

ORIGINAL ARTICLE

Diagnostic evaluation of hypersensitivity reactions to beta-lactam antibiotics in a large population of children

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Keywords

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Abstract

Introduction: Hypersensitivity reactions to beta-lactams (BLs) are often reported in children, with amoxicillin and, to a lesser extent, cephalosporins being the most frequent drugs involved. Although many of these children are considered to be allergic, a careful evaluation only confirms a low percentage.

Objectives: To analyse the clinical data, sensitization profile and diagnostic methods used in a large group of children with a clinical history of hypersensitivity reactions to BLs.

Methods: The study included children aged 1–14 yr with symptoms suggestive of hypersensitivity to BLs from January 2006–December 2012. Diagnosis was confirmed from a clinical history, specific IgE determination, skin testing and, if necessary, a drug provocation test (DPT).

Results: Of a total of 783 patients studied, only 62 (7.92%) were confirmed as being allergic, 9 (14.52%) with immediate and 53 (85.48%) with non-immediate reactions. In those with immediate reactions, 2 (22.22%) were diagnosed by *in vitro* test, 2 (22.22%) by skin testing and 5 (55.56%) by DPT; in those with non-immediate reactions, 2 (3.77%) were diagnosed by skin testing and 51 (96.23%) by DPT. In all cases, DPT was positive to the culprit drug (29 AX-CLV, 26 AX, 1 cefixime and 1 cefaclor), and the most usual symptoms were exanthema in 43 cases, urticaria in 12, urticaria–angio-oedema in 1 and erythema in 1 case.

Conclusion: After an allergological work-up, over 90% of the children evaluated were finally confirmed as tolerant to BLs. Most reactions were of the non-immediate type, and DPT was an essential tool for diagnosis.

Adverse drug reactions are frequently reported in children, (10.2%) and although many are considered allergic, after a careful evaluation, only a few are finally confirmed (1). In fact, drug hypersensitivity in children is 1.5 times less likely to be confirmed than in adults, and it is particularly lower in those with maculopapular exanthema (2). These reactions are classified as immediate or non-immediate according to the time between drug intake and appearance of symptoms (3). Immediate reactions usually appear within 1 h of drug intake are mediated by specific IgE antibodies, and urticaria and anaphylaxis are the most reported entities. Non-immediate reactions usually occur 24–48 h after drug intake, although the time interval can be as short as 1 or 2 h; they are usually T-cell mediated, and the most frequent are maculopapular exanthema followed by non-immediate urticaria (4, 5).

Beta-lactams (BLs) are drugs frequently prescribed in children, and hypersensitivity is often reported by parents and paediatricians, although confirmation after an allergological workup varies from 7 to 60% of cases (6–13). This wide range may be due to the mechanisms involved, as the possibility of confirming BL hypersensitivity is higher in patients with IgE-mediated reactions and lower in those with maculopapular exanthema (2, 6–13). One reason contributing to these differences is that very often mild exanthematic reactions are of viral origin, producing similar symptoms to those appearing during a drug reaction, thus making it necessary to carry out a differential diagnosis (14, 15).

Although all BLs can induce allergic reactions, amoxicillin (AX), and to a lesser extent cephalosporins, are currently the

drugs most frequently involved (9, 11–13). However, this can be subject to change, as happens in adults (16), with selective reactions to clavulanic acid also occurring in children (12). These variations in the BLs involved in allergic reactions are thus a reflection of the changes in their pattern of prescription and consumption (17, 18).

The diagnostic workup of BL hypersensitivity has become complex, time-consuming and sometimes risky, requiring skilled personnel and an appropriate setting for carrying out the evaluation (19–21). The evaluation includes a detailed clinical history, followed by skin testing, in some cases *in vitro* evaluation, and a drug provocation test (DPT) when indicated (3). The ENDA/EAACI (European Network of Drug Allergy/European Academy of Allergy and Clinical Immunology) has standardized the procedures and developed several guidelines for the diagnosis of BL hypersensitivity (19–21). However, in daily practice, the diagnosis of BL hypersensitivity in children is often based solely on the clinical history, thereby leading to over-diagnosis.

The aim of this study was to evaluate a large group of children with a clear history of hypersensitivity reactions to BLs and with a diagnosis established by *in vitro* test, skin testing or a DPT. An analysis of the clinical data, including a detailed description of the sensitization profile and the methods used for diagnosis as well as assessment of cross-reactivity was also carried out.

Methods

Patients

We included children aged 1–14 yr with symptoms suggestive of hypersensitivity reactions to BLs. They were studied in the Allergy Unit of the Paediatric Service of Carlos Haya Hospital (Malaga, Spain) from January 2006 to December 2012, following the ENDA/EAACI procedure (19–21), including IgE determination (only in immediate reactions), skin testing and if negative DPT.

For diagnostic purposes and following the ENDA/EAACI recommendations (19), on the basis of the time of appearance of the reaction after drug intake, and clinical symptoms, hypersensitivity reactions to BLs were classified as immediate or non-immediate. The former usually appear within 1 h of drug intake and are mediated by specific IgE antibodies. Non-immediate reactions are those occurring more than 1 h after drug intake and can be T-cell mediated.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the hospital ethics committee. All the children's tutors as well as those children aged over 12 yr were informed orally about the study and signed the corresponding informed consent.

In vitro test

In patients with immediate reactions, specific IgE determination was performed by CAP-FEIA system (Thermo Fisher Scientific, Uppsala, Sweden), using c1 (benzylpenicilloyl, BPO) and c6 (amoxicilloyl, AXO) following the manufacturer's instructions. The results were obtained by direct comparison with standards run in parallel, considering a value ≥ 0.35 kUA/l as positive (22).

Skin test

In those cases with negative CAP-FEIA, skin prick tests were carried out, and if negative, intradermal tests were performed. Skin tests were carried out as previously described (19–21), using 0.02–0.03 ml of solution prepared daily. The reagents used were benzylpenicilloyl polylysine (PPL) (5×10^{-5} M) and minor determinant mixture (MDM) (2×10^{-2} M) (Diater, Madrid, Spain), AX and amoxicillin–clavulanic acid (AX-CLV) (Glaxo Smithkline Beecham, Madrid, Spain) and cefuroxime (Normon, Madrid, Spain) at 2 mg/ml.

In skin prick testing, a wheal larger than 3 mm surrounded by erythema, with a negative response to the control saline, was considered positive. In intradermal tests, the wheal area was marked initially and 20 min after testing, and an increase in diameter >3 mm surrounded by erythema was considered positive. A reading was taken after 48 h in the case of non-immediate reactions.

Oral drug provocation test

Oral DPT was performed in a single-blind procedure following the ENDA/EAACI recommendations in all children with skin test and *in vitro* tests negative (23). We administered escalating doses of the drug at intervals of 30–90 min up to the full therapeutic dose (Table 1). If cutaneous and/or respiratory symptoms or alterations in vital signs (rhythm alterations, decrease in peak expiratory flow rate or hypotension) appeared, the procedure was stopped and the symptoms were evaluated and treated. If no symptoms appeared during the

Table 1 Doses of the different drugs used in the drug provocation tests (DPT)

Drug	Doses used in DPT	Total cumulative dose (TCD) (mg/kg/dose)
Penicillin V	¼, ¼ and ½ of the TCD	7–12
Amoxicillin	¼, ¼ and ½ of the TCD	16–26
Amoxicillin–clavulanic	¼, ¼ and ½ of the TCD	16/5–26/15
Cefuroxime	¼, ¼ and ½ of the TCD	7–15
Cefixime	¼, ¼ and ½ of the TCD	4–5
Cefaclor	¼, ¼ and ½ of the TCD	10–20

DPT, the therapeutic dose was achieved. If good tolerance occurred, a therapeutic course of 2 days was given 24 h afterwards. No DPT was performed with the culprit drug in patients with non-immediate severe reactions such as bullous reactions and acute generalized exanthematic pustulosis. In addition, since January 2012, in all cases with confirmed hypersensitivity to AX-CLV, tolerance to AX was assessed.

Assessment of cross-reactivity

To analyse cross-reactivity between penicillins and cephalosporins, tolerance to cefuroxime was evaluated in all cases with confirmed hypersensitivity to AX or AX-CLV by skin testing and DPT.

Statistical analysis

Comparisons for quantitative variables without normal distributions were made by the Mann–Whitney and Wilcoxon tests and between qualitative variables by the chi-square test. All reported *p* values represent two-tailed tests, with values <0.05 considered statistically significant.

Results

A total of 783 patients with a history compatible with hypersensitivity reactions to BLs was evaluated over a 7-yr period (January 2006–December 2012). Of these, only 62 (7.92%) were confirmed as having hypersensitivity reactions, whereas 721 (92.08%) tolerated the culprit BL and therefore considered as being non-hypersensitive. The clinical characteristics of both groups of patients, with or without hypersensitivity, are shown in Table 2. Regarding severity, in immediate reactions, although five children had a clinical history of anaphylaxis, none of them developed shock, and in those non-immediate, no cases were severe. Patients with hypersensitivity were significantly older than those confirmed as non-allergic (6 vs. 4 yr). No significant differences were found in the other variables analysed.

Considering the total number of patients evaluated, confirmation was obtained in 9 of 66 children with a history compatible with an immediate reaction, representing 13.64%, and 53 of the 717 children with a history compatible with non-immediate reactions, representing 7.39%. Thus, confirmation was obtained in nearly twice the number of immediate reactions as compared to non-immediate reactions. This indicates that of the 62 patients with confirmed hypersensitivity, 9 (14.52%) were diagnosed as having an immediate and 53 (85.48%) a non-immediate reaction.

Analysing those children with immediate reactions (*N* = 9), 2 (22.22%) were diagnosed by *in vitro* test, 2 (22.22%) by skin testing and 5 (55.56%) by DPT. The two children diagnosed by *in vitro* test had immediate urticaria after BL administration (one with cefuroxime and the other with AX-CLV). The first case was CAP positive to BPO (2.48 kIU/l) and the second to both BPO (7.85 kIU/l) and AXO (4.32 kIU/l). In those with non-immediate reactions (*N* = 53), 2 (3.70%), children were diagnosed by skin testing (both of them developed a negative

Table 2 Clinical characteristics of the patients with hypersensitivity reactions and non-hypersensitivity reactions

	Hypersensitivity	Non-hypersensitivity	<i>p</i>
(<i>N</i> , %)	62 (7.92)	721 (92.08)	
Age (yr, median, IR)	6 (3–9)	4 (2–6)	0.000
Sex (male, <i>N</i>)	37 (59.67)	336 (46.60)	0.063
Fever (yes, <i>N</i> , %)	59 (95.16)	650 (90.15)	0.241
Atopy (yes, <i>N</i> , %)	2 (3.23)	69 (9.57)	0.072
Interval reaction-study (months, median, IR)	9 (5.75–12)	9 (4–12)	0.253
Time to reaction (h, median, IR)			0.263
< 1	9 (14.52)	57 (7.91)	
1–6	4 (6.45)	161 (22.33)	
6–24	46 (74.19)	467 (64.77)	
24–48	2 (3.23)	21 (2.91)	
> 48	1 (1.61)	15 (2.08)	
Clinical history (<i>N</i> , %)			0.321
Urticaria/angio-oedema	21 (33.87)	203 (28.16)	
Exanthema	37 (59.68)	497 (68.93)	
Erythema	1 (1.61)	9 (1.25)	
Anaphylaxis	2 (3.23)	3 (0.42)	
Serum sickness-like syndrome	1 (1.61)	2 (0.27)	
Unspecific	0 (0)	7 (0.97)	
Route (<i>N</i> , %)			0.277
Oral	62 (100)	707 (98.06)	
Parenteral	0 (0)	14 (1.94)	
Drug involved (<i>N</i> , %)			0.100
Benzympenicillin	0 (0)	15 (2.08)	
Amoxicillin	27 (43.55)	313 (43.41)	
Amoxicillin–clavulanic acid	32 (51.61)	330 (45.77)	
Cephalosporins	3 (4.84)	63 (8.74)	

prick tests and a positive intradermal tests to AX at 24 h reading) and 51 (96.22%) by DPT.

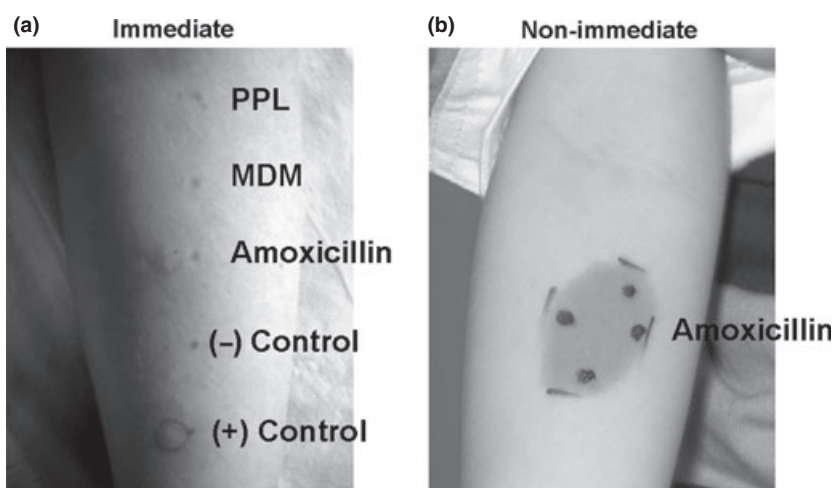
Data for the four children diagnosed by skin testing are shown in Table 3. All were skin test positive to AX, (one by prick and three by intradermal tests), two at the immediate reading and two at the delayed reading. In those with an immediate reaction, the culprit drug was AX, and in those with non-immediate reactions, it was the combination AX-CLV. Regarding the clinical entity, in those with immediate reactions, one patient had urticaria and the other anaphylaxis, and the two children with non-immediate reactions both had maculopapular exanthema. No patient developed systemic symptoms after skin testing. Figure 1 shows a case with an immediate positive prick test to AX (patient 1 of Table 1) and another with a non-immediate positive intradermal test to AX (patient 3 of Table 1).

Table 4 shows the results of 57 positive DPT obtained in 56 children (five with immediate and 51 with non-immediate

Table 3 Skin test and drug provocation test results in those cases with positive skin tests

Pat	Type	Skin test					Drug provocation test		
		PPL	MDM	AX	AX-CLV	CEF	AX	AX-CLV	CEF
1	I	–	–	P + (8 × 6 mm) 20 min	–	–	nd	nd	Cefuroxime (–)
2	I	–	–	ID + (128 × 8 mm) 30 min	–	–	nd	nd	Cefuroxime (–)
3	NI	–	–	ID + (108 × 8 mm) 24 h	–	–	nd	nd	Cefuroxime (–)
4	NI	–	–	ID + (128 × 10 mm) 24 h	–	–	nd	nd	Cefuroxime (–)

AX, amoxicillin; AX-CLV, amoxicillin–clavulanic acid; CEF, cefuroxime; I, immediate; ID, intradermal; MDM, minor determinants mixture; nd, not done; NI, non-immediate; P, prick; Pat, patient; PPL, penicilloyl-polylysine.

**Figure 1** (a) Immediate positive response to amoxicillin (b) Non-immediate positive response to amoxicillin.

reactions). In all cases, DPT was positive to the culprit drug (29 AX-CLV, 25 AX, 1 cefixime and 1 cefaclor); one patient who responded to cefixime also responded to AX. The most usual clinical symptoms were exanthema in 43 cases, urticaria in 12, urticaria–angio-oedema in 1 and erythema in 1 case. The median time interval to the response in the DPT was 12 h (IR: 5.5–19 h), with 8.77% of responses appearing within 1 h, 15.79% between 1 and 6 h, 64.91% between 6 and 24 h and 10.53% from 24 to 48 h. The reactions were usually mild and controlled by antihistamines (dexchlorpheniramine: 0.04 mg/kg/dose) and glucocorticoids (prednisolone: 1 mg/kg/dose) with no patient needing adrenaline.

An analysis of the symptoms appearing after DPT showed that they were similar to those reported in the clinical history, except for 10 cases (6.20%): 6 with symptoms indicative of urticaria according to the clinical history developed exanthema after DPT, 1 with a history of anaphylaxis developed exanthema, 1 with angio-oedema developed urticaria, 1 with urticaria–angio-oedema only developed urticaria, and finally 1 with symptoms attributed to serum sickness-like syndrome developed exanthema. The analysis of the whole group showed significant differences ($p < 0.003$) in the clinical symptoms reported by the patients compared with those appearing after DPT, with more exanthema and less urticaria appearing after the DPT (Fig. 2a). Comparisons between the time interval to

the response with that recorded from the clinical history (Fig. 2b) showed no significant differences ($p = 0.893$).

The analysis of the selectivity of the response to AX or to clavulanic acid in those with a positive DPT with AX-CLV showed that all cases (32, 33, 34, 36, 44, 47, 49 and 50) tolerated AX and were therefore considered as selective responders to clavulanic acid. To evaluate cross-reactivity, all cases ($N = 54$) with a DPT positive to AX or AX-CLV and those with a positive skin test to AX ($N = 4$) were given cefuroxime, with all of them tolerating its administration (Tables 3 and 4). In addition, one patient with a positive response to cefixime was also challenged with AX (case 4), with a positive response.

Discussion

In this study, we evaluated a large group of children with a history compatible with hypersensitivity reactions to BLs over a 7-yr period and found that only 8% were eventually confirmed as allergic. These data are similar to those found by Caubet (7%) (10), Romano (10%) (11) and Rubio (11%) (2), although lower than those reported by Ponvert (16%) (12). Overall, these results show that the percentage of children who are truly allergic is low and that if we consider just the clinical history there is an over-diagnosis. This finding is very impor-

Table 4 Clinical characteristics and drug provocation test results in patients diagnosed by drug provocation test

Pat	Age (yr)	Type	Reaction	Drug	DPT (+)	Reaction DPT	Interval (min)	DPT (–)
1	6	NI	Erythema	AX-CLV	AX-CLV	Erythema	1080	Cefuroxime
2	9	NI	Urticaria	AX-CLV	AX-CLV	Urticaria	180	Cefuroxime
3	10	NI	Exanthema	AX	AX	Exanthema	720	Cefuroxime
4	3	NI	Urticaria	Cefixime	Cefixime	Urticaria	480	nd
					AX	Urticaria	210	
5	4	NI	Exanthema	AX	AX	Exanthema	960	Cefuroxime
6	12	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	120	Cefuroxime
7	7	I	Exanthema	AX-CLV	AX-CLV	Exanthema	40	Cefuroxime
8	2	NI	Exanthema	AX	AX	Exanthema	1380	Cefuroxime
9	3	NI	Urticaria-angio-oedema	AX-CLV	AX-CLV	Urticaria-angio-oedema	720	Cefuroxime
10	12	NI	Urticaria	AX-CLV	AX-CLV	Urticaria	480	Cefuroxime
11	3	NI	Exanthema	AX	AX	Exanthema	1200	Cefuroxime
12	2	NI	Exanthema	AX	AX	Exanthema	780	Cefuroxime
13	13	NI	Urticaria	AX-CLV	AX-CLV	Exanthema	420	Cefuroxime
14	2	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	180	Cefuroxime
15	2	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	1080	Cefuroxime
16	7	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	480	Cefuroxime
17	12	NI	Urticaria	AX-CLV	AX-CLV	Exanthema	840	Cefuroxime
18	4	NI	Exanthema	AX	AX	Exanthema	240	Cefuroxime
								Cefpodoxime
19	7	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	960	Cefuroxime
20	6	NI	Anaphylaxis	Cefaclor	Cefaclor	Exanthema	1080	nd
21	10	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	1320	Cefuroxime
22	5	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	1440	Cefuroxime
23	9	I	Urticaria-angio-oedema	AX-CLV	AX-CLV	Urticaria	30	Cefuroxime
24	10	NI	Exanthema	AX	AX	Exanthema	600	Cefuroxime
25	7	NI	Urticaria	AX	AX	Urticaria	720	Cefuroxime
26	13	NI	Exanthema	AX	AX	Exanthema	1080	Cefuroxime
27	9	NI	Exanthema	AX	AX	Exanthema	300	Cefuroxime
28	8	NI	Exanthema	AX	AX	Exanthema	1320	Cefuroxime
29	7	NI	Serum sickness-like syndrome	AX	AX	Exanthema	1440	Cefuroxime
30	6	NI	Exanthema	AX	AX	Exanthema	1440	Cefuroxime
31	2	NI	Urticaria	AX	AX	Urticaria	480	Cefuroxime
32	1	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	180	AX
								Cefuroxime
33	6	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	720	AX
								Cefuroxime
34	2	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	720	Cefuroxime
35	4	NI	Exanthema	AX	AX	Exanthema	480	Cefuroxime
36	6	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	840	Cefuroxime
37	12	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	300	Cefuroxime
38	6	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	1320	Cefuroxime
39	7	NI	Urticaria	AX-CLV	AX-CLV	Urticaria	1440	Cefuroxime
40	3	NI	Exanthema	AX	AX	Exanthema	720	Cefuroxime
41	8	NI	Urticaria	AX	AX	Urticaria	720	Cefuroxime
42	6	NI	Exanthema	AX	AX	Exanthema	1440	Cefuroxime
43	8	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	480	Cefuroxime
44	2	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	360	Cefuroxime
45	2	NI	Exanthema	AX	AX	Exanthema	840	Cefuroxime
46	4	NI	Exanthema	AX	AX	Exanthema	1380	Cefuroxime
47	2	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	840	Cefuroxime
48	3	NI	Exanthema	AX	AX	Exanthema	1020	Cefuroxime
49	5	NI	Exanthema	AX-CLV	AX-CLV	Exanthema	1380	Cefuroxime
50	3	NI	Urticaria	AX-CLV	AX-CLV	Exanthema	1380	AX
								Cefuroxime

Table 4. (Continued).

Pat	Age (yr)	Type	Reaction	Drug	DPT (+)	Reaction DPT	Interval (min)	DPT (–)
51	7	NI	Urticaria	AX-CLV	AX-CLV	Exanthema	600	Cefuroxime
52	6	NI	Urticaria	AX-CLV	AX-CLV	Exanthema	1800	Cefuroxime
53	3	NI	Urticaria	AX	AX	Urticaria	180	Cefuroxime
54	10	I	Angio-oedema	AX	AX	Urticaria	25	Cefuroxime
55	3	I	Urticaria	AX	AX	Urticaria	30	Cefuroxime
56	11	I	Urticaria	AX	AX	Exanthema	45	Cefuroxime

AX, amoxicillin; AX-CLV, amoxicillin–clavulanic; I, immediate; NI, non-immediate; Pat, patient.

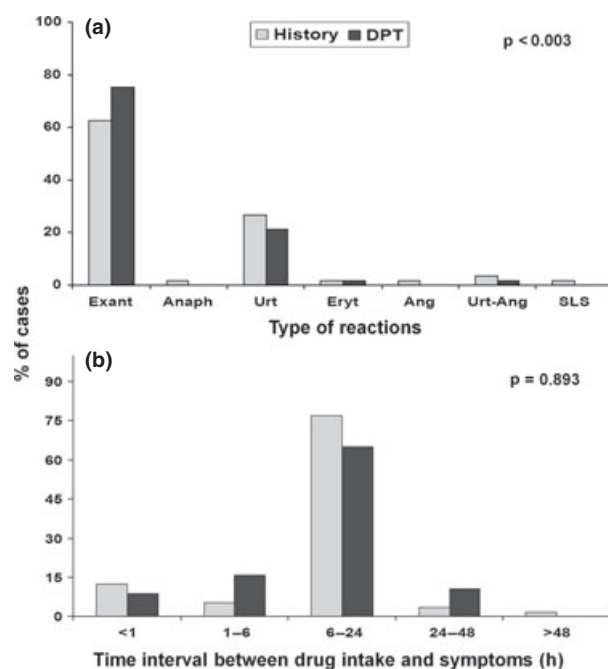


Figure 2 (a) Comparison between the clinical symptoms (Exant: exanthema; Anaph: anaphylaxis; Urt: urticaria; Eryt: erythema; Ang: Angio-oedema; Urt-Ang: Urticaria–angio-oedema; SLS: Serum sickness-like syndrome) in the original reaction (clinical history) and after the drug provocation test (DPT). (b) Comparison of the time interval between drug intake and development of symptoms (h) in the clinical history and after the DPT.

tant given that a diagnosis of penicillin allergy may persist for years, and even in children confirmed as non-allergic a significant proportion of parents do not administer BLs again (24), resulting in the use of alternative antibiotics that increase cost (25, 26) and bacterial resistance (27). It is therefore critical to make a precise diagnosis.

The analysis of our results shows that although the possibility of confirming a reaction as allergic was twice as likely in those with immediate compared with non-immediate reactions (13.6% vs. 7.39%), the greater number of children with non-immediate reactions meant that 85.5% of those finally confirmed belonged to this group. These data indicate

that the possibility of diagnosing BL hypersensitivity is higher with immediate reactions compared with non-immediate reactions, as previously described (2, 6–13). This suggests that a substantial proportion of patients have exanthema of viral origin, and as both viral and drug-induced exanthema share clinical symptoms and a T-cell mediated mechanism (4, 14), an accurate differential diagnosis is necessary.

Of the various methods available to confirm a diagnosis, in children with immediate reactions, we first performed *in vitro* IgE determination. This method has the advantage of being less expensive, less time-consuming and with no risk as compared with *in vivo* testing. However, using the cut-off values recommended by manufacturers, false positive results may appear, especially with penicillin V (28, 29). In our study, no penicillin V was used in the CAP assay and the cases diagnosed by *in vitro* testing had a sufficiently high specific IgE value to BPO or AXO above the cut-off point not to be considered false positive. Moreover, skin testing diagnosed nearly one-fourth of cases, a figure that would probably have been higher if it had been performed in those diagnosed by *in vitro* testing.

On the other hand, most children (96.2%) with non-immediate reactions were diagnosed by means of DPT. The lack of sensitivity of skin testing in the diagnosis of these reactions has been previously shown in children (10–13), as well as in adults (30), reinforcing the need for a DPT. Although in the present study, patch tests were not included in the allergological workup, this does not seem to have influenced the low sensitivity of skin tests results as it has been reported that intradermal testing appears to be more sensitive than patch testing (20).

Analysing the time of symptom appearance after DPT, we found that 65% of the children responded within 6–24 h, and 10% from 24 to 48 h, with no differences between this interval after DPT and the interval reported in the original reaction. The reaction occurred at home in 73% of the children and after the second dose taken at home in 11%. These data confirmed that a 3-day DPT protocol (one in the hospital and two at home) is safe and accurate for diagnosis (7, 8, 12, 13, 30).

Concerning the drug involved, in 95% of the confirmed hypersensitivity reactions, the BL involved was AX or AX-CLV compared with just 5% cephalosporins. This percentage for cephalosporins is lower than that reported in other studies (6,9,12), probably reflecting a lower consumption in our

population. Moreover, in 8 children with hypersensitivity to AX-CLV, AX was re-administered with good tolerance in all cases, thus confirming reports for children (12) and adults (16) that selective reactions to clavulanic acid do exist. This figure is expected to rise as the consumption of this combination increases, as it has in adults.

We evaluated cross-reactivity in all the children confirmed as allergic and found that all those responding to penicillins tolerated cefuroxime, a cephalosporin with a different side chain, as has been reported previously (6,7,9,12,20). Regarding cross-reactivity in those with cephalosporin allergy, although there were only three cases, one also had specific IgE antibodies to penicillin, another had a positive skin test to AX, and in the other no information was available. These results suggest that cross-reactivity in children with cephalosporin allergy is higher than previously thought (6,7,9,12), although this needs to be determined with a higher number of cases.

Regarding the clinical symptoms most often reported by those children with hypersensitivity confirmed by DPT, we found that 62% developed maculopapular exanthema and 32% urticaria and/or angio-oedema. The percentage of exanthema increased significantly to 75% and that of urticaria/angio-oedema decreased to 22.8% after the DPT. Thus, maculopapular exanthema occurs in two-thirds of hypersensitivity reactions to BL; this is important, as these hypersensitivity reactions are more easily confused with viral reactions, as reported by others (10–12). Moreover, we did not diagnose any serum sickness-like syndrome, and although one child had

clinical symptoms compatible with this disorder, he developed maculopapular exanthema after the DPT.

Summarizing, we analysed an important number of children with a history compatible with hypersensitivity reactions to beta-lactams and found that just 8% were finally confirmed as allergic, most with non-immediate reactions. The drug provocation test was shown to be a necessary and safe tool for diagnosing these children.

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Conflict of interest

None of the authors has any conflict of interest. None received money for this study. Research is part of their daily activities. All authors had full access to all the data (including statistical reports) and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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