reactivity with aminopenicillins likely due to a shared side chain amino group. The index cephalosporin was tolerated by all 86 patients with negative skin tests who agreed to challenge [204].

Cross-reactivity among cephalosporins

Cephalosporins cause immune-mediated reactions in 1–3% of patients even in the absence of a history of penicillin allergy reviewed in [89].

Immediate allergic reactions to cephalosporins exhibit two patterns of immune response: one group of patients respond only to cephalosporin determinants (and some of these patients only to a single cephalosporin) and the second group cross-react with penicillin [11, 205]. Clinical cross-reactivity among cephalosporins mainly relates to the R1 side chain (in position 7) and possibly to the R2 side chain (in position 3) rather than to the beta-lactam ring [183].

As shown in Table 4a, cefalexin, cefadroxil and cefradine have the same R2 side chain while there is identity or similarity of the R1 side group in ceftriaxone, cefixime, cefotaxime, ceftazidime and cefpodoxime (Table 3a). Side chain structure does not correlate with antimicrobial classification.

Therefore, if a patient reacts to a specific cephalosporin, skin testing to a cephalosporin with a different side chain can be considered, and if this is negative, drug challenge may be undertaken with that cephalosporin (Tables 3 and 4).

Oral provocation for immediate reactions

For safety reasons, there is consensus among allergists to avoid drug challenge if skin tests are positive. Thus, positive predictive values of beta-lactam skin tests have not been determined.

Skin test detection rates vary among different populations, with penicillin allergy diagnosed in up to 69.3% of patients by skin testing in the European studies [155, 156] and in 50% of patients in a more recent American study [35]. From all these studies, however, it is evident that drug challenge is required to either confirm or exclude drug allergy. In European studies, the diagnosis of drug allergy is confirmed by drug challenge in one-third, and in American studies, approximately half of patients are diagnosed by drug challenge.

Protocols for challenge testing have been published [154], but each should be individually tailored according to the severity and timing of the original reaction. Previous drug allergy expertise is an absolute requirement because a graded challenge which is too cautious may induce tolerance leading to a false-negative result and if too rapid may provoke a life-threatening reaction. It is important to differentiate subjective symptoms such as pruritus and dizziness during the challenge. Such symptoms have been recorded in 3% of oral challenges in patients who eventually tolerated the challenge [206]. Limitations of drug challenge are given in Box 4.

In most cases, drug challenge in patients with immediate reactions to beta-lactam is undertaken by the oral route. The dosing interval is between 30 [154], Appendix table A2, and 90 min for oral challenge and 30 min for intramuscular or intravenous challenge. If drug provocation is negative, the patient should continue the challenge at home for a further 3–5 days at the therapeutic dose. A seven-day challenge has been suggested by one recent study [150], but BSACI does has not recommended a change in practice.

A management plan and emergency treatment should be provided for allergic reactions developing at home. Appendix Table A2 shows examples of increasing drug doses during provocation.

Box 4. Limitations of drug challenge

- Drug challenge can provoke life-threatening reactions.
- Resensitization occurs in a minority of cases.
- Drug challenges can give a false-negative result in 3–6% due to the absence of cofactors which contribute to non-immediate hypersensitivity reactions.
- Drug challenge is not recommended in patients at high risk of delayed, life-threatening reactions such as TENS, SJS, AGEP, etc. or for patients with unstable asthma or on beta-blockers.

The negative predictive value of oral provocation is high. In a multicentre study, patients with a negative provocation test were followed up for 6 months and only 9/118 (7.6%) who took a beta-lactam reacted with a non-immediate reaction. This gave a negative predictive value for beta-lactam oral provocation of 94% [162]. The high predictive value of oral provocation was confirmed in a separate study where new reactions were reported in only 4.5% of patients exposed to penicillin over 90 days [35].

Oral provocation in non-immediate reactions

As both delayed reading of intradermal skin tests and patch tests have low sensitivity, oral provocation is an important diagnostic tool. Drug challenge is contraindicated in patients who have suffered from a severe cutaneous systemic reaction such as DRESS or SJS/TEN. However, in mild cutaneous delayed-type reactions without systemic involvement, drug challenge can be used. One published protocol recommends 1/100 of the therapeutic dose as an initial dose, followed by 1/10 of the therapeutic dose 3 days to one week later and followed by the full dose 3 days to one week later [134]. Another protocol recommends incremental doses culminating in up to one-fifth of the therapeutic dose on day one, followed by increments to the full therapeutic regime 48 h later [11]. In the UK, it is recommended that depending on the severity of the original reaction, either a fraction of the dose or the full dose is administered on the first day followed by a course of treatment one week later in the absence of a delayed reaction.

Desensitization

The term desensitization traditionally applies to IgE-mediated drug reactions and relates to the induction of a temporary state of unresponsiveness to the drug which caused the original hypersensitivity reaction. This 'tolerant' state is lost 24–36 h after discontinuation of the drug. The underlying mechanisms involved have not been clearly defined although cytokines and other mediators from activated immune cells, especially mast cells, appear to play a role. Desensitization should only be considered when an alternative drug is either not available or when a specific drug is necessary for the treatment or more effective than any alternative. Before desensitization is undertaken, a careful evaluation of the risks and benefits must be considered and discussed with the patient. Indications and contraindications concerning the desensitization procedure are outlined in a position paper by the ENDA interest group [207].

Desensitization comprises incremental administration of doses of the drug to which the patient is sensitized, with the aim of reducing immune responsiveness. Drug desensitization requires considerable experience and specialist knowledge and should only be undertaken in specialist centres. Full resuscitation facilities, expertise in the acute management of anaphylaxis and access to an intensive care unit are essential [207].

Approximately one-third of patients will develop an allergic reaction during the procedure. These reactions tend to be mild, but must be treated promptly. If a reaction occurs, then the next dose should be 10-fold lower. With more severe reactions, the dosing schedule is taken back further, but then updosing continued until tolerance is achieved. The success rate of desensitization has been estimated between 58% and 100%, reviewed in [208].

Beta-lactam desensitization was first reported in 1946, but the first description of penicillin desensitization in a large series was published in 1982 [209]. Many protocols have been published since [210–214]. An example is given in Appendix Table A3.

There have been no large comparative studies between oral and IV routes of desensitization although both have been successfully utilized [215–217]. Continuous monitoring for adverse reactions is necessary for both routes. The oral route leads to slower-onset allergic reactions. Potential reactions are identified earlier with the IV route [214].

Historically desensitization protocols started with an initial dilution of 10^{-3}–10^{-2} lower than the concentration that gave a positive skin test response, but in current practice, the starting dose is usually a 10^{-5} to 10^{-4} dilution of the usual therapeutic concentration depending on the original reaction. The dose is increased by half-log or doubling increments at 15-min intervals for IV desensitization or at 45–60 min for oral desensitization until the therapeutic dose is achieved [207] (Appendix, Table A3). Standard protocols for IV desensitization have been published and can be adapted for a range of drugs [218–220]. These protocols are

based on three pre-prepared solutions of 10-fold drug dilutions from which doses are gradually increased by increasing the volume delivered at each 15-min step until the therapeutic dose is reached.

Although desensitization was originally conceived for type I hypersensitivity reactions, a similar approach has been adopted for patients with delayed non-life-threatening, maculopapular reactions and often found to be useful in the management of patients with cystic fibrosis who have frequent requirements for IV antibiotics and high rates of adverse antibiotic-related reactions [221, 222]. In these cases, initial doses are generally higher (mg vs. μg) with a variable interval between doses (from hours to days). Again, this procedure should be attempted only by experienced staff in the presence of full resuscitation facilities. Desensitization must not be undertaken in patients with severe cutaneous reactions with systemic features such as SJS, TENS or DRESS.

A position paper on desensitization in non-immediate hypersensitivity has been published with protocols for antibiotics including beta-lactams attached [223].

Management summary

Diagnostic algorithms are shown in Figs 2 and 3

History of type 1 hypersensitivity requiring penicillin (grades in bold according to Powell and colleagues [1])

- Patients with positive skin tests to PPL/MDM should avoid penicillins. (B) However, in selected cases, if skin tests to amoxicillin/ampicillin are negative, a cautious oral challenge with an aminopenicillin may be considered. (D)
- If skin tests or challenge is positive and there is no alternative to beta-lactams, drug desensitization should be considered. (B)
- Patients with negative PPL/MDM/benzylpenicillin/amoxicillin/ampicillin skin tests should undergo oral challenge with the penicillin implicated in the original reaction. (B)
- Patients with negative skin tests to PPL/MDM and benzylpenicillin but positive to a specific beta-lactam may have side chain sensitization, and a cautious oral challenge with penicillin V can be considered. (D)

History of penicillin allergy requiring cephalosporin

- If there is a history of penicillin allergy, patients requiring a cephalosporin should undergo skin testing to both penicillin and to the specific cephalosporin. Results from skin testing or oral provocation to a single cephalosporin cannot be generalized to the whole class, and in patients with confirmed penicillin allergy, each cephalosporin will require separate evaluation.
- If skin tests to both penicillin and cephalosporin are negative, the patient should undergo challenge with the penicillin implicated in the original reaction. In this way, if drug challenge is negative, avoidance of any beta-lactam is unnecessary, but

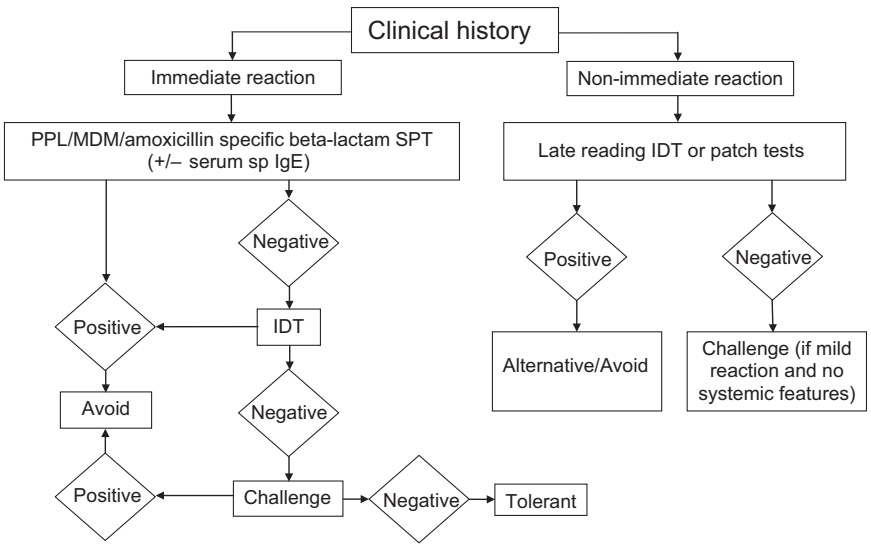

Fig. 2. Overview of investigations for immediate and non-immediate beta-lactam reactions. (SPT=Skin prick tests; IDT = intradermal tests).

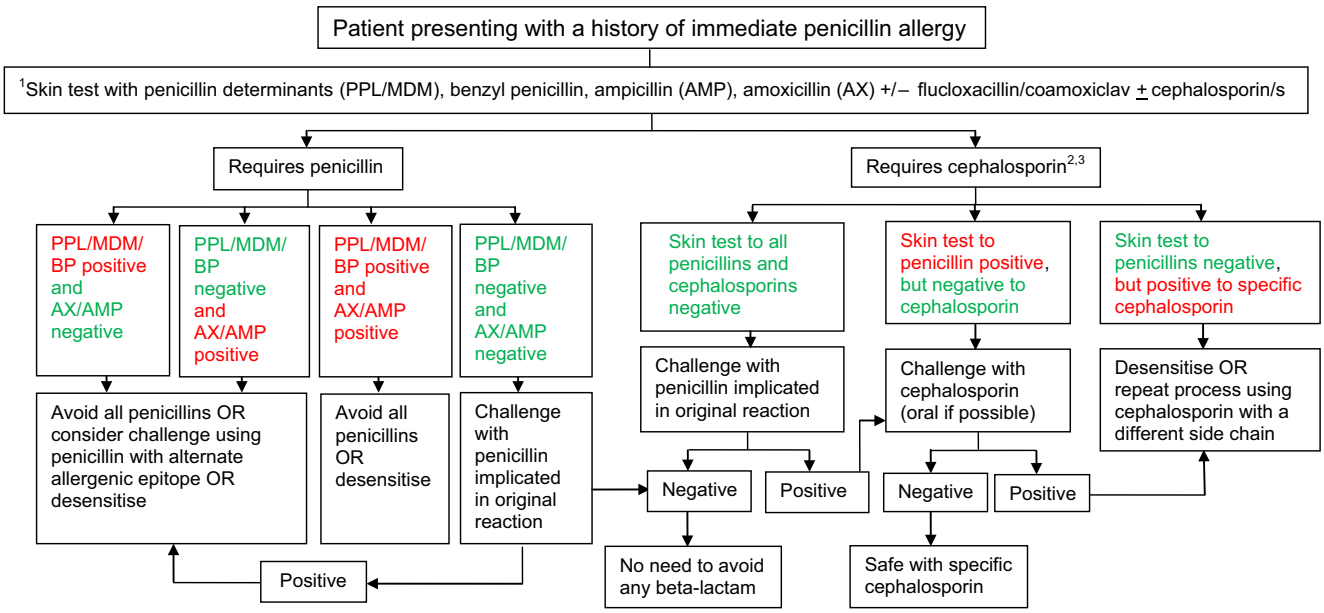

Fig. 3. Management of a patient with a history of penicillin allergy requiring either penicillin or a cephalosporin. [1]Routine use of specific IgE testing to penicillin and cephalosporins is not recommended, although may be useful in individual cases. [2]Greatest risk of cross-reactivity with 1st- and 2nd-generation cephalosporins in patients with penicillin allergy. Reduced risk with 3rd-generation cephalosporins, but caution is still required in subjects with a history of a life-threatening reaction. [3]Cephalosporin skin tests are not validated, and therefore, the predictive value of negative skin tests is unknown.

if positive, then cephalosporin challenge will be necessary. (D)

- If the skin test is positive for penicillin but negative to the required cephalosporin, then the patient should undergo provocation with the cephalosporin. (D)
- If the patient has a history of penicillin allergy but subsequently tolerated a course of cephalosporin, then the same cephalosporin can be taken again without testing.
- If skin testing for penicillin is negative but positive for cephalosporin, then the patient should undergo challenge with the penicillin implicated in the original reaction and, if still required, skin testing and challenge using a cephalosporin with a different side chain. (D)

History of cephalosporin allergy requiring penicillin

- These patients should undergo skin testing for PPL, MDM, benzylpenicillin, amoxicillin and the implicated cephalosporin. If skin tests are negative, beta-lactam allergy can be excluded after a negative cephalosporin challenge to the index cephalosporin. (B) However, if either the skin test or challenge to cephalosporin is positive, drug challenge with the required penicillin should be undertaken. If any of the penicillin tests are positive, the options are to either avoid penicillins or undertake desensitization. (B)
- In patients with selective skin test responses to penicillins, a graded challenge can be undertaken to the penicillin negative on skin testing. (D)

History of cephalosporin allergy and requirement for cephalosporin

- Skin testing should be undertaken with penicillin determinants, benzylpenicillin, aminopenicillin, the cephalosporin implicated in the original reaction and the required cephalosporin.
- If skin tests to penicillins and cephalosporins are negative, then provocation with the implicated cephalosporin should be undertaken preferably using an oral preparation if available. (D)
- If skin tests to penicillin are positive, the patient should undergo skin testing to a cephalosporin with a different side chain followed by provocation if negative. (D)
- A positive skin test to a cephalosporin in the presence of a negative skin test for penicillin may indicate the presence of side chain-specific IgE. Further skin testing and provocation with an alternative cephalosporin with a different side chain should be undertaken or the patient offered desensitization. (D)

Following specialist allergy assessment the patient must be issued with precise recommendations for future use [98] (Box 5).

Box 5. Drug allergy proforma

PRIVATE & CONFIDENTIAL	
GP details	
DRUG ALLERGY NOTIFICATION **To whom it may concern**	
Re:*(Patient details)*	**DOB: .....**
Drug:	
Clinical reaction (and if allergic or non-allergic):	
Diagnosis confirmed by:	
RECOMMENDATIONS	
Avoid:	
Safe alternatives:	
Consultant/Registrar:	

Beta-lactam allergy in children

Introduction

True allergic reactions to beta-lactams are less common in children than adults [96, 224]. Children treated with beta-lactams frequently develop skin rashes. These are usually maculopapular or urticarial. Although often assumed to be due to a drug allergy, most are due to viral infections (commonly enterovirus) [225], and the skin rash is rarely reproduced by challenge. Beta-lactam allergy is frequently over-diagnosed and may lead to an increase in health costs and antibiotic resistance and potentially places the child at risk when prescribed less effective antibiotics. It is a cause of concern for patients and physicians who fear future reactions. There are no in vitro diagnostic tests to distinguish between viral and drug-induced exanthema.

Epidemiology

Beta-lactam allergy in children is usually diagnosed in primary care or by the parent, in the absence of investigations. The prevalence of self-reported reactions to beta-lactams in children varies from 1.7% to 5.2% [226–228]. The most frequent causes are amoxicillin (1.4%), other penicillins (1.2%) and cephalosporins (0.7%) [227]. Most are non-immediate cutaneous reactions, occurring >1 h following administration of a dose, of mild to moderate severity, in children below 4 years of age [226, 227, 229]. There are no predisposing risk factors for beta-lactam allergy in children, and only a minority (7-16%) of children with suspected beta-lactam hypersensitivity are found to be allergic following investigation [225, 230].

Symptoms

The patient's history is essential for confirming the diagnosis. Common presentations are maculopapular rash (55%) and urticaria (35%). The likelihood of beta-lactam hypersensitivity increases if the reaction was either immediate or severe [230]. Fixed drug eruptions are uncommon [231]; SJS is rare and usually due to viral infections in childhood. Erythema multiforme and serum sickness-like reactions are not IgE or T-cell-mediated but often result from viral infections (Fig. 4).

Diagnostic testing

Skin tests

Skin testing is useful in children with a history of anaphylaxis, to assess IgE sensitization. In children with non-immediate reactions, the diagnostic value of skin testing is lower [230, 232]. Intradermal testing is unpleasant in younger children and often not possible to undertake. Skin tests are not useful in children presenting with hypersensitivity reactions which are non-IgE and non-T-cell-mediated such as erythema multiforme or those resembling serum sickness.

Specific IgE

The role of specific IgE in children with immediate reactions to beta-lactams requires further evaluation [229]. In children with non-immediate reactions, measurement of specific IgE is not useful [225].

Oral challenge testing

The oral challenge test is the gold standard for the diagnosis of beta-lactam allergy and the best diagnostic tool for benign skin rashes in children [230]. Oral drug challenges are safe in children without a history of anaphylaxis and should be considered in all children who develop a rash. Fewer than 7% of children are allergic on re-exposure [225, 226, 229]. Reactions are usually mild to moderate and less severe than the index event and resolve with oral antihistamines and/or oral corticosteroids [225, 230]. The mean time between the start of the challenge and the reaction is 3.8 days [230]. The likelihood of a positive oral challenge is therefore increased by undertaking a 5-day challenge with a full therapeutic dose. It has been suggested that children with mild to moderate, non-immediate reactions to beta-lactams could undertake a prolonged drug challenge at home [230]. To improve safety, however, it is recommended

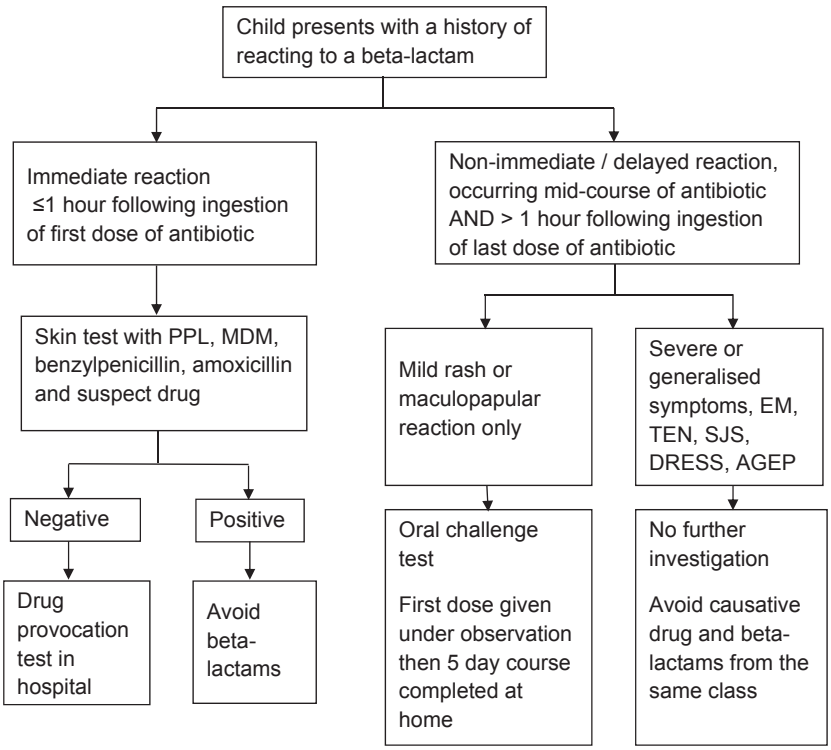

Fig. 4. Management of child presenting with a suspected allergic reaction to a beta-lactam antibiotic. Children with SJS, EM, AGEP, TEN and DRESS should not be tested. Avoid proceeding directly to challenge if details of the clinical history are not well documented.

that the first dose is administered in hospital, followed by a period of monitoring of at least 2 h [225].

Cross-reactivity and resensitization

Cross-reactivity between beta-lactams is more frequent in children reporting immediate reactions and uncommon in children with delayed reactions [230]. The risk of resensitization is low. It is unnecessary to repeat skin testing before every course of treatment [224, 233].

Complex beta-lactam allergy

In children with non-immediate hypersensitivity reactions, delayed reading intradermal testing, followed by drug challenge in children with negative results, can be performed [230]. In children with SJS, AGEP, TEN and DRESS, challenge tests with the suspected drug are contraindicated because of the risk of relapse.

Recommendations

1. Children with a history of non-immediate urticaria or maculopapular rashes should undergo a test dose in hospital followed by the full therapeutic dose for 5 days (prolonged oral challenge test). Children relapsing during the challenge should continue to avoid the beta-lactam [225, 227, 229, 230]. (C)
2. Children with anaphylaxis or an immediate reaction to penicillin should undergo skin prick and intradermal testing. If skin tests are negative, challenge with the drug implicated in the reaction should be undertaken in hospital [230]. (C)
3. Children with SJS, AGEP, TEN and DRESS should not be tested or challenged. They should avoid beta-lactams from the same class. However, there is a role for testing and controlled challenge using beta-lactams from other classes. (C)

Future research

1. To identify and validate a greater range of beta-lactam determinants allowing greater in vivo and in vitro diagnostic accuracy.
2. Identification of the metabolites of cephalosporins will contribute to the diagnosis of those reactions which are not caused by the parental cephalosporin drug.
3. Research to develop sensitive and accessible laboratory tests which can be used to diagnose drug allergy in both immediate and non-immediate reactions.
4. Genome-wide association studies in patients with severe type I and type IV hypersensitivity reactions should be established. This research may not be useful immediately in clinical practice but will allow understanding of the underlying mechanisms underpinning beta-lactam allergy.

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This *guideline* informs the management of beta-lactam allergy. Adherence to this guideline does not constitute an automatic defence for negligence, and conversely, non-adherence is not indicative of negligence. The expert group will be monitoring clinical management changes, for example with national audits (see Appendix B). Any significant changes will trigger a review of this guideline. It is anticipated that this guideline will be reviewed 5 yearly with an assessment at the half point of this period.

Conflict of interest: Conflict of interests was recorded by the SOCC; none jeopardized unbiased guideline development.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1.

Table S1. Non-irritating test concentrations for beta-lactam antibiotics (reproduced with permission from Brockow et al. 2013).

Table S2. Examples of increasing drug doses during provocation, modified from Messaad and colleagues [150].

Table S3. Penicillin oral desensitisation protocol (Adapted from Sullivan [210]).

Appendix S2. Clinical Audit: Assessment of penicillin allergy.