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Non-immediate hypersensitivity reactions to beta-lactam antibiotics in children – our 10-year experience in allergy work-up

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allergy work-up; beta-lactams; children; non-immediate hypersensitivity reactions; provocation test; skin test

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Abstract

Background: Non-immediate reactions to beta-lactam antibiotics (BL) occur more than one hour after drug administration, and the most common manifestations are maculopapular exanthemas and delayed-appearing urticaria and/or angioedema. Infections can lead to skin eruptions and mimic drug hypersensitivity reactions (DHR), if a drug is taken at the same time. The most of children are labeled as 'drug allergic' after considering only the clinical history.
Objective: To diagnose/detect a hypersensitivity or an infection which mimic DHR in children with non-immediate reactions to BL
Methods: A prospective survey was conducted in a group of 1026 children with histories of non-immediate reactions to BL by performing patch tests, skin tests, and in case of negative results, drug provocation tests (DPTs). In 300 children, a study was performed to detect infections by viruses or Mycoplasma pneumoniae.
Results: Urticaria and maculopapular exanthemas were the most reported non-immediate reactions. Only 76 (7.4%) of 1026 children had confirmed non-immediate hypersensitivity reactions to BL. Fifty-seven children had positive delayed-reading intradermal tests (18 of these with a positive patch test). Nineteen children had positive DPT. Sixty-six of 300 children had positive tests for viruses or Mycoplasma pneumoniae and 2 of them had a positive allergy work-up.
Conclusions: A diagnostic work-up should be performed in all children with non-immediate reactions to BL, to remove a false label of hypersensitivity. Even though only 57 (5.5%) of 1026 children displayed positive responses to delayed-reading intradermal tests to BL, such tests appear to be useful in order to reduce the risk for positive DPTs.

Drug hypersensitivity reactions (DHR) are adverse effects of drugs that clinically resemble allergic reactions (1). Clinically, hypersensitivity reactions to drugs are commonly classified as immediate and non-immediate according to the last drug administration and their onset. Immediate reactions occur within the first hour after drug administration and are induced by an IgE-mediated mechanism. Non-immediate reactions occur more than one hour after drug administration and are often associated with a delayed T-cell-dependent type of allergic mechanism. The most common non-immediate reactions are maculopapular exanthemas and delayed-appearing urticaria and/or angioedema. Rarely, severe reactions such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction/rash with eosinophilia and systemic symptoms (DRESS) can be elicited (2–6). This classification is important in clinical practice for work-up planning. A precise description of the morphology and chronology of the reaction is mandatory. The route of administration, the role of drug metabolites, and the presence of cofactors and coprescribed

drugs may accelerate or slow down the onset or progression of a reaction (1, 7). There is another limitation in children, as, in many cases, parents did not provide a precise description of the beginning of reactions, because the last dose of the culprit drug is usually administered during the night.

Infection, especially by viruses, can lead to skin eruptions and mimic DHR, if a drug is taken at the same time. Viruses can also interact with drugs, leading to mild eruptions, as in the case of the rash associated with aminopenicillin therapy during an Epstein–Barr virus (EBV) infection (1, 8, 9).

Beta-lactams (BL) are the most prescribed antibiotics in children and hence most frequently provoke hypersensitivity reactions mediated by immunologic mechanisms. Penicillin allergy is the most commonly reported drug allergy, with a prevalence rate of 5% to 10% in children and adults (2). Non-immediate reactions, such as delayed-appearing urticaria or maculopapular rashes, are the most reported manifestations in children, with an estimated frequency of 1% to 5% rashes per prescription, and it is significantly lower than in adults (2, 10). Although hypersensitivity reactions to BL are often reported in children, only a few are finally confirmed, after a careful evaluation (11–13).

The purpose of our study was to confirm or rule out the diagnosis of non-immediate hypersensitivity reactions to BL in children by evaluating them according to the guidelines of the European Network for Drug Allergy (ENDA), the European Academy of Allergy and Clinical Immunology (EAACI) interest group on drug hypersensitivity (5, 6).

Methods

Patient selection

All children ranging in age from 1 to 18 years were recruited prospectively from a large outpatient population in the University Children's Hospital of Belgrade between January 2005 and December 2014 because of histories of non-immediate reactions to BL. Children and their parents completed a standardized questionnaire (14). The exclusion criteria consisted in severely compromised cardiovascular, renal, or respiratory functions.

The study was approved by the hospital ethics committee, and prior to the study, the parents of all the children received information about the possible risks of skin and challenge tests, and written informed consent was obtained from them.

Skin tests (patch and intradermal tests)

Children underwent skin tests and patch tests according to the ENDA guidelines (5, 6).

On the first day, we carried out skin prick and intradermal tests using penicilloyl-polylysine (PPL, Diater, Madrid, Spain), minor determinant mixture (MDM, Diater), and benzylpenicillin.

Patch tests were also administered with benzylpenicillin, ampicillin, amoxicillin, and any suspect BL (5% in petrolatum), as previously described (2, 15). All reagents were applied to uninvolved skin on the interscapular region of the children's back, using acrylate adhesive strips with small plates attached for test allergens (Curatest, Lohmann & Rauscher International GmbH & Co. KG, Rengsdorf, Germany). Occlusion time was 48 h. Readings were made, as recommended by Brockow et al. (16), 15 min after removal of the strips and 24 h later.

Two days later, ampicillin and amoxicillin (at concentrations of 1 and 20 mg/ml after dilution in normal saline), as well as any other suspect BL, were used for prick and intradermal tests.

After having evaluated the first 100 subjects, we modified our skin test protocol by performing intradermal tests only with the suspect BL at the highest concentration, indicated in parentheses: benzylpenicillin and phenoxymethylpenicillin (10,000 IU/ml), ampicillin and amoxicillin (20 mg/ml), cephalexin, ceftriaxone, cefprozil, cefixime, ceftibuten, cefaclor, cefotaxime, and cefuroxime (2 mg/ml). For injectable drugs, we used the intravenous form, while for non-injectable ones we prepared a solution, as previously described (17). All reagents were freshly prepared every day under sterile conditions. 0.02 ml of the reagent solution was injected intradermally on volar forearm skin. Readings were made 20 min, and 24–48 h after injections. Late reactions to intradermal tests were considered positive when any infiltrated erythema appeared with a diameter larger than 5 mm (16). Positive controls were performed with histamine (at 1 mg/ml) and negative ones with normal saline.

Drug provocation tests (DPTs)

According to the indications and contraindications of the ENDA position paper (18), controlled administrations of therapeutic doses of suspected drugs were also performed in children who displayed negative results in allergy tests. In hospital, we administered an initial dose of one-hundredth of the therapeutic one (which depended on the children's weight). In case with negative results, 1 h later we administered a dose of one-tenth and if result was negative, after another hour a full dose. If good tolerance occurred, a therapeutic course of full dose was given 3 days afterward, at home. Since June 2011, after the publication of the study by Caubet et al. (8), we modified our allergy work-up, reducing the duration of the therapeutic course at home from 3 to 2 days (in 316 children). The parents of the children were advised to stop treatment, to take therapy (antihistamines), and to call the physician if they experienced a reaction.

Infectious agent study

From 2010, we performed also a serologic screening for viral or Mycoplasma pneumoniae infections in 300 children. Blood was drawn to perform assays for antibodies to viruses known to be associated with childhood skin rashes and urticaria (Epstein–Barr virus—EBV, parvovirus B19, adenovirus, cytomegalovirus —CMV, and herpes virus 6—HHV6) and for Mycoplasma pneumoniae. All children with positive IgM antibodies to Mycoplasma pneumoniae also had a throat swab for mycoplasma screening by PCR.

Results

A total of 1026 subjects had histories of non-immediate reactions to BL antibiotics (Table 1); none of them met the exclusion criteria.

Subjects reported a total of 1066 reactions: 826 to penicillins and 240 to cephalosporins. The responsible BL and clinical manifestations are shown in Table 1.

Nine hundred and eighty-seven children reported hypersensitivity reactions to one drug (787 to penicillins and 200 to cephalosporins); 37 children had reacted to two drugs (4–2 penicillins, 5–2 cephalosporins, and 28 to a penicillin and a cephalosporin), and only 2 children had reacted to three drugs (both to two different penicillins and a cephalosporin).

Fifty-seven children presented a total of 63 positive delayed-reading intradermal tests, 18 of these children were also positive to patch tests (Table 1). Four subjects were positive to immediate-reading intradermal tests (3 to benzylpenicillin and 1 to amoxicillin).

Nineteen children had positive DPT (10 to amoxicillin, 3 to benzylpenicillin, 1 to ampicillin, 1 to ceftriaxone, 2 to cephalexin, 1 to cefprozil, and 1 to cefixime), and in all cases, we observed reactions similar or identical to those reported in the history: 13 urticaria, three urticaria and angioedema, and three maculopapular exanthema; one of these subjects displayed a positive patch test with penicillin and a positive DPT with ceftriaxone. Six reactions were induced by DPT performed in the hospital. All of these reactions occurred once the children were back home. Thirteen reactions were reported to the therapeutic course at home. Three of them were in children who continued therapy for 2 days at home.

The median time interval to the response in the DPT was 13 h (2–48 h after the last dose of drug). The reactions were usually mild and controlled by corticosteroids and antihistamines. Comparison between the time intervals to response with recorded from clinical history showed no significant differences.

Six children were positive to two culprit drugs. Two of them were positive to two cephalosporins and four to a penicillin and a cephalosporin which are presented in Table 2.

Overall, a T-cell-mediated hypersensitivity was diagnosed in 76 children on the basis of positive responses to patch tests and/or delayed-reading intradermal tests, or provocation tests with the culprit BL (Table 1).

Comparison between hypersensitivity those identified and those not are presented in Table 3.

Of the 300 children who underwent a serologic screening for infectious agents, 66 were positive; two of them had also a positive allergy work-up. The results of such tests are presented in Table 4.

Discussion

In this study, we diagnosed a delayed hypersensitivity in only 7.4% of 1026 children with histories of non-immediate reactions to BL. Our data are in agreement with those of

Table 1 Clinical data of patients

	All patients (no 1026)
Age (years), mean (SD)	1–18 (7.7 ± 4.34)
Female, n (%)	502 (49.9)
Time since last drug reaction* (median)	1–60 (11)
Family history of drug allergy, n (%)	21(2)
of Personal history allergic disease, n (%)	8 (0.8)

Responsible β-lactams, n (%)	All reactions (no 1066)
Amoxicillin	490 (45.9) [354 + 136 clavulanic acid]
Benzylpenicillin	227 (21.3)
Cephalexin	96 (9)
Ampicillin	55 (5.2)
Phenoxymethylpenicillin	54 (5.1)
Ceftriaxone	46 (4.3)
Cefprozil	43 (4)
Cefixime	40 (3.7)
Ceftibuten	7 (0.7)
Cefaclor	6 (0.6)
Cefotaxime	1 (0.1)
Cefuroxime	1 (0.1)

Manifestation, n (%)	All reactions (no 1066)
Urticaria	545 (51.1)
Maculopapular exanthema	423 (39.7)
Urticaria plus angioedema	85 (8)
Angioedema	11 (1)
Stevens–Johnson syndrome (SJS)	2 (0.2)

Positive delayed-reading skin test results, n (%)	All reactions (no 1066)
Phenoxymethylpenicillin	4 (0.4)
Benzylpenicillin	7 (0.7) [2 also patch test positive]
Ampicillin	3 (0.3)
Amoxicillin	28 (2.6) [12 also patch test positive]
Cephalexin	3 (0.3)
Cefprozil	4 (0.4) [1 also patch test positive]
Ceftriaxone	10 (1) [2 also patch test positive]
Cefixime	4 (0.4) [1 also patch test positive]

Confirmed hypersensitivity after whole allergy work-up, n (%)	All reactions (no 1066)
Phenoxymethylpenicillin	4 (0.4)
Benzylpenicillin	10 (0.9)
Ampicillin	4 (0.4)
Amoxicillin	38 (3.6)
Cephalexin	5 (0.5)
Cefprozil	5 (0.5)
Ceftriaxone	11 (1.0)
Cefixime	6 (0.6)

*Time (months) elapsed between last adverse reaction to β-lactams and current allergy examination.

Table 2 Children with positive allergy work-up to two culprit drugs

Patient/Gender	Age (years)	Clinical manifestation	Culprit drugs	Patch test	Intradermal test delayed reading	DPT
1/F	16	U	Cephalexin	neg	pos	np
		UA	Ceftriaxone	neg	pos	np
2/F	4	UA	Cephalexin	neg	pos	np
		UA	Ceftriaxone	neg	pos	np
3/M	5	U	AM	neg	pos	np
		U	Ceftriaxone	neg	pos	np
4/M	4	U	AM	pos	neg	np
		U	Ceftriaxone	neg	neg	U/24 h
5/M	4	U	BP	neg	pos	np
		U	Ceftriaxone	neg	pos	np
6/F*	8	SJS	BP	pos	np	np
		SJS	Ceftriaxone	neg	pos	np

U, urticaria; UA, urticaria and angioedema; SJS, Stevens–Johnson syndrome; DPT, drug provocation tests; np, not performed; pos, positive; neg, negative; BP, benzylpenicillin; AM, ampicillin.
*This case has been previously described (reference 32).

Table 3 Comparison between hypersensitivity those identified and those not (Results of intradermal tests and drug provocation tests)

	U			ME			UA			A			SJS		
	POS			POS			POS			POS			POS		
Drugs	ID	DPT	NEG	ID	DPT	NEG	ID	DPT	NEG	ID	DPT	NEG	ID	DPT	All reactions
Amoxicillin	16	7	224	7	2	185	5	1	40	0	0	3	0	0	490
Benzylpenicillin	2	3	100	2	0	105	2	0	12	0	0	0	1*	0	227
Cephalexin	1	1	44	0	1	38	2	0	7	0	0	2	0	0	96
Ampicillin	2	1	26	1	0	22	0	0	1	0	0	2	0	0	55
Phenoxymethylpenicillin	1	0	20	0	0	28	3	0	1	0	0	1	0	0	54
Ceftriaxone	7	0	32	0	0	2	2	1	1	0	0	0	1	0	46
Cefprozil	2	0	20	0	0	15	2	1	3	0	0	0	0	0	43
Cefixime	3	1	22	0	0	12	1	0	0	1	0	0	0	0	40
Ceftibuten	0	0	5	0	0	2	0	0	0	0	0	0	0	0	7
Cefaclor	0	0	4	0	0	0	0	0	0	0	0	2	0	0	6
Cefotaxime	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
Cefuroxime	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
All reactions	545			423			85			11			2		1066

U, urticaria; ME, maculopapular exanthema; UA, urticaria plus angioedema; A, angioedema; SJS, Stevens–Johnson syndrome; ID, intradermal test delayed reading; DPT, drug provocation tests; POS, positive; NEG, negative.
*This case actually was positive to patch test and has been previously described (reference 32).

other studies performed in children with histories of hypersensitivity reactions to BL (8, 12, 13, 19–21), which ruled out such hypersensitivity in the majority of subjects. Therefore, it is crucial to make a precise diagnosis, because overdiagnosis of BL allergy is a major public health problem, which results in use of alternative antibiotics, increasing health costs, and bacterial resistance (12, 22).

With regard to children with negative results in allergy tests, including DPT, these results seem to indicate that most of the non-immediate cutaneous eruptions associated with BL are not hypersensitivity reactions but rather manifestations of the underlying infectious diseases, particularly those affecting the respiratory and urinary tracts for which the antibiotics were prescribed (23, 24). Some non-immediate reactions, including urticarial and maculopapular eruptions, may result from interactions between viruses and antibiotics (25). In fact, in many hypersensitivity reactions to drugs, stimulation of the immune system by viruses such as Epstein–Barr virus or HIV leads to reactions in more than 50% of infected individuals (26).

Literature data indicate that maculopapular exanthemas occur in two-thirds of hypersensitivity reactions to BL, and these reactions can be confused with the viral infections (8, 12, 13, 19). Viral infections are the most common cause of maculopapular rashes or urticaria, independently of the taken drug. Caubet et al. (8) showed that 65.9% of children had at

Table 4 Results of infectious agent study

Infectious agent	Positive serologic analysis (positive IgM antibody) n = 300 (%)
Mycoplasma pneumoniae	40 (13.3)
Adenovirus	13 (4.3)
EBV	12 (4)
Parvovirus B19	1 (0.3)

least 1 positive viral study (picornavirus, coronavirus, bocavirus, hMPV, influenza A-B, parainfluenza 1-3, respiratory syncytial virus, EBV, parvovirus, CMV, HHV6) in the group of negative oral provocation test (OPT), and 3 of the 6 (50%) children who had a positive OPT had findings suggestive of an acute EBV or of a recent EBV infection.

We found 66 children with positive studies for infectious agents, and two of them had positive allergy work-up. An acute Mycoplasma pneumoniae infection was indentified in 40 children (2 of them had positive allergy work-up), adenovirus in 13, EBV in 12 children, and parvovirus B19 in only one, respectively. In 64 children, therefore, urticaria or maculopapular rashes were due to the underlying infections and not to non-immediate hypersensitivity reactions to BL. Considering that there are not specific tests to distinguish between a viral infection and hypersensitivity reactions to drug in the acute phase, a diagnostic work-up should be performed in all children with a suspicion of drug hypersensitivity, ideally 2 months later (8, 22).

Regarding the diagnostic value of allergy tests for non-immediate reactions to BL, in the two largest studies that evaluated children with histories of such reactions (12, 13), delayed-reading intradermal tests were positive in 0.2% (2 of 717 children) (12) and 4.7% (60 of 1269) (13), respectively, whereas DPTs were positive in 7.1% (51 of 717) (12) and 9.2% (117 of 1269) (13). In a study by Caubet et al. (8), 88 children with mild eruptions associated with BL therapy were evaluated by skin tests, patch tests, and DPT. All 88 children underwent DPT: 6 (6.8%) reacted; 4 were intradermal test positive and 2 intradermal test negative. The sensitivity of intradermal testing was 66.7%, and the specificity was 91.5%; 88 children needed to undergo skin testing to identify only 4 patients (4.5%) with BL hypersensitivity. Based on these results and taking also into account the results of other studies (22, 27), some authors believe that a physician-supervised DPT, administered as one dose followed by standard dosing for 48 h at home, is a safe and efficient diagnostic procedure (22, 23).

We found 5.5% positivity of delayed-reading intradermal tests, which is higher than that of the aforementioned large studies (12, 13). This higher rate might be due to differences in the samples assessed and protocol used. For example, we performed delayed-reading intradermal tests also with non-injectable BL, such as cephalexin, cefaclor, cefprozil, cefixime, ceftibuten, and phenoxymethylpenicillin. The concentration used for non-injectable cephalosporins, such as cephalexin, cefaclor, cefprozil, and ceftibuten, had proved to be non-irritating in previous studies performed in adults (28, 29) and in children (15, 30) and is lower than the highest (20 mg/ml) suggested in the recent position paper by the ENDA (31).

As far as the protocol of skin tests is concerned, considering that, in the first 100 subjects, we had observed positive responses only to delayed-reading intradermal tests with the suspect BL, we modified this protocol by performing only these tests with the suspect BL at the highest concentration.

With regard to the four subjects positive to immediate-reading intradermal tests, it should be considered that parents do not provide a precise description of beginning of reactions, because the last dose of culprit drug is usually given during the night. Therefore, when the time interval between reaction and exposure is not clear in the history, children should be evaluated according to the diagnostic algorithm which includes both immediate- and delayed-reading skin tests, as well as DPT (2).

We also included patch tests in allergy work-up. However, only 1.7% of children displayed positive results. Therefore, we confirmed that intradermal testing is more sensitive than patch testing.

Nineteen children had positive reactions to DPT (OPT and parenteral provocation tests). Our data confirmed that a 3-day DPT protocol is safe and accurate for diagnosis (2, 8, 12, 22, 23, 27).

Concerning the drug involved, 45.8% of confirmed reactions were to amoxicillin and 24% to ceftriaxone.

It is interesting to note that, in the present study, the positivity of *in vivo* tests is over two times more frequent in children with histories of reactions to more than one BL (15.4%, 6 of 39 children) when compared with those who reacted to only one BL(7.1%, 70 of 987). Therefore, a history of reactions to more than one BL seems to be an indicator of a delayed hypersensitivity.

In conclusion, our study demonstrates that only 7.4% children had confirmed non-immediate hypersensitivity reactions to BL. A T-cell-mediated hypersensitivity was diagnosed in 57 (5.5%) of 1026 children on the basis of positive responses to delayed-reading intradermal tests. Considering these data and the fact that in the study by Caubet et al. (8), children with positive intradermal tests had a higher rate of positive DPT than those without a positive test ($p < 0.05$), we believe that it is still advisable performing delayed-reading intradermal tests only with the suspect BL at the highest concentration and, in case of negative results, DPTs. In fact, such an approach would allow the physician to diagnose by skin testing those patients with true delayed hypersensitivity, thus reducing the risk of positive DPT.

Considering the results of the present study, patch testing is not indicated in subjects with mild non-immediate reactions to BL, such as maculopapular and urticarial rashes.

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