

Ampicillin and Amoxicillin Delayed Hypersensitivity: Side-Chain-Specific Allergic Reactions in a Child

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ABSTRACT

Background: Maculopapular rashes are common cutaneous adverse reactions to ampicillin and amoxicillin. Usually they are not due to a known allergic mechanism. However, type I (IgE mediated) and type IV (T cell mediated, delayed hypersensitivity) cutaneous reactions to beta-lactams in general, and especially to ampicillin and amoxicillin, can be side-chain-specific.

Case Report: A 30-month-old boy developed a generalized maculopapular rash which progressed to desquamation while the child was being treated intravenously for 7 days with ampicillin.

Results: When the child was 40 months old, the maculopapular rash was reproduced (onset, 5–8 hours) by a diagnostic oral challenge with amoxicillin (one dose, 62.5 mg). Three days after onset of the rash, he was treated with methylprednisolone, and the rash resolved without desquamation. Penicillin V (phenoxymethyl penicillin) challenge (62.5 mg orally) and trial (125 mg orally three times a day for 10 days) were negative. Radioallergosorbent tests to penicilloyl G and penicilloyl V were negative. Immediate (15 minutes) and delayed (48 hours) skin tests to penicillin G, its major and minor determinants, and cefazolin were negative before and after the challenges with amoxicillin and penicillin V. Immediate intradermal skin tests (0.02 mL) to ampicillin (0.25 and 2.5 mg/mL) were negative. However, induration and erythema (7 × 8 mm and 10 × 10 mm) began 5 to 8 hours and reached a maximum at 48 hours after the tests were applied. Biopsies were not done.

Conclusions: These observations emphasize that (1) ampicillin/amoxicillin maculopapular desquamative rashes in children can be due to delayed hypersensitivity mechanisms, (2) beta-lactam ampicillin/amoxicillin delayed reactions can be side-chain-specific (amino-benzyl group), (3) ampicillin should be included in skin testing protocols, (4) skin test sites should be examined not only at 15 minutes but also at 48 hours after the tests are applied, and (5) other beta-lactam (not amino-benzyl) antibiotics may be tolerated.

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INTRODUCTION

ADVERSE CUTANEOUS REACTIONS to beta-lactam antibiotic drugs (penicillins and cephalosporins) are frequently suspected of being immune mediated. Urticarial reactions due to penicillin are usually IgE mediated. They can be predicted by positive immediate (15–20 minutes) skin tests to the major (octa-benzylpenicilloyl-octalysine) and minor (potassium benzylpenicillin, benzylpenicilloate, and benzylpenicilloyl-N-propylamine) derivatives of penicillin.^(1,2) However, until recently, maculopapular rashes seen in patients treated with aminopenicillins (ampicillin and amoxicillin) have not been considered to be IgE mediated. An early study of children and adults showed that of 34 patients who had maculopapular rashes to ampicillin, none had a positive immediate or delayed skin test reaction and none reacted to the readministration of ampicillin.⁽³⁾ In contrast, a recent study of adults with a history of maculopapular eruptions while on aminopenicillins showed that 55% (N = 33/60) had positive delayed skin test reactions (48 hours) to the aminopenicillins. The diagnoses were confirmed by oral challenge in 55% (N = 18/33).⁽⁴⁾ Ninety-one percent (N = 30/33) had negative delayed skin tests to penicillin G and its major and minor derivatives. These observations indicate that both delayed hypersensitivity and side-chain-specific (amino-benzyl group) mechanisms can be responsible for maculopapular eruptions. In addition, side-chain-specific, delayed skin test reactions in the absence of immediate skin test responses in patients with late onset cutaneous reactions have been reported to occur with other beta-lactams, supporting the notion that cell-mediated mechanisms are involved in these instances also.^(5–8) Direct evidence that specific cellular responses are involved in penicillin allergy includes the observation that T-cell clones from different penicillin-allergic patients proliferate in response to penicillin epitopes. These epitopes represent the side-chain, which is different in every member of the penicillin family, as well as the thiazolidine ring common to all penicillins.⁽⁹⁾

We report a reproducible aminopenicillin side-chain-specific (amino-benzyl group), delayed hypersensitivity reaction in a child.

CASE REPORT

K.E. is A 40-month-old white boy with past history of biliary atresia. He underwent a Kasai operation (hepatic portoenterostomy) at 2 months of age and currently has portal hypertension and hepatosplenomegaly. Pruritus, associated with his chronic hepatic condition, has been treated with hydroxyzine.

At 30 months of age, he presented with dark urine, light green-colored stools, irritability, fever, lethargy, jaundice, and abdominal pain. These signs and symptoms were consistent with the diagnosis of cholangitis. He was treated with parenteral ampicillin, gentamicin, and clindamycin. Because of the persistence of fever, the antibiotics were changed to vancomycin and ceftazidime. Prior to discharge, the antibiotics were again changed to cefoperazone and ampicillin. After 7 days on these antibiotics, he developed a generalized, erythematous, maculopapular rash involving his arms, trunk, shoulders, back, and diaper area. He also had a low-grade fever. The antibiotic therapy was switched to gentamicin. The rash persisted for 5 to 7 days, desquamated, and then resolved by the end of the second week.

K.E. was referred by his pediatrician (L.F.N.) for an opinion (to the extent that testing allows) as to whether this rash really represented an allergy to penicillin or cephalosporin, or both.

RESULTS

Radioallergosorbent tests (Metpath, Teterboro, NJ) for penicilloyl G-specific serum IgE and penicilloyl V-specific serum IgE were negative. The total serum IgE level (2 IU/mL) was within normal limits. Prick and intradermal (0.02 mL) skin tests were done 5½ months after the drug reaction. Hydroxyzine was withheld for 2 weeks prior to skin testing and challenge testing. The histamine control was positive (wheal, 8 × 10 mm). Immediate (15 minutes) prick and intradermal skin test responses were negative to penicillin G (1000 U/mL and 10,000 U/mL), the major determinant (benzylpenicilloylpolylysine, 6.0×10^{-6} mol/L and 6.0×10^{-5} mol/L; Pre-Pen, Schwarz Pharmaceuticals, Milwaukee, WI), and an alkaline hydrolysate minor determinant mixture (MDM) of penicillin G, ampicillin (0.25 mg/mL and 2.5 mg/mL), and cefazolin (0.25

mg/mL and 2.5 mg/mL).⁽¹⁰⁾ However, when the patient returned 48 hours after the skin testing for a scheduled oral challenge, erythema and induration were noted at both ampicillin skin test sites (7×8 mm at 0.25 mg/mL; 10×10 mm at 2.5 mg/mL). On further inquiry, it was determined that the reactions had started 5 hours after skin testing and were most intense at 24 to 48 hours after testing. The patient was then given a single oral dose (62.5 mg) of amoxicillin. Five hours later, he developed an erythematous, generalized, maculopapular, pruritic rash, similar to the initial rash, involving the ampicillin skin test sites. This eruption peaked at 24 to 48 hours after administration of the amoxicillin. He was treated with hydroxyzine (15 mg twice a day) and methylprednisolone (7.5 mg three times a day) for 5 days. The rash resolved within 3 days. It did not progress to desquamation.

An open oral challenge with a single dose (62.5 mg) of penicillin V (phenoxymethylpenicillin) was negative as was an open oral trial (125 mg orally three times a day for 10 days) with penicillin VK. Immediate and delayed skin tests to penicillin G and cefazolin before and after this challenge were negative. The delayed (48 hours) skin test response to ampicillin (2.5 mg/mL) was again positive (9×9 mm of erythema and induration).

DISCUSSION

It is important to note that this child was asymptomatic at the time that the amoxicillin challenge was undertaken. Therefore, it is unlikely that the rash was due to a concomitant viral infection. Maculopapular rashes are commonly seen in amoxicillin/ampicillin-treated patients with infectious mononucleosis, influenza, or cytomegalovirus. Many of these patients will be able to tolerate amoxicillin/ampicillin again once the infection is resolved.

Our patient had a desquamative rash when treated with ampicillin for the first time but not when challenged with amoxicillin. The large amount of drug given prior to the occurrence of the rash in the first instance could account for this difference. Alternatively, the kind of aminopenicillin employed, ampicillin versus amoxicillin, may have been important. In a series of patients reported by Terrados et al. in 1995,⁽⁶⁾ desquamative lesions were reported to be more frequent in the ampicillin-treated group than in the amoxicillin-treated group. We believe the most likely explanation for the absence of a desquamative phase in the second instance was the early treatment with methylprednisolone.

Early and accelerated reactions (anaphylaxis, angioedema, and urticaria) to beta-lactam antibiotics are usually IgE mediated. This association is supported by positive immediate skin tests to appropriate penicillin skin test reagents and/or positive radioallergosorbent tests. Most exanthems occurring later (average, 7 days) during the course of therapy are thought to be nonimmunologic, not reproducible by challenge, and not predictable by skin testing.⁽³⁾ De Haan et al.,⁽¹¹⁾ in their series in 1986, reported that early onset reactions are common with use of benzylpenicillin, whereas their late onset rashes (mostly maculopapular) are common with the use of the aminopenicillins. It is estimated that some 5% to 10% of patients treated with ampicillin develop exanthems. The role of skin testing in patients who have had isolated delayed cutaneous reactions to beta-lactams is not well established. We had doubts that skin testing would be useful in our case with a delayed cutaneous reaction. However, because of the chronicity of this child's illness and the likelihood of need for future antibiotic therapy, we felt it was necessary to define whether this child is predisposed to a potentially life-threatening, IgE-mediated drug hypersensitivity or severe cutaneous reaction to beta-lactams. In addition, we hoped we could identify other antibiotics in this class that may be safe to administer.

Benzylpenicillin (penicillin G) has at least three epitopes that are responsible for its antigenicity: the thiazolidine ring, the side-chain attached to the penicilloyl group, and a new antigenic determinant that arises after coupling of the beta-lactam ring to lysine epsilon amino groups of a carrier protein (see Fig. 1).^(9,12) Penicillin G and other semisynthetic penicillins cross-react to some degree because of recognition of a common thiazolidine ring. Cephalosporins, which are also beta-lactams, have a dihydrothiazine ring instead of a thiazolidine ring. Some have side-chains in common with the penicillins. Theoretically, they cross-react with the penicillins because of either the side-chains attached to the beta-lactam ring or a new antigenic determinant arising after the hapten couples with a carrier protein. The aminopenicillins differ from penicillin

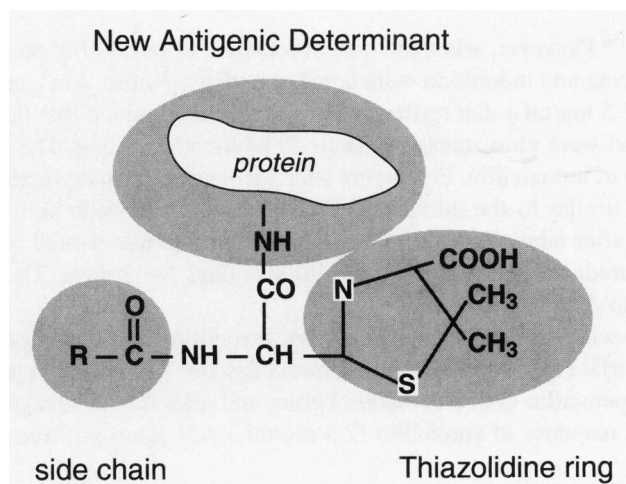


FIG. 1. Three possible epitopes in the penicilloyl group. (Modified from de Haan, 1985)

G (benzylpenicillin) only by the addition of an amino group in the acyl side-chain. Amoxicillin is ampicillin with a hydroxylated phenyl side-chain (Fig. 2).

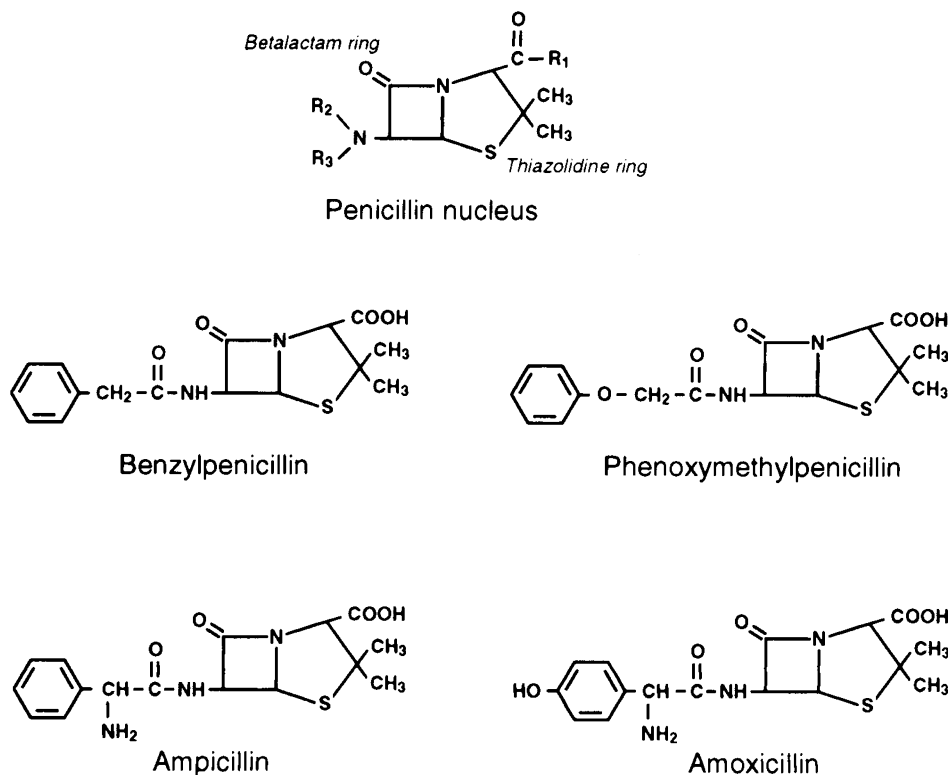
In our patient, the delayed skin test reactivity to ampicillin and not to penicillin G, benzylpenicilloypolylysine, or MDM, and the positive challenge reaction (maculopapular rash) to amoxicillin and not to penicillin V implies that the amino acyl side-chain of these aminopenicillins is the important determinant for the hypersensitivity reaction. There have been reports published about this type of delayed hypersensitivity, side-chain-specific reaction in adults but only one in children.⁽³⁾ A recent study implicated this mechanism to be operative in over 50% of adult patients with a past history of maculopapular eruptions while being treated with aminopenicillins.⁽⁴⁾ Direct evidence for side-chain specificity in delayed-type reactions was demonstrated by Voorhorst and Sparreboom⁽¹³⁾ using patch testing with stereoisomers of different antibiotics in the beta-lactam group. They found consistent positive delayed reactions in one patient for amoxicillin, ampicillin, epicillin, pivampicillin, and bacampicillin, all of which possess an amino acyl group. Patch tests to other beta-lactams without the amino acyl group were negative in this patient with a history of cutaneous reaction associated with the use of ampicillin. The amino group in the *D*(-)-alpha-position was essential for the delayed-type allergic reactivity. The *L*(+)-alpha ampicillin did not react.

Besides reports of positive delayed skin tests to specific beta-lactams and tolerance to other penicillins in patients with histories of late cutaneous reactions, direct evidence for the immunogenic contribution of the acyl side-chain has been demonstrated using monoclonal antibodies developed in immunized mice.⁽¹²⁾ The binding of some monoclonal antibodies to various penicilloyl conjugates is dependent on the structure of the side-chain. The affinity of other antibodies is dependent on binding of the hapten to its protein conjugate. A common thiazolidine ring alone or in its haptened form contributes to the observed cross-reaction between semisynthetic beta-lactams. The investigators who performed these studies postulated that in humans, variability of penicillin side-chains may add epitopes, which may be independently recognized by antibodies generated against them.

In vitro studies of generated T-cell lines and clones from penicillin-allergic patients not only implicate side-chain-specific, reactive T cells in delayed-type reactions to beta-lactams but also suggest the possibility for a broader determinant site comprised of the penicilloyl structure together with the side-chain, because absence of proliferation was noted in the cephalosporins possessing similar side-chains but a different core structure (dihydrothiazine) from the penicillin thiazolidine ring.⁽¹⁴⁾ In addition, the penicillin molecule can stimulate T-cell subsets either by associating with a formed major histocompatibility complex surface molecule or by binding to human serum albumin.^(15,16)

Currently, the usefulness and predictive value of skin tests for delayed-type cutaneous reactions to semisynthetic penicillins in children is not known.⁽¹⁷⁾ However, a positive skin test will be informative for the individual patient who has a history of delayed onset cutaneous reactions, including a maculopapular eruption with desquamation. The concomitant occurrence of fever may be another important clinical clue.

A



B

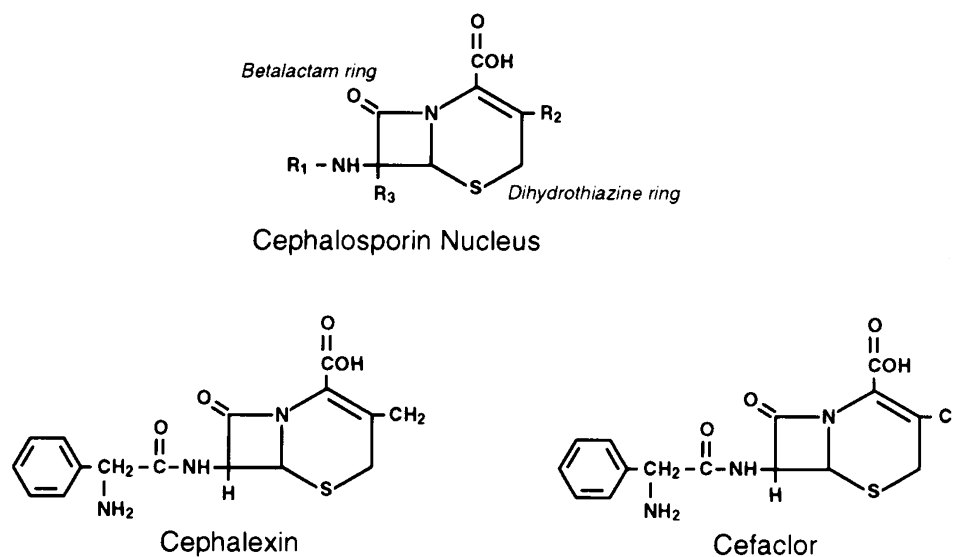


FIG. 2. A. Penicillin nucleus and examples of penicillin and amino penicillins. B. Cephalosporin nucleus and examples of aminocephalosporins.

Romano et al.⁽⁴⁾ reported that the aminopenicillin-associated maculopapular rash in 8 of 33 (24%) patients underwent a desquamative phase, and the cutaneous symptoms were accompanied by high fever in 3 of 33 (9%) patients.

Based on this case and on a review of the recent pertinent literature, we recommend that children who develop maculopapular skin rashes while being treated with ampicillin or amoxicillin, especially when accompanied by desquamation and fever, should be investigated for the presence of side-chain-specific delayed hypersensitivity to these aminopenicillins. We stress the importance of reading the skin test sites at 15 to 20 minutes after the tests are applied, and again at 48 hours, and of including an aminopenicillin skin test reagent. These testing conditions are not clearly delineated in recently published studies of penicillin allergy, reviews of penicillin allergy, and procedures for evaluating penicillin allergy.^(1,2,10,17-20) If there is a delayed rash other than life-threatening erythema multiforme and toxic epidermal necrolysis and if immediate and delayed skin tests are negative, challenge testing is reasonable. When challenge tests are negative, the original diagnosis of penicillin allergy may have been erroneous or hypersensitivity may no longer exist.⁽¹⁷⁾ In addition, we would like to emphasize that there is a potential for both immediate and delayed hypersensitivity side-chain-specific reactions and cross-reactions among and between the aminopenicillins and aminocephalosporins. The aminopenicillins (ampicillin, amoxicillin, bacampicillin), first-generation aminocephalosporins (cephalexin, cephadrine, cephadroxil), and second-generation aminocephalosporin (cefactor) have similar side-chains.^(19,21,22) The importance of these types of relationships have been known since Karl Landsteiner and Merrill W. Chase published their classical observations more than 50 years ago.^(23,24)

Finally, allergy to one type of beta-lactam antibiotic need not lead to avoidance of the entire beta-lactam family. This is particularly important in childhood, when primary care physicians frequently choose amoxicillin to treat upper respiratory bacterial infections. Skin testing can help the physician to select a safe substitute.⁽¹⁷⁾

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