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Penicillin allergy – recommendations for diagnostic work up and patient management

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Abstract
Background Allergy to penicillins or cephalosporins manifests either within a few minutes after intake or infusion in the form of acute anaphylaxis symptoms, or several hours to days later as exanthematous skin reactions. Exanthematous skin eruptions caused by amoxicillin or ampicillin are currently the most frequently diagnosed clinical reaction pattern within the spectrum of penicillin allergy. Certain single cephalosporins such as cefazolin, ceftriaxone, and cefuroxime are gaining in relevance as triggers of β-lactam antibiotic-induced IgE(Immunglobulin E)-mediated anaphylaxis reactions.
Methods This article provides an overview of selected scientific articles and is based on research in PubMed, studies, and specialist databases.
Results Penicillin allergy work-up is based on patient history and documented medical findings; serological IgE determinations, as well as skin and provocation testing, are routinely performed. While the determination of IgE directed to certain penicillin determinants is one of the few reliable laboratory tests for the diagnosis of drug hypersensitivity, the basophil activation test or the lymphocyte transformation test are reserved for experienced laboratories which are able to critically evaluate their test results. Wheal-and-flare reactions in skin prick and intradermal testing suggest IgE-mediated allergy, while infiltrated erythematous or exanthematous plaques in patch or intradermal testing point to delayed-type hypersensitivity.
Conclusion The overall predictive value of combined in vitro and in vivo allergy testing with β-lactam antibiotics is approximately 90%. However, subsequent controlled provocation testing is recommended in order to reliably exclude allergic hypersensitivity.

Keywords Beta-lactam · Cephalosporin · Cross-reactivity · Drug allergy · Drug hypersensitivity

Abbreviations

AGEP	Acute generalized exanthematous pustulosis
BAT	Basophil activation test
BP-OL	Benzylpenicilloyl octa-L-lysine
DRESS	Drug rash with eosinophilia and systemic symptoms
GPT	Glutamic pyruvic transaminase
IgE	Immunglobulin E
i. v.	Intravenous
LTT	Lymphocyte transformation test
MD	Minor determinant
SDRIFE	Symmetrical drug-related intertriginous and flexural exanthema
SJS	Stevens–Johnson syndrome
TEN	Toxic epidermal necrolysis

Background

β-Lactam antibiotics, i. e., penicillins, semi-synthetic penicillin derivatives, cephalosporins, carbapenems, monobactams, and β-lactamase inhibitors, share a common β-lactam ring in their chemical structure. Ring structures containing intracyclic amide bonds are called lactams by combining the terms lactone and amide; β-lactams are 4-atom rings (γ = 5-ring, δ = 6-ring, etc.). Due to their favorable bene-

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Table 1 Classification of hypersensitivity reactions to β-lactam antibiotics. (Modified from [6])

	Immediate-type reactions	Delayed-type reactions
Pathogenesis	IgE-mediated	T-lymphocyte-mediated
Latency periods	Minutes	Several hours
Symptoms	Anaphylaxis spectrum ranging from urticaria with or without angioedema to anaphylactic shock	*1. Uncomplicated maculopapular exanthema* *2. Morphological variants of skin reactions* Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) Pustular exanthema (AGEP) Fixed drug reactions *3. Drug rash with eosinophilia and systemic symptoms (hypersensitivity syndrome, DRESS)* *4. Severe bullous skin reactions: SJS, TEN*
Resolves within	A few hours	Several days to weeks

SDRIFE symmetrical drug-related intertriginous and flexural exanthema, *AGEP* acute generalized exanthematous pustulosis, *DRESS* drug rash with eosinophilia and systemic symptoms, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

fit:side-effect ratio, β-lactam antibiotics are still the treatment of first choice for numerous infectious diseases. Amoxicillin is the most frequently prescribed antibiotic in Germany.

The selection of antibiotics for treatment of infectious diseases is directed not only by guidelines, but also by patients' statements. Currently, up to 10% of the population report penicillin allergy in their medical history. Published data vary, but it seems that diagnostic allergy testing confirms only 2% to maximum 25% of suspected cases [1–3]. The main reasons for this obvious discrepancy are acute-onset exanthematous or urticarial skin reactions in temporal relationship with intake of β-lactam antibiotics, which were prescribed for acute febrile infectious diseases. If cutaneous symptoms develop, the antibiotic drug rather than the infectious disease is regularly claimed to be responsible, not only by patients, but also by treating physicians.

Although the somewhat simplistic term "penicillin allergy" is common parlance, the term is vague given the heterogeneity of β-lactam antibiotics. Authors themselves sometimes use "penicillin allergy" due to its better legibility, although the term β-lactam antibiotic allergy is more appropriate. A precise denomination, e. g., amoxicillin/ampicillin allergy or cefuroxime allergy, is mandatory in allergy documents.

Clinical symptoms

Allergic hypersensitivity to penicillins or other β-lactam antibiotics can manifest as IgE-mediated anaphylaxis or as non-IgE-mediated delayed-type exanthematous skin reactions (Table 1). Aminopenicillin-induced exanthema due to amoxicillin or ampicillin is currently the most commonly diagnosed form of penicillin allergy. IgE-mediated anaphylaxis is rarer and mainly caused by certain cephalosporins such as cefazolin, ceftriaxone, or cefuroxime [4]. Intraoperatively as antibiotic prophylaxis administered cephalosporins are nowadays besides muscle relaxants most common cause of anaphylactic anesthesia incidents [5].

IgE-mediated type I hypersensitivity reactions cause anaphylaxis within a few minutes; the spectrum of symptoms includes various combinations of individual signs, such as urticaria with or without angioedema, stridor due to laryngeal edema, bronchospasm, hypotension and tachycardia, nausea, vomiting, dizziness, and loss of consciousness, among others.

The complex pathogenesis of delayed-type penicillin hypersensitivity reactions leads to heterogeneous clinical pictures of exanthematous skin reactions (Table 1). Exanthema is usually noticeable within a few hours after initiating tablet intake or infusion administration in already sensitized patients. In case of de novo sensitization during ongoing therapy, exanthema occurs at earliest after 7–10 days. β-Lactam antibiotics most commonly cause uncomplicated exanthema, which means merely maculopapular skin reactions with mild or no systemic symptoms such as subfebrile temperatures and, e. g., glutamic pyruvic transaminase (GPT) elevated to less than twice of the normal level. Far more rarely, β-lactams induce morphological variants of skin reactions, such as symmetrical drug-related intertriginous and flexural exanthema, pustular exanthema (acute generalized exanthematous pustulosis), or fixed drug reactions, as well as life-threatening systemic hypersensitivity reactions involving hepatitis and/or nephritis (drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms) or bullous skin reactions (Stevens–Johnson syndrome and toxic epidermal necrolysis).

Diagnostic allergy testing

The protocol for diagnostic allergy testing in case of suspected β-lactam antibiotic hypersensitivity includes, in a stepwise approach, patient history, laboratory tests, as well as skin and provocation testing (Fig. 1; [7]). Ideally, diagnostic testing should be performed within 1 year after the clinical reaction, since it is assumed that sensitization levels may gradually diminish over time and diagnostic tests may then yield (false) negative results. It is possible that more than 1 year after the clinical reaction IgE-mediated sensitization is no longer detectable serologically and

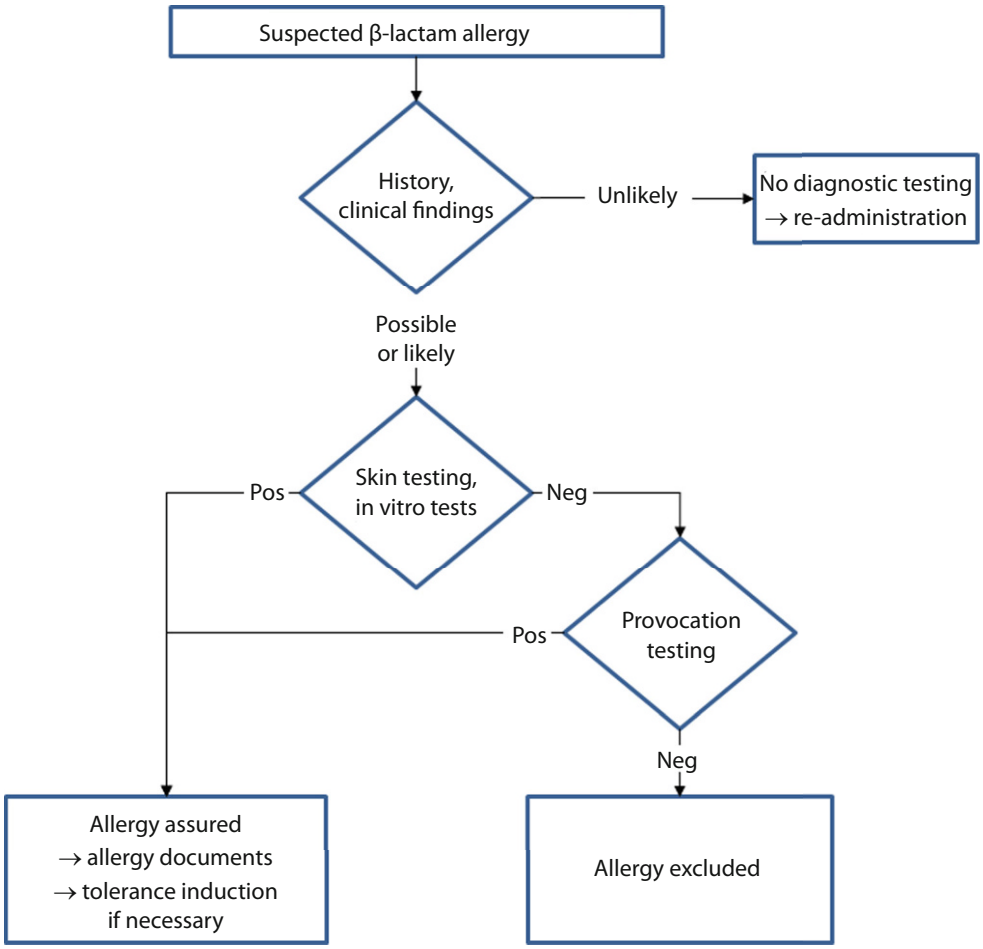

Fig. 1 Diagnostic algorithm for β-lactam antibiotic hypersensitivity. *Neg* negative, *Pos* positive

Table 2 Skin testing with a panel of important β-lactam antibiotics. If there is a history of exanthema, delayed readings on days 2, 3, and 4 are necessary

Skin prick and patch tests	Intradermal tests (only with i. v. preparations)
BP-OL and MD (for prick testing)	BP-OL and MD
Benzylpenicillin (penicillin G)	Benzylpenicillin (penicillin G)
Phenoxymethylpenicillin (penicillin V)	–
Amoxicillin	–
Ampicillin	Ampicillin
Ceftriaxone	Ceftriaxone
Cefuroxime	Cefuroxime
Cefpodoxime	–

BP-OL benzylpenicilloyl octa-L-lysine, *MD* minor determinant

in skin tests; however, this cannot be equated with clinical tolerance [8].

Patient history

In the majority of cases, the allergist does not see the clinical symptoms himself and must rely on descriptions provided by patients, documentation in medical records, or information provided by treating colleagues. In addition to precisely identify the suspected β-lactam antibiotic, the classification of symptoms as either immediate-type anaphylaxis or delayed-type exanthematous skin reactions is of particular importance for planning further diagnostic work-up (Table 1).

Laboratory tests

Allergen-specific IgE levels to penicilloyl G, penicilloyl V, amoxicilloyl, ampicilloyl, and cefaclor can be determined using a commercially available immunoassay [9]. The diagnostic sensitivity values of these determinations are between 50% and 60%, while specificity is as high as 95%; however, in several studies highly different statistical diagnostic values were published. The time interval between clinical reaction and IgE determination may be responsible for the broad variation of sensitivity data. A timely IgE measurement is therefore recommended, because in some patients β-lactam-specific IgE values are already negative after less than one year after the clinical reaction [8, 10]. Nowadays, certain cephalosporins have been identified as leading cause of β-lactam antibiotic-induced anaphylaxis. Unfortunately, to date there are no validated IgE measurements available for, for example, cefazolin, ceftriaxone or cefuroxime.

Table 3 Non-irritant skin test concentrations of β-lactam antibiotics [14]

β-Lactam structures	Skin prick tests	Intradermal tests (only i. v. β-lactams)	Patch tests
Benzylpenicilloyl octa-L-lysine (BP-OL)	8.6×10^{-5} mol/l	8.6×10^{-5} mol/l	Not applicable
Minor determinants (MD): Benzylpenicilloat	1.5×10^{-3} mol/l	1.5×10^{-3} mol/l	
Benzylpenicillin (penicillin G)	10,000 I. E./ml	10,000 I. E./ml	5%
Amoxicillin	20 mg/ml	Not applicable	
Ampicillin		20 mg/ml	
Cephalosporins	2 mg/ml[a]	2 mg/ml[a]	

*For a 20 mg/ml test concentration of cefalexine, cefaclor, cefadroxil, cefuroxime, ceftriaxone, cefotaxime, ceftazidime, and cefazolin, studies indicate improved sensitivity without affecting specificity [17]

Both the basophil activation test (BAT) for immediate-type reactions and the lymphocyte transformation test (LTT) for delayed-type reactions to β-lactam antibiotics are subject of controversy due to methodological variability, lack of standard values as well as economic considerations and, as such, are still reserved for specialized allergy centers. Findings of BAT and LTT can only be evaluated reasonably in close synopsis with results of other diagnostics tools [11]. A prospective study in patients with amoxicillin- or ampicillin-induced exanthema determined the diagnostic sensitivity value of LTT to be about 55%, while specificity was about 90% [12]. However, cellular in vitro diagnostic tests pose no risk to the patient and may therefore provide helpful diagnostic clues in, for example, cases of severe anaphylactic reactions.

Skin testing

The next diagnostic step following patient history and IgE determination is skin testing, whereby combining prick, intradermal, and patch tests may optimize overall diagnostic sensitivity. Wheal-and-flare reactions after 15 min enable diagnosis of IgE-mediated hypersensitivity, while test reactions with erythematous or eczematous infiltrated plaques after 2, 3, and 4 days suggest delayed-type hypersensitivity. Skin-prick and intradermal tests on the forearm, as well as patch tests on the back, should be performed and evaluated according to published guidelines [13, 14].

In addition to the suspected β-lactam drug based on patient history, a range of several different β-lactam antibiotics should be tested. This approach allows the detection of cross-reactions, on the one hand, while yielding information on potentially tolerated alternative β-lactams, on the other (Table 2). The β-lactamase inhibitor clavulanic acid is component of some penicillin preparations and was also described as potential cause of allergic hypersensitivity reactions [15]. Unfortunately, approved penicillin test preparations are not available in Germany. If skin testing with non-approved test substances is performed, a notification of the responsible institution at the monitoring authority is required in Germany [16]. Diater Laboratories (Madrid, Spain) offers standardized penicillin prick/intradermal test solutions: BP-OL (benzylpenicilloyl octa-L-lysine), MD (minor determinant, i. e., benzylpenicilloate), amoxicillin, and clavulanic acid. Skin test sensitivity in case of suspected IgE-mediated penicillin allergy can be increased using the test preparations BP-OL and MD, whereas complementary testing of BP-OL and MD confers no additional diagnostic benefit for the diagnosis of delayed-type aminopenicillin hypersensitivity. β-Lactam antibiotic solutions approved for intravenous injection/infusion are generally the most suitable preparations for skin testing; see Table 3 for non-irritant test concentrations. It is sometimes necessary to modify the test procedure in view of the clinical drug reaction. In case of severe anaphylactic reactions, for instance, stepwise testing is recommended, i. e., lower test concentrations, skin prick testing first, followed by intradermal testing.

Provocation tests

Provocation tests should also be performed and evaluated according to published guidelines [14, 18]. The following rules need to be observed: (a) exanthematous skin reactions should have been completely healed for at least 6 weeks prior to provocation testing; (b) provocation tests are preferably performed orally; (c) requirements for provocation testing include not only emergency equipment but also trained personnel; (d) in provocation testing, an age-, renal function-, and weight-adapted average daily dose should be administered (in cases with history of severe anaphylaxis, a stepwise dose increase with a low initial dose is recommended, i. e., four to five dose steps with time intervals between 30 min and 1 h); (e) patient informed consent should be documented. When performing provocation tests with several different β-lactam antibiotics, the frequency (daily or every 2nd to 3rd day) depends on the required follow-up period and symptoms expected on the base of patient history.

Drug provocation tests should only be performed once skin tests and in vitro tests have been completed [19]. The risk of re-sensitization through provocation testing seems to be extremely low; therefore, repeating skin and provocation tests appears to be justified only in cases of risk of severe anaphylaxis [20,

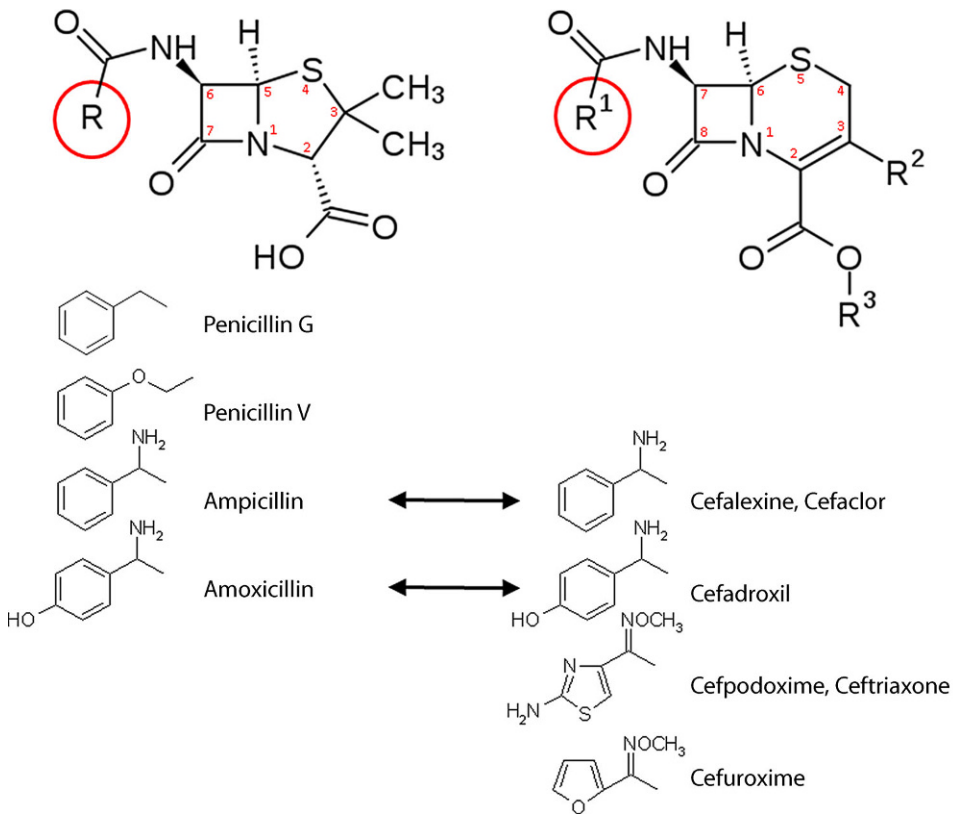

Fig. 2 Comparison of R-penicillin and R1-cephalosporin side chains at C6 and C7, respectively. (Modified from [6])

21]. Provocation tests are also needed to identify alternative β-lactam antibiotics, e. g., whether certain cephalosporins are tolerated despite penicillin allergy. Second and third generation cephalosporins, such as cefpodoxime, cefixime, ceftriaxone, and cefuroxime, are generally tolerated by patients with proven benzylpenicillin (penicillin G, penicillin V) allergy [22, 23].

Discussion

Diagnostic allergy testing with aminobenzylpenicillins (abbreviated as aminopenicillins) is of particular practical importance, since amoxicillin and ampicillin belong to the most commonly prescribed antibiotics and are relatively common triggers of delayed-type allergic hypersensitivity. Aminopenicillin-induced exanthema can be diagnosed or ruled out with high sensitivity and specificity by means of ampicillin and amoxicillin skin testing [24]. Broad cross-reactivity between the main classes of different β-lactam antibiotics, i. e. benzylpenicillins, aminopenicillins, and cephalosporins, seems to be quite rare, although the shared chemical-pharmacological group name β-lactam suggests the opposite [25].

The most important antigenic component of aminopenicillins is their aminobenzyl-R side chain on C6 of the β-lactam ring, but in individual cases the antigenic structures/conformations may include other areas of the complex molecule [26]. Due to their similar aminobenzyl-R side chain structure, amoxicillin and ampicillin seem to be nearly 100% cross-reactive. Cross-reactions between aminopenicillins and certain cephalosporins, such as cefalexin, cefaclor, and cefadroxil, are possible due to shared aminobenzyl-R1 side chains (Fig. 2). In a study of patients with delayed-type reactions, the cross-reactivity was 40% [27]. Whereas cross-reactions between aminobenzylpenicillins and benzyl-/phenoxymethylpenicillin are observed in at least 20–30% of cases, aminopenicillin-allergic individuals generally tolerate cephalosporins with different R1 side chains, such as cefpodoxime, ceftriaxone, or cefuroxime (Fig. 2; [28]).

Once β-lactam hypersensitivity has been diagnosed, e. g., amoxicillin/ampicillin allergy or cefuroxime allergy, cross-reactivity with other β-lactam antibiotics is, however, principally possible. Diagnostic allergy testing is recommended prior to antibiotic treatment with alternative β-lactams, the test results should be recorded in allergy documents. For example, patients with confirmed aminopenicillin allergy generally tolerate cephalosporins with structurally different R1 side chains [28]. It should be clear from allergy documentation whether provocation tests with alternative β-lactam antibiotics have been carried out. The selection of alternative β-lactams for testing should be based not only on different R and R1 side chain structures, but also on therapeutic requirements.

If no therapeutic alternatives are available, e. g., intravenous neurosyphilis treatment with penicillin G, tolerance induction should be considered in individual cases of confirmed IgE-mediated benzylpenicillin

allergy (history of anaphylaxis, positive IgE tests; [6]). Since penicillin tolerance achieved by a corresponding protocol is only transient (= short-term tolerance), one should assume that tolerance will be lost after end of a treatment cycle.

Not only allergy diagnosis but also reliable exclusion of penicillin allergy is an important task for allergists, since it facilitates future antibiotic treatment. Outcomes of exclusion of penicillin allergy are the following: (a) better efficacy of antibiotic therapy, since in certain indications β-lactams are more effective than alternatives; (b) fewer side effects; (c) less development of bacterial resistance, which can be promoted by using unnecessarily reserve antibiotics; (d) cost reduction.

Conflict of interest A. Trautmann and G. Wurpts declare that they have no competing interests.

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