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# Aminopenicillin-induced exanthema allows treatment with certain cephalosporins or phenoxymethyl penicillin

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***Objectives*: Aminopenicillin-induced exanthema poses a problem in the management of infectious diseases. Due to theoretically possible immunological cross-reactivity, all β-lactam drugs, i.e. penicillins, penicillin derivatives and cephalosporins, are usually avoided. The available alternative antibiotics (macrolides, quinolones and glycopeptides) may be less effective, have more side effects, and their use increases medical costs. Moreover, their use contributes to the increasing bacterial resistance to antibiotics. The aim of the study is to demonstrate that patients with aminopenicillin-induced exanthema may receive specific β-lactams for future antibiotic therapy.**

***Methods*: Skin testing followed by oral challenges to identify β-lactams that are tolerated by patients despite confirmed delayed-type non-immunoglobulin E (IgE)-mediated allergic hypersensitivity to aminopenicillins.**

***Results*: Sixty-nine out of 71 patients (97.2%) with non-IgE-mediated allergic hypersensitivity to aminopenicillins tolerate cephalosporins without an aminobenzyl side chain such as cefpodoxime or cefixime and 51 patients (71.8%) also tolerate phenoxymethyl penicillin.**

***Conclusions*: The majority of patients with non-IgE-mediated allergic hypersensitivity to aminopenicillins do not cross-react to certain cephalosporins or phenoxymethyl penicillin. Skin and drug challenge tests can be helpful to determine individual cross-reactivity.**

Keywords: drug challenge, drug provocation, non-IgE-mediated allergic hypersensitivity, skin tests

## Introduction

During treatment with aminopenicillins, delayed-type non-immunoglobulin E (IgE)-mediated allergic hypersensitivity (DTH) may occur as macular or maculopapular exanthemata.[1] In contrast to immediate-type reactions involving IgE antibodies, the mechanisms of non-IgE-mediated reactions to amoxicillin or ampicillin are heterogeneous. At least some of the observed exanthemata are due to true T cell- and/or IgG-mediated DTH and most of these cases can be confirmed by positive late skin tests to aminopenicillins.[2–6] These skin test reactions show histological features similar to those of acute allergic contact dermatitis.[7–9] Amoxicillin- or ampicillin-induced exanthemata appear 1–2 weeks after start of the medication. Re-exposure after sensitization may lead as early as 6–12 h to development of exanthema.

Several reports showed that DTH to aminopenicillins can be diagnosed with skin tests.[10–13] Antigenic determinants of aminopenicillins may be the aminobenzyl side chain, the β-lactam core structure, or both (i.e. the whole molecule) resulting in different potential cross-reactivities to benzyl/phenoxymethyl penicillin or to specific cephalosporins.[14,15] Cross-reactivity between aminopenicillins and cephalosporins carrying an aminobenzyl R1 side chain, such as cefalexin, cefaclor and cefadroxil, is likely (Figure 1). In contrast, cephalosporins such as cefpodoxime or cefixime share the β-lactam core structure but have different R1 side chains.

In this study, we prospectively investigated allergic cross-reactivity between aminopenicillins, cefpodoxime, cefixime and phenoxymethyl penicillin in patients with confirmed DTH to aminopenicillins. By using skin testing and oral challenges, we tried to identify β-lactams that are tolerated by patients despite their DTH to aminopenicillins. Our aim is to demonstrate that patients with DTH to aminopenicillins may receive specific β-lactams for future antibiotic therapy.

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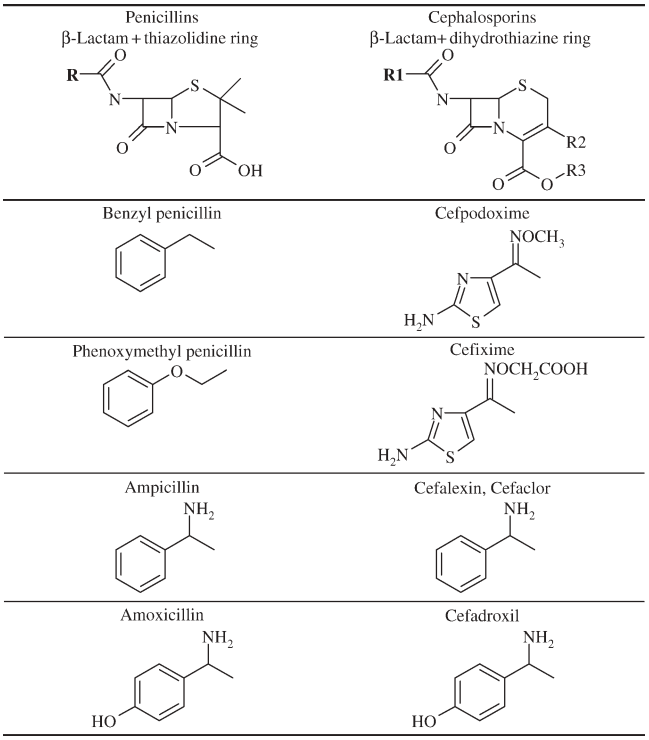


**Figure 1.** Side chains of β-lactams. Left-hand column, R side chains of different penicillins; right-hand column, R1 side chains of different cephalosporins.

## Materials and methods

### *Patients*

Seventy-one patients (50 females and 21 males) with confirmed DTH to aminopenicillins presenting between 2000 and 2005 were further evaluated. Informed consent for allergologic work-up was obtained. Since determination of potential cross-reactivity with other β-lactams is part of routine diagnostic practice, further ethical approval was not required. The average age of the patients at the time of aminopenicillin-induced exanthema was 49 years (ranging from 15 to 78 years). Patients with acute generalized exanthematous pustulosis, hypersensitivity syndrome, severe bullous skin reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis were excluded. *In vitro* assays for antigen-specific IgE to benzyl penicilloyl, phenoxymethyl penicilloyl, amoxicillin, ampicillin and cefixime (to rule out IgE-mediated allergic hypersensitivity) were performed using the Pharmacia CAP$^{TM}$ system (Pharmacia, Freiburg, Germany).[16,17]

### *Skin tests*

Intradermal tests at the forearm and patch tests at the upper back were performed according to international standards.[18] To exclude IgE-mediated allergic hypersensitivity, intradermal tests were read after 20 min. Late reactions were evaluated after 2, 3 and 4 days. Late reactions to intradermal tests were documented according to patch tests, i.e. faint macular erythema (?; doubtful reaction), erythematous infiltration (1+; weak positive reaction), erythematous infiltration with papules and vesicles (2+; strong positive reaction) and bullous reaction (3+; extreme positive reaction). The agents used for the skin tests are detailed in Table 1. For patch testing, tablets were ground in a mortar and diluted with 30 μL of physiological saline solution in Finn-chambers. Parenteral preparations were used in a 1:10 dilution for intradermal tests. All agents were freshly reconstituted and physiological saline solution was used as negative control.

**Table 1.** Compounds used for skin testing

| | | |
|---|---|---|
| Patch test | benzyl penicillin solution | 60 mg/mL |
| | phenoxymethyl penicillin tablets | 700 mg |
| | amoxicillin tablets | 500 mg |
| | ampicillin tablets | 1.000 mg |
| | cefpodoxime tablets | 100 mg |
| | cefixime tablets | 200 mg |
| Intradermal test | benzyl penicillin solution | 6 mg/mL |
| | ampicillin solution | 5 mg/mL |

**Table 2.** β-Lactams and doses used in single-blinded, oral challenge tests

| Drug | Dose |
|---|---|
| Phenoxymethyl penicillin | 150 000; 300 000; 600 000; 1 200 000 IU (equivalent to 87.5; 175; 350; 700 mg) |
| Amoxicillin | 250; 500; 1000 mg |
| Cefpodoxime | 25; 50; 100; 200 mg |
| Cefixime | 25; 50; 100; 200 mg |

IU, international units.

### *Single-blinded, oral β-lactam challenge*

All included patients were challenged according to our established protocol using standardized doses of β-lactams (Table 2). General principles of our challenge protocol were as follows: (i) the time interval since the exanthematous hypersensitivity reaction was at least 6 weeks; (ii) oral challenge was used; (iii) during the entire challenge procedure the patient was observed and equipment for emergency treatment was available; (iv) the dosage of β-lactams increased stepwise to a normal dose of daily intake; (v) strict adherence to absolute and relative contraindications for drug challenge tests; and (vi) prior to challenge testing written informed consent was obtained from each patient.[19] Only one β-lactam drug was challenged every second day with intervals of 1 h between the individual doses. In general, the sequence of the different β-lactams administered to each patient was: cefpodoxime, cefixime and phenoxymethyl penicillin. The challenge test was considered positive, if objective cutaneous symptoms occurred.

## Results

### *Patients*

Fifty-seven (80.3%) patients reported a history of macular or maculopapular exanthema and two patients suffered from an erythema multiforme-like exanthema. Interestingly, nine patients described the symptoms of an acute urticaria with transient urticae; in three other patients, the reported symptoms could not be classified definitely. Forty-nine patients had experienced the

**Table 3.** Results of skin tests

| | Skin tested drugs | Patients with positive skin tests | Total |
|---|---|---|---|
| Aminopenicillins | amoxicillin | 4 | 48 |
| | ampicillin | 11 | |
| | amoxicillin + ampicillin | 33 | |
| Aminopenicillins + benzyl/phenoxymethyl penicillin | amoxicillin + ampicillin + benzyl/ phenoxymethyl penicillin | 16 | 20 |
| | amoxicillin + ampicillin + benzyl penicillin | 4 | |
| Cephalosporins | cefpodoxime | 0 | 0 |
| | cefixime | 0 | |

Sixty-eight out of 71 tested patients were skin test positive.
At least one 1+ reaction was observed for a positive intradermal and/or patch test.

skin eruption within 12 months prior to testing, 11 patients between 1 and 5 years, 2 patients between 6 and 10 years and 8 patients more than 10 years prior to testing. For one patient, the exact time point of the exanthema could not be elucidated. In 56.3%, amoxicillin was the suspected β-lactam followed by ampicillin (23.9%). Using case history and/or patients records in 14 patients, the responsible aminopenicillin could not be identified. Specific IgE antibodies to benzyl/phenoxymethyl penicillin, amoxicillin, ampicillin or cefixime were not detectable in any of the patients.

### *Skin tests*

The results of intradermal and patch tests are summarized in Table 3. No immediate skin reaction was observed in any of our patients. Sixty-eight out of the 71 patients with DTH to aminopenicillins had at least one positive skin test with ampicillin or amoxicillin either in the intradermal or patch test (positive at day 2 to maximum day 4). Forty-eight patients showed positive test reactions with either ampicillin or amoxicillin but with no other tested penicillin derivatives, whereas 20 patients developed positive skin test reactions to aminopenicillins and penicillin derivatives as well. Besides the positive skin tests with aminopenicillins, 16 out of these 20 patients tested additionally positive for both benzyl penicillin and phenoxymethyl penicillin, 4 only for benzyl penicillin. Skin testing is a safe procedure and was well tolerated. Only one patient developed 2 days after a 3-fold (3+) positive patch test to amoxicillin a systemic skin reaction spreading to the extremities which disappeared after treatment with local steroids after 1 week. In 10 patients, our standard test protocol had to be modified because patients refused the complete panel of diagnostic tests; main reasons were the time consuming procedure, no immediate therapeutic need for antimicrobial drugs and the fear of adverse effects. In these cases, we had to limit the diagnostic procedure, i.e. a subset of the skin tests to unequivocally diagnose DTH to aminopenicillins (data not shown).

### *Single-blinded, oral β-lactam challenge*

Challenge tests were exclusively performed with skin-test negative β-lactams. The results of the performed challenge tests are summarized in Table 4. Sixty-nine of 71 patients (97.2%) with DTH to aminopenicillins tolerated at least one of the cephalosporins: cefpodoxime and cefixime. Fifty-one of 71 patients had an exclusive DTH to aminopenicillins and tolerated not only the mentioned cephalosporins but also phenoxymethyl penicillin. Among a total of 148 challenge tests (data not shown), we observed 5 (3.4%) positive late reactions occurring as exanthemata, which were controlled by symptomatic therapy with antihistamines and glucocorticoids. Three patients with negative skin tests were diagnosed as DTH to aminopenicillins after developing a maculopapular exanthema after amoxicillin-challenge. These three patients tolerated phenoxymethyl penicillin and cefpodoxime. Two patients with DTH to aminopenicillins developed an exanthema in challenge tests with cefpodoxime and cefixime, respectively.

**Table 4.** Results of challenge tests; 48 patients received phenoxymethyl penicillin and cephalosporins, 20 patients received cephalosporins and 3 patients received amoxicillin, phenoxymethyl penicillin and cephalosporins [the total number of patients with positive (+) and negative (−) challenges is shown in the columns on the right-hand side]

| | Patients ($n = 71$) | | | Patients with positive or negative challenges | |
|---|---|---|---|---|---|
| Challenged drug | 48 (+/−) | 20 (+/−) | 3 (+/−) | positive | negative |
| Amoxicillin | | | 3/0 | 3 | 0 |
| Phenoxymethyl penicillin | 0/48 | | 0/3 | 0 | 51 |
| Cefpodoxime and/or cefixime | 0/48 | 2/18 | 0/3 | 2 | 69 |

## Discussion

The main cause for the increase in DTH to aminopenicillins may be the frequent use of amoxicillin and ampicillin, whereas

the number of patients exposed to benzyl/phenoxymethyl penicillin is decreasing.[20] After diagnosis of an aminopenicillin allergy, the physician is forced to avoid all β-lactams, e.g. penicillin, penicillin derivatives and cephalosporins, and will be prescribing alternative antibiotics. However, exclusion of the entire β-lactam group may result in more harm than benefit for the patient due to prescribing second-line antibiotics with increased toxicity, potential side effects and treatment failures. In our study of 71 patients, sequential skin testing followed by oral challenges showed that patients with confirmed DTH to aminopenicillins tolerate specific β-lactams without skin reactions. Sixty-nine of 71 patients (97.2%) tolerate cefpodoxime or cefixime, and 51 (71.8%) also tolerate phenoxymethyl penicillin. Recurrent infections by β-lactam-susceptible bacteria may then be treated by administration of these tolerated β-lactams at lower costs and with higher efficacy.

Intradermal and patch tests are reliable tools for diagnosis of DTH to aminopenicillins with a high sensitivity.[8,13,21–24] We were able to confirm DTH to aminopenicillins in 68 of 71 patients by combined skin testing using intradermal and patch tests with a sensitivity of 95.8%. In our study, we found 11 cases with positive patch but negative intradermal tests, and on the other hand 7 patients with positive intradermal but negative patch tests to aminopenicillins (data not shown). Therefore, combined skin testing should be performed in all patients with suspected DTH to aminopenicillins because in some cases positive skin tests can be obtained with only one test method.[25] According to previous reports, our data also show that in case of a true DTH to aminopenicillins positive skin tests can be reliably observed even after years of last exposure to the suspected aminopenicillin.[11,12,26] Twenty of our 21 patients with exanthema more than 1 year prior to testing had positive reactions in intradermal or patch tests to ampicillin or amoxicillin (data not shown). A positive test result is not always seen with both aminopenicillins and therefore testing of both ampicillin and amoxicillin is recommended.[12,25]

The suspected incidence of hypersensitivity to penicillin reaches endemic rates of up to 10% within a given population. One always has to keep in mind that maculopapular exanthemata occurring during therapy with aminopenicillins (the incidence has been estimated at 9.5%) are almost always attributed by the patient and physician to the drug rather than to the underlying infectious disease. Sequential skin testing followed by challenge tests proves that at least 75% of patients with suspected allergy to penicillin tolerate β-lactams.[27–29] In the years 2000–2005, we have excluded DTH to aminopenicillins in more than 300 patients using our sequential diagnostic procedure (negative skin and challenge tests) (data not shown). Careful interpretation of anamnestic details after penicillin exposure is crucial. However, retrospectively, urticaria and exanthema may not be differentiated by patients and physicians and for this reason combined testing for immediate-type reactions (IgE antibodies, evaluation of intradermal tests after 20 min) and late reactions (evaluation of intradermal and patch test after 2, 3 and 4 days) is recommended. In our series only 3 of 71 patients had a false-negative skin test and DTH to aminopenicillins was finally confirmed by positive oral challenge. This is in agreement with the findings of Romano *et al*. who found that 1 of 64 patients with negative skin tests tolerated challenge tests with the suspected aminopenicillin, indicating that the vast majority of the skin test results are not false negative.[11] Therefore, our data and previous studies indicate that negative results in skin tests almost always exclude the allergic nature of a maculopapular exanthema occurring during treatment with aminopenicillins.[9,30] False positive skin test reactions are theoretically possible, but are minimized due to the long experience in test methods, well-established concentration of reagents and reliable reading of test results including morphology and crescendo pattern. Romano *et al*. conclude that in case of late skin test positivity to aminopenicillins or phenoxymethyl penicillin oral challenges are obsolete because in general patients often develop severe reactions when provoked with the culprit β-lactam drug.[9,31]

In DTH to aminopenicillins, the aminobenzyl side chain plays the predominant role. This aminobenzyl side chain appears to be a major factor for the cross-reactivity between aminopenicillins and cephalosporins such as cefalexin, cefaclor and cefadroxil, i.e. the same side chain presented by different core structures may be recognized.[32,33] The main reason for the importance of the R1 cephalosporin side chain in drug allergy may be that during the generation of cephalosporoyl antigens the R1 side chain and part of the β-lactam core structure remain bound to the carrier protein whereas the R2 side chain is lost.[34] The amoxicillin side chain is the same as the R1 side chain of cefadroxil, and ampicillin has the same side chain as cefalexin and cefaclor (Figure 1). Unfortunately, this cross-reactivity often cannot be diagnosed by skin tests due to false negative cefaclor, cefalexin and cefadroxil tests. Cross-reactivity between aminopenicillins and these cephalosporins is frequent, since only few cases of clinical tolerance are reported in the literature.[35] Interestingly, two of our patients with allergy to aminopenicillins tolerated challenge tests with cefalexin and cefaclor (data not shown), implying that in some patients other parts of the ampicillin/amoxicillin molecule in addition to the aminobenzyl side chain may be required for the optimal formation of antigenic determinants. In contrast, cross-reactivity between aminopenicillins and cephalosporins with a different R1 side chain is very low. In our group of patients with DTH to aminopenicillins, only two developed a macular exanthema after oral challenge with cefixime and cefpodoxime, respectively. In a study by Novalbos *et al*., all 41 patients with penicillin allergy tolerated the intramuscular administration of cefazolin, cefuroxime and ceftriaxone.[36] However, unlike our series of patients in the study by Novalbos *et al*. only four patients had a history of exanthema due to aminopenicillins.

Several reports showed that 40–90% of all patients with a DTH to aminopenicillins have negative skin tests for benzyl or phenoxymethyl penicillin.[12,37] In our study, all 51 patients (71.8%) with negative skin tests for benzyl and phenoxymethyl penicillin tolerated oral phenoxymethyl penicillin challenge. On the other side, we observed positive skin tests with benzyl/phenoxymethyl penicillin in 20 patients (28.2%) who therefore showed cross-reactivity between aminopenicillins and benzyl/phenoxymethyl penicillin. This indicates that in a significant portion of aminopenicillin-allergic patients not the aminobenzyl side chain but rather the β-lactam core structure is the responsible antigenic determinant.

## *Conclusions*

In the present study, 69 of 71 patients (97.2%) with well-documented DTH to aminopenicillins tolerated at least one of the cephalosporins, cefpodoxime and cefixime, in oral challenge

tests. Fifty-one of 71 patients had an exclusive DTH to aminopenicillins and tolerated not only the mentioned cephalosporins but also phenoxymethyl penicillin. These data indicate that patients with confirmed DTH to aminopenicillins may receive cephalosporins without an aminobenzyl R1 side chain with a low risk (2.8%) of developing an allergic reaction. More than two-thirds of the examined patients (71.8%) also tolerate phenoxymethyl penicillin. Future therapy with antibiotic compounds will be crucially facilitated for patients with confirmed DTH to aminopenicillins by application of tolerated β-lactams.

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## Transparency declarations

None to declare.

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