

ORIGINAL PAPER

Beta lactam allergy and resensitization in children with suspected beta lactam allergy

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Summary

Background In patients who were clinically diagnosed as having beta lactam allergy and had negative skin tests, the rates of reported resensitization to beta lactams after subsequent exposures, vary significantly. Some allergists advocate skin testing before every exposure to beta lactams.

Objective We sought to determine the true rate of beta lactam allergy and of resensitization in children with a positive history for suspected beta lactam allergy.

Methods The study was conducted from July 1998 to May 2004, with follow-up during 2007. Beta lactam allergy tests with the major determinant and freshly prepared minor determinant mixtures were offered to history positive children. Negative skin tests were followed by oral challenge. The tests were performed again 1–5 months later in order to address the possibility of resensitization.

Results Tests were performed on 166 children: 150 for penicillins alone, 14 for penicillin in combination with cephalosporins, and an additional 2 patients solely for cephalosporins. Only 10 children (6%) were positive in the initial evaluation, four by skin test and six by oral challenge. A second set of tests was performed in 98 children with a negative initial evaluation; only two children (2%) were resensitized. On a follow-up survey of 71 of the 96 patients, 59 (83%) had received beta lactams; only one had developed a minor rash after subsequent exposure to amoxicillin.

Conclusions Most children with suspected beta lactam allergy were not allergic to beta lactams. Resensitization to beta lactam antibiotics in children in this study was infrequent. In children with a clinical diagnosis of beta lactam allergy and negative skin tests, repeated skin testing before every exposure is usually unnecessary.

Keywords beta lactam, children, resensitization

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Introduction

Allergy to beta lactam antibiotics is a well-known phenomenon that may cause anaphylaxis and mortality [1]. In patients who received repeated penicillin injections, anaphylaxis was found in 0.2%, with a fatality rate of 0.31/10 000 injections [2]. In patients who had anaphylaxis following penicillin injections, one out of four died [2]. In patients with a positive history for beta lactam allergy, penicillin allergy can be diagnosed by skin tests to the major and minor determinants of penicillin and the

diagnosis of cephalosporin and semi-synthetic penicillin allergy can be evaluated with skin tests with these antibiotics and minor determinant mixtures (MDM) followed by an oral challenge [3]. However, there are few data on the predictive values of positive and negative skin tests to cephalosporins.

Beta lactam allergy is over-reported. Many patients who have a history compatible with allergy have negative skin tests to the suspected antibiotic [4–7]. The reasons for the discrepancy between the higher rate of suspected allergy by history vs. the confirmed allergy rate as defined

by a history compatible with beta lactam allergy and positive skin tests is probably due to multiple factors including non-allergic adverse events, rash as part of the natural history of the disease for which antibiotics were prescribed, and loss of the specific IgE conferring the allergy years after the exposure. It has been shown that in patients with a positive history for penicillin allergy, the rate of positive skin tests was related to the time that elapsed after the initial reaction; in one study, 93% were positive 7–12 months after the reaction compared with only 22% after 10 years [8]. These data suggest that allergic patients may lose specific IgE to beta lactams and become skin test negative; however, they can still become skin test positive after subsequent exposure [9–16]. This phenomenon is defined as resensitization. The exact rate of resensitization to penicillin antibiotics is not known and various reports have shown an extremely wide range varying from 0% to 27.9% [9–16]. However, most of the studies revealed resensitization rates below 5% [10, 11, 13–15].

The risk of resensitization is the justification for the practice of not performing beta lactam skin tests to determine if a patient is allergic to beta lactams ahead of need. Some guidelines suggest performing such tests only before therapy is indicated and redoing the same skin tests before every treatment with the antibiotic [1]. Because the evaluation for beta lactam is not readily available in common paediatric practice, many patients are not evaluated before receiving a therapeutic course of antibiotics and are denied of the benefits of beta lactam medications. If the risk of resensitization is negligible, it would be reasonable to perform beta lactam allergy evaluation at an elective time ahead of need, using a protocol that addresses this concern.

We sought to determine the true rate of beta lactam allergy and resensitization in children with a diagnosis of beta lactam allergy by performing two consecutive skin tests followed by an oral challenge and a follow-up survey.

Methods

The study was approved by the institutional Ethics Committee, and was carried out at the Paediatric Allergy Clinic, Soroka Medical Center, Beer-Sheva, Israel. Written informed consent was obtained from parents or legal guardians of every child, and verbal assent from the child whenever appropriate.

The inclusion criteria included: patients <18 years of age with a diagnosis of beta lactam allergy that may be compatible with IgE-mediated allergy. The exclusion criteria included anaphylactic shock and diagnosis of allergy that was clearly not compatible with IgE-mediated allergy.

Skin tests and oral challenges were carried out from July 1998 until May 2004. The evaluation included skin

tests with a positive histamine control, a negative saline control, and for the suspected allergens: major and minor determinants of penicillin, MDM of penicillin semi-synthetic derivatives and cephalosporins; and oral challenge with the suspected antibiotic. Prick tests were considered positive if after 15 min a weal and flare reaction appeared, in which the weal was more than 3 mm larger than that of the negative control. If the prick test was negative, the patient was observed for an additional 15 min and then underwent an intradermal test creating a weal with 0.02 mL of the relevant reagent, with a negative saline control. The intradermal test was considered positive if after 10–20 min the induced weal reaction was more than 3 mm larger than the saline control and larger than the original vesicle. If both the prick and intradermal tests were negative, the patient was observed for additional 15 min and then received an oral challenge with 10% of the usual therapeutic dose of the specific antibiotic. If no allergic reaction occurred within 30 min, a full therapeutic dose of the antibiotic was given orally. Following this, the patient remained under observation for 1 h, with a telephone follow-up 72 h later. The reagents for these tests were PPL (Pre-Pen[®], Kremers Urban Co., Milwaukee, WI, USA) 6×10^{-5} M, benzylpenicillin diluted with normal saline to a concentration of 10^{-4} Units/mL, MDM: equal parts of benzylpenicillin and benzyl penilloate to a concentration of 2×10^{-2} M as described [17, 18], and MDM of the semi-synthetic derivatives of penicillin: ampicillin and cloxacillin, and cephalosporins: cefuroxime and cefamezin at a concentration of 2×10^{-2} M as described [6, 19, 20]. The MDMs were prepared by alkaline hydrolysis of benzylpenicillin, frozen and lyophilized. The preparation was dissolved in saline immediately before use as previously described [5–7, 17, 20–22].

To evaluate resensitization, 1–5 months following the negative challenge test, the patient underwent repeated skin and challenge tests with the specific antibiotics for which he/she was considered allergic (penicillin VK, amoxicillin, amoxicillin-clavulanate, cefuroxime, cefaclor, or cephalexin). If the repeated skin and challenge tests were negative, the patient received a letter addressed to his/her primary physician, indicating that he or she was not found to be at a greater risk for an adverse allergic reaction to penicillin, to its semi-synthetic derivatives or to cephalosporins, than children who are not suspected of being allergic to beta lactams.

Between October and November of 2007 (3–9 years after performing the tests), the primary care physicians of patients who had two negative skin tests and challenges were contacted and asked to review the patients' medical records for prescription of the specific antibiotic following the negative tests and for possible repeated reactions to the suspected beta lactam.

Table 1. Antibiotic for which the patient was considered allergic

Antibiotic	No. of patients
Penicillin VK	24
Amoxicillin	125
Amoxicillin and clavulanic acid	35
Cefuroxime	6
Cefaclor	8
Cephalexin	2

38 patients were considered as being allergic to more than one antibiotic.

Table 2. Clinical signs that lead to the diagnosis of suspected beta lactam allergy

Non-urticarial rash	95	(57.2%)
Urticaria	10	(6%)
Angioedema	1	(0.6%)
Urticaria and angioedema	8	(4.8%)
Additional combinations*	30	(18%)
Unknown†	22	(13.2%)
Total	166	(100%)

*Additional combinations included at least two of the following: non-urticarial rash, urticaria, angioedema, vomiting, diarrhea, abdominal pain, shortness of breath, joint swelling and joint pain.

†Unknown: patients with suspected beta lactam allergy in whom the parents did not remember the exact presentation and the medical records did not include the clinical symptoms that lead to the diagnosis.

Results

In total, 166 patients were studied: 150 patients were studied for penicillins only, 14 for penicillins in combination with cephalosporins and an additional two patients were studied for cephalosporins only. The antibiotics that led to the diagnosis of suspected beta lactam allergy are presented in Table 1. Forty children (24.5%) were between the ages of 12–23 months, 27 (14.7%) between 24 months and 10 years, and 99 (58.5%) patients were 11–16 years of age. Eighty-eight (53%) of the patients were male. The clinical signs that led to the diagnosis of beta lactam allergy are presented in Table 2.

One hundred and sixty-six patients with a positive history of an allergic reaction to a beta lactam antibiotic were evaluated. Four patients had a positive skin test and six had a positive challenge in the initial evaluation (Table 3); these 10 children were considered allergic and were not studied further. Of the remaining 156 patients, 98 completed the study protocol and had two sets of skin tests and oral challenges. Only two patients (2%) had a positive skin test after the initial negative skin test and were considered as resensitized (Table 3). One of the resensitized patients had a positive intradermal skin test to penicillin after the initial negative test and challenge; her initial clinical presentation that led to the diagnosis of suspected penicillin allergy included rash and facial swelling. The second patient had a rash as the initial presenta-

Table 3. Type of test that determined allergy

Test	Children (n)
Positive ST to Clox+Cpl	1
Positive ST to MDM of Pnc	1
Positive ST to Amp+Cpl	1
Positive ST to multiple Cpls	1
Negative ST, immediate positive challenge to Amox	3
Negative ST, delayed positive challenge to Amox*	3
Positive ST to MDM of Pnc, resensitization†	1
Negative ST, immediate positive challenge to Amox, resensitization†	1
Total	12

ST, skin test; MDM, minor determinant mixture; Clox, cloxacillin; Cpl, cephalosporin; Pnc, penicillin VK; Amp, ampicillin; Amox, amoxicillin.

*Delayed reactions included skin rashes that began more than 4 h after the challenge.

†Positive at second evaluation.

tion, and had a self-limiting maculopapular skin rash that appeared within 30 min after the second challenge and disappeared after 2 h.

The 96 patients who were not allergic after two consecutive evaluations received a letter stating that they were not found to be at a greater risk for an immediate-type allergic reaction than a child who was not suspected of being allergic to these medications. Follow-up of 71 (74%) of the patients who had two consecutive negative skin tests and challenges was performed, with a median time of follow-up of 73 months and range of 44–112 months. Fifty-nine of the 71 (83%) patients received beta lactams following the allergic tests, and only one developed a rash after a fifth course of oral amoxicillin; once again, she had been diagnosed by her paediatrician, 'allergic to penicillin'.

Discussion

Our study revealed that only 2 out of 98 paediatric patients with a positive history for penicillin allergy were resensitized to penicillin after initial negative skin tests and oral challenge, and a single additional patient who developed a minor rash after a fifth exposure to amoxicillin following two sets of negative tests, leading to a resensitization rate of 3%. In patients with a positive history and negative skin tests, Mendelson et al. reported 219 children and adolescents with a resensitization rate of 0.9% [10]; however, Parker et al. showed a 16% rate of resensitization to penicillins in 18 patients (one child and 17 adults). It is noteworthy that the three patients who were resensitized were treated intravenously [9]. Lopez-Serrano et al. reported 207 skin test- and challenge-negative, history-positive patients who were retested 10–30 days after the initial skin test and challenge: five adult patients were resensitized, five more had an adverse

reaction even though the skin test was negative, and one additional patient became resensitized with subsequent exposure [11]. Pichichero and Pichichero reported 26 out of 189 skin test- and oral challenge-negative children and adolescents whose skin tests became positive after a 5–10-day oral antibiotic challenge, revealing a resensitization rate of 13.7% [12]. Solensky et al. reported zero resensitization when retesting 46 adult patients after three consecutive doses of oral penicillin [13]. Macy et al. reported 568 predominantly adult patients with negative skin test and a positive history who were treated with penicillin, with 65 patients having an adverse reaction after receiving routine antibiotic therapy at the time of need. Of these 65 patients, 33 underwent repeated skin tests and only one became resensitized [14]. Bittner and Greenberger showed no resensitization after multiple courses of beta lactam antibiotics, including intravenous therapy in 33 adult patients; however, three patients had cutaneous eruptions that were not considered IgE-mediated [15]. In striking contrast, Goldberg and Confino-Cohen studied 161 patients from a predominantly adult population and found a resensitization rate of 27.9% after skin testing and oral challenges, the highest rate reported so far [16].

The different resensitization rates reported in various studies can be attributed to different methodology, relatively small sample sizes in most studies, and failure to perform skin tests to confirm resensitization in some of the patients who had a suspected adverse reaction after an initial negative skin test.

It is noteworthy that the study, which showed a relatively high rate of resensitization, 16%, included 18 patients of whom three received penicillin intravenously [9]. These data suggest a higher rate of resensitization after intravenous infusion of antibiotics than following oral route of administration. However, this finding was not corroborated by the study by Bittner and Greenberger in which no resensitization occurred even though 30 of the 33 patients received at least one course of parenteral beta lactam antibiotic [15].

Another controversial issue is the age of the patients as a contributing factor for resensitization. In paediatric patients, Mendelson et al. reported a low resensitization rate [10], as compared with Pichichero and Pichichero, who reported a much higher rate [12]. Similarly, Parker et al. found a 16% rate of resensitization evaluating an older population [9]; however, in opposition to this view are the findings of Bittner and Greenberger who reported no resensitization in 33 adult patients [15].

Lopez-Serrano et al. reported a patient who became resensitized after a third exposure to amoxicillin [11]. The concern of resensitization after more than two antibiotic courses was also addressed by Solensky et al. who challenged the skin test-negative history-positive patients with three successive courses of 10 days of penicillin, without any case of resensitization [13], showing that

resensitization after two negative skin tests and challenges is extremely rare. In our study, one patient who was negative on two sets of skin tests and challenges, was rediagnosed later as allergic to penicillin after a fifth course of amoxicillin. We were unable to repeat amoxicillin allergy tests to confirm this diagnosis.

In the 164 patients that were evaluated for suspected penicillin allergy by skin test and challenge at least once, it is noteworthy that in the 10 patients who were found to be allergic to penicillin during the first evaluation, four patients were diagnosed by positive skin tests and an additional six patients were diagnosed by challenge to amoxicillin; three patients with a reaction compatible with IgE-mediated allergy and three patients with a delayed reaction. In patients with suspected amoxicillin allergy, the evaluation included skin test to MDM of ampicillin, and we had only one patient who had a positive skin test to ampicillin. These data may suggest that the use of MDM to ampicillin for the evaluation of suspected amoxicillin allergy is not sufficient to diagnose correctly most of the patients with IgE-mediated allergy to amoxicillin.

Skin testing for penicillin antibiotics is considered to be the gold standard for the diagnosis of penicillin allergy and positive skin tests are considered to indicate a high risk for an allergic reaction. Recently however, Goldberg and Confino-Cohen have challenged this view. In a relatively small preliminary study, they have shown that even skin-positive patients with a history of remote penicillin allergy may have a negative penicillin challenge and subsequent therapy at the time of need [16]. If these data are confirmed in larger studies, it may mean that some of the patients resensitized to penicillin will be able to tolerate this therapy safely.

We conclude that in our study only 6% of children with a history of beta lactam allergy may be truly allergic. The rate of resensitization to beta lactam antibiotics in children in our study was rare. A protocol for the evaluation of allergy to beta lactam antibiotics may be employed safely at an elective time, ahead of need.

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