

PATTERNS OF RESPONSE AND DRUGS INVOLVED IN HYPERSENSITIVITY REACTIONS TO BETA-LACTAMS IN CHILDREN.

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Abstract

Background Beta-lactams generate different allergenic determinants that induce selective or cross-reactive drug hypersensitivity reactions (DHRs). We aimed to identify the drugs involved, the selectivity of the response, the mechanism, and the value of the different diagnostic tests for establishing a diagnosis in children evaluated for DHRs to beta-lactams. Methods Prospective study evaluating children aged under 16 years reporting DHRs to beta-lactams. Reactions were classified as immediate and nonimmediate reactions. The work-up included sIgE, skin testing and drug provocation tests (DPTs) for immediate reactions and patch testing and DPTs for nonimmediate ones. Results Of the 510 included children, 133 were evaluated for immediate reactions and confirmed in 8.3%. Skin test/in vitro IgE contributed to diagnosing half of the cases. Selective reactions occurred with amoxicillin (63%), followed by common penicillin determinants (27%) and cephalosporins (0.9%). Among nonimmediate reactions (11,4% of the 377 children evaluated), most required DPTs, 52.7% of which were positive at 6–7 days of drug challenge. Selective reactions were identified with amoxicillin (80%), penicillin G (7.5%), cephalosporins (7.5%), and clavulanic acid (5%). Urticaria and maculopapular exanthema were the most frequent entities. Conclusions There were few confirmed cases of either type of reaction. Skin testing proved less valuable in nonimmediate reactions, over half of which would also have been lost in a short DPT protocol. Selective responders to amoxicillin were more likely to have nonimmediate reactions, while clavulanic acid-selectivity was exclusive to the nonimmediate typology. Over half the cases with DPTs required 6-7 days of treatment for DHR confirmation.

Title : Patterns of response and drugs involved in hypersensitivity reactions to beta-lactams in children.

Conflict of interest statement:

The authors declare that there are no conflicts of interest.

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Statement of Ethics:

Ethical approval: The study was approved by our Institutional Ethics Committee.

Informed consent: a written informed consent was obtained from parents or guardians of all individual participants included in the study.

Background

Beta-lactams generate different allergenic determinants that induce selective or cross-reactive drug hypersensitivity reactions (DHRs). We aimed to identify the drugs involved, the selectivity of the response, the mechanism, and the value of the different diagnostic tests for establishing a diagnosis in children evaluated for DHRs to beta-lactams.

Methods

Prospective study evaluating children aged under 16 years reporting DHRs to beta-lactams. Reactions were classified as immediate and nonimmediate reactions. The work-up included sIgE, skin testing and drug provocation tests (DPTs) for immediate reactions and patch testing and DPTs for nonimmediate ones.

Results Of the 510 included children, 133 were evaluated for immediate reactions and confirmed in 8.3%. Skin test/in vitro IgE contributed to diagnosing half of the cases. Selective reactions occurred with amoxicillin (63%), followed by common penicillin determinants (27%) and cephalosporins (0.9%).

Among nonimmediate reactions (11,4% of the 377 children evaluated), most required DPTs, 52.7% of which were positive at 6–7 days of drug challenge. Selective reactions were identified with amoxicillin (80%), penicillin G (7.5%), cephalosporins (7.5%), and clavulanic acid (5%). Urticaria and maculopapular exanthema were the most frequent entities.

Conclusions

There were few confirmed cases of either type of reaction. Skin testing proved less valuable in nonimmediate reactions, over half of which would also have been lost in a short DPT protocol. Selective responders to amoxicillin were more likely to have nonimmediate reactions, while clavulanic acid-selectivity was exclusive to the nonimmediate typology. Over half the cases with DPTs required 6-7 days of treatment for DHR confirmation.

Key words: hypersensitivity, betalactams, immediate reaction, nonimmediate reactions, children.

Key Message

Beta-lactams are the first-line antibiotic to control many bacterial infections. Traditionally, the most frequently prescribed antibiotic in children has been amoxicillin, which has been increasingly combined with clavulanic acid. An accurate diagnosis is essential for avoiding the prescription of alternative antibiotics which may be less effective, more toxic. Betalactams drug hypersensitivity reactions are classified as immediate and nonimmediate, being the last one the most frequent in children. The aim of our study was to identify the drugs involved, the selectivity of the response, the mechanism, and the value of the different diagnostic tests for establishing a diagnosis in children evaluated for DHRs to BLs. After the allergological study we conclude that only few cases were confirmed of either type of reaction. Skin testing proved less valuable in nonimmediate reactions, over half of which would also have been lost in a short DPT protocol. Selective responders to amoxicillin were more likely to have nonimmediate reactions, while clavulanic acid-selectivity was exclusive to the nonimmediate typology. Over half the cases with DPTs required 6-7 days of treatment for DHR confirmation.

Introduction

Beta-lactams (BLs) are the first-line antibiotic to control many bacterial infections¹. Traditionally, the most frequently prescribed antibiotic in children has been amoxicillin (AX), which has been increasingly combined with clavulanic acid (CLAV); in recent years, this formulation has become the most dominant¹⁻². BLs are also the most common inducers of drug hypersensitivity reactions (DHR) in children. Since systematic

reporting of side-chain-specific reactions to AX were first published in the late 1980s, diagnosis has required more determinants for evaluating DHRs³. In many countries, penicillin G (PG)(benzylpenicillin) is no longer the major determinant, and classical penicillin determinants yield low sensitivity, making drug provocation tests (DPTs) necessary for diagnosis⁴.

The prevalence of DHR in children ranges from 2.5% to 10.2%⁵. More than 10% of children develop skin rashes over the course of an antibiotic treatment for a viral infection. Allergological evaluation confirms that only a few cases are confirmed allergic^{5,6}, while most skin exanthemas are due to underlying viral infections or to interactions between drugs and infectious agents^{5,7,8}.

An accurate diagnosis is essential for avoiding the prescription of alternative antibiotics which may be less effective, more toxic, and larger contributors to bacterial resistance. Significant differences exist between European centers in terms of diagnosing BL hypersensitivity, particularly in children^{7,9}. Although consensus protocols have helped to ensure patient safety and accurate diagnosis, these must be adapted to between-country variations in both patients' response to BLs and health system capacities for diagnosis.

BLs DHRs are classified as immediate (IR) and nonimmediate reactions (NIR)¹⁰. IRs usually appear within 1 h after drug administration and include urticaria, angioedema, rhinitis, bronchospasm, and anaphylaxis¹¹. NIRs, although assumed to occur 24-48 h after drug intake⁵, can actually occur anytime from 1 h after taking the medication¹². Clinical presentation ranges from mild reactions, such as nonimmediate urticaria (NIU) and maculopapular exanthema (MPE), to more severe reactions like acute generalized exanthematous pustulosis, drug-induced hypersensitivity syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis (13).

The diagnostic approach varies depending on whether the reaction is immediate (IgE mediated) or non-immediate (T cell effector response), as well as the severity, symptoms elicited, and patient risk factors. Although they have low sensitivity, skin and SIgE testing may have a role in IR^{12,14}. Several studies support direct DPT without skin testing (ST), especially in children with mild NIR^{7,15-17}. However, if the results are positive, avoidance of the BL involved or all the drug group is controversial because reactions can be side-chain-specific to AX, cephalosporins, or another BLs, meaning that a different class of BL could still be administered^{3,18}.

The aim of our study was to identify the drugs involved, the selectivity of the response, the mechanism, and the value of the different diagnostic tests for establishing a diagnosis in children evaluated for DHRs to BLs.

Material and methods

Patients

This 10-year prospective study (2010-2019) included children aged under 16 years who were referred to our allergy unit for an evaluation of BL DHR. Reactions were classified as IR or NIR according to established criteria^{5,10}. For IRs, ST (prick tests and intradermal tests) were carried out as recommended, with some modifications¹⁹. For NIRs, we also followed the pediatric adaptation^{5,8,21} of the 2004 general recommendations made by the European Network for Drug Allergy (ENDA) and the European Academy of Allergy and Clinical Immunology (EAACI)²⁰, that is, ST (delayed intradermal tests and patch tests) followed by DPT when appropriate.

Evaluation of IR

Before ST, SIgE testing was carried out by fluoroimmunoassay (CAP system, Thermofisher Diagnosis, Uppsala, Sweden R). Results of 0.35 kUA/l or more were considered positive¹¹.

The determinants used for ST were penicilloyl-polylysine (PPL) (5×10^{-5} mol/l), minor determinant mixture (2×10^{-2} mol/l), and PG (10^4 UI/ml). If negative, we proceeded to the graded administration of penicillin V until achieving the therapeutic dose^{5,19}. If tolerated well, we evaluated the response to AX if this drug was involved alone or in combination with CLAV; if tolerance was still good, we proceeded to ST with CLAV to test if this was the culprit, and then finally to a DPT with AX-CLAV. If a cephalosporin was involved, we

tested first with common determinants of PG, and if negative, we proceeded to cephalosporin (first ST and if negative, DPT when indicated).

DPT was performed in a single-blind, placebo-controlled way as described elsewhere¹⁸, under strict hospital surveillance with emergency room facilities. We gave escalating doses of the drug at intervals of 30 min to 60 min until reaching the weight-adjusted therapeutic dose⁵. BLs were administered orally at the following doses: 5 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 250 mg, with a final observation period of at least 1 h after the last dose administered.

Evaluation of NIR

Patch testing was performed on the patient's back, as described elsewhere²². Drugs were mixed in petrolatum 50% w/w at a final concentration of 20 mg. Readings were done at 48h and 72h after patch application, and if negative, patients were recommended to monitor the patch site to detect any eventual reaction. Due to the very low sensitivity of the test and the lack of systemic effects in cases with mild reactions⁵⁻¹⁰, in most instances all BLs were tested on the same day. In case of negative results, we proceeded to DPT as described⁵. DPT was considered positive if any objective symptoms indicative of an allergic reaction appeared during the treatment or within 48h after the last dose⁵.

Statistical analysis

A descriptive analysis of clinical characteristics was undertaken, and mean age, age range, gender distribution, and mean time between reaction and workup were calculated. The chi-square test was used to compare qualitative variables between patients with IR versus NIR. P values of less than 0.05 were considered significant. Mean age was compared using the Mann-Whitney U test.

Results

A total of 510 children (229 [45%] girls; median age 4.3 years [range 0.5 to 16]) with a clinical history indicative of BL DHR were evaluated. Based on clinical history, AX was involved in 349 (68.5%) cases, AX-CLAV in 123 (24.1%), penicillin in 23 (4.5%), and different cephalosporins in 15 (2.9%).

After the allergological workup, 54 cases (10.6%) were finally confirmed as allergic. The median time between the reaction and the allergological study was 30 days (range 1 to 1095). Of the 54 allergic patients, 30 (55.5%) were girls, with an age range of 0.5 to 16 years (mean 6.2), and 42.6% were atopic. AX produced reactions in 72% of the positive cases, AX-CLAV acid in 20.4%, and cephalosporins in 7.6%. When comparing cases finally diagnosed as allergic versus non-allergic, we did not observe differences in gender or the BL involved, but we found differences in the mean age ($p < 0.001$), which was higher in cases confirmed as allergic.

Among positive cases, 20.4% were classified as IRs and the 79.6% as NIRs. Figure 1 shows the allergological algorithm with the evaluation of all cases.

Immediate reactions

Diagnosis of IR was established in 11 of the 133 cases evaluated (8.3%), nearly three-quarters (72.7%) of whom were girls. Reactions were induced by AX (72.7%), AX-CLAV (18.2%), and cephalosporins (9.1%).

sIgE was detected in two cases. One patient presented values of sIgE to AX of 0.37 kU/l; to ampicillin, 0.37 kU/l; to PG, 0.36 kU/l; and to PV, 0.35 kU/l. Another showed sIgE to AX of 0.52kU/l; to ampicillin, 0.49kU/l; to PG, 0.37 kU/l; and to PV, 0.35 kU/l.

Different ST were positive in 4 out of 131 children, all to AX: by prick test at 20 mg/ml ($n = 1$), intradermal test at 2 mg/ml ($n = 1$), and intradermal test at 20 mg/ml ($n = 2$).

DPTs were performed in the remaining 127 patients, yielding positive results in 5 (Table 1), in all cases within 45 minutes or less. Three cases were positive to AX but showed good tolerance to PG and PV; one case was positive to PV; and one to cefaclor. Most of the reactions observed during the DPT were mild (urticaria in 1 case and angioedema in 3 cases), with only one child developing skin involvement plus

bronchospasm and good recovery after treatment. The remaining 122 cases presented good tolerance to AX or another culprit BL until reaching therapeutic doses.

In summary, of the total 8.3 % positives cases within this group SIgE contributed to the diagnosis in the 1.5%, ST with all the determinants in the 3% and DPT in the 3.7%. Selective reactions occurred with AX (63%), followed by common penicillin determinants (27%) and cephalosporins (0.9%).

Nonimmediate reactions

Of 377 patients evaluated for NIRs, diagnoses were confirmed in 43 (11.4%). Half (51%) were girls, and 39.5% atopic. The BLs involved were AX (72%), AX-CLAV (21%) and cephalosporins (7%).

Severe reactions were reported in three cases (one acute generalized exanthematous pustulosis, one exudative erythema multiforme, and one drug-induced hypersensitivity syndrome). Patients were diagnosed based on their clinical history; neither ST nor DPT were carried out because of the risks.

Except for the three patients with severe reactions, patch testing was carried out in all other children evaluated (n = 374). Two were positive to AX, one to PG, and one to cefotaxime.

A controlled DPT was performed in 370 children, yielding positive results in 36 cases (9.7%) (Table 2). Thirty cases were positive to AX, all with good tolerance to PV; two were positive to CLAV, with good tolerance to PV and AX; two were positive to PV; one to cefaclor, and one to cefixime. These latter two cases both showed good tolerance to PV and to AX.

Clinical entities induced by DPT included NIU in 21 (58.3%) cases (plus angioedema in 5), and MPE in 15 (41.6%)(See table 2). In all cases a full therapeutic dose was required to elicit a response. However, when we analyzed the interval from drug administration to reaction, there was a clear divergence: 30% of the positive cases presented a reaction within 24 h, while 52.7% responded only at day 6 or 7 (Figure 2). Less than 10% of positives started showing symptoms between days 2 and 5.

In summary, of the total 11.4% positives cases within this group ST contributed to the diagnosis in the 1.1% and DPT in the 9.5%. Selective reactions were identified with AX (80%), PG (7.5%), cephalosporins (7.5%), and CLAV (5%). NIU and MPE were the most frequent entities.

Discussion

This study included a large cohort of children referred to our center for BL allergy evaluation. We followed the classification of IR versus NIR, as initially reported by Terrados et al.¹⁰ and used extensively in the literature^{8,16,18,21-25}.

Of the total patients evaluated, 10.6% were confirmed as allergic, most of whom were diagnosed by DPT. This proportion is lower than that reported by Ponvert et al.²¹, but consistent with other studies^{8,16,18,24}.

Regarding the drugs involved, AX was implicated in 68.5% of the cases and AX-CLAV in 24%, very similar to results reported elsewhere¹⁶. Penicillin and cephalosporins accounted for 4.5% and 3% of the positive cases, respectively. Of interest is the important role of AX-CLAV, coherent with the high pattern of prescription^{1,2}. The reported involvement of this formulation in DHR has changed from 12%⁸ to over 70% in recent years^{15,22,23}. Considered less immunogenic than other BLs²⁶, its contribution to both IR and NIR in adults has been reported²⁷.

The proportion of confirmed IRs was 8.3%, with positive ST or SIgE contributing in the 5.4%. These values are lower than the 17% reported by Ibañez et al.¹⁶ but higher than the results observed by Mill et al.²⁸ One study even reported a proportion of 86% positive ST²¹, but these data have not been supported by other studies^{8,16,23}.

Regarding the different BLs, 63% of cases were selective reactors to AX, with no contribution from CLAV. This result contrasts with other studies published in adults, where 22% of participants were selective responders to CLAV²⁷.

Although AX was involved in 92.5% of the cases initially evaluated, 27% of the confirmed responders belonged to the common group of penicillin reactor. The contribution of cephalosporins was less than 1%.

Symptoms suggestive of a NIR were reported in 377 cases, nearly 80% of the cases evaluated. Three cases with a severe reaction were diagnosed based on the clinical history. ST were positive in 1% of cases (2 cases to AX, 1 to PG and 1 to a cefotaxime). CLAV did not induce any positive ST. DPT was needed for confirmation in 36 of the 43 cases (83%) finally classified as positive. In total, considering all cases diagnosed based on clinical history, ST or DPT, the final proportion of positive NIRs was 11.4%. In our study, 52% of positive DPTs induced urticaria, with or without angioedema, while this reaction occurred in 72% of positive cases in the study by Ibañez et al.¹⁶ and 64% of cases included in Mori et al.'s report²⁵. Data on the frequency of MPE versus NIU are variable in the literature. In large series like ours, the proportion of MPE reactions ranges anywhere from 18% to 80%^{15,18,22} which is in line with the 41.6% we observed in our study.

The interval between drug administration and symptoms onset was under an hour in IR, similar to what occurs in adults, although the dose required for eliciting a response was higher in children after correcting it for body weight²⁹.

In NIRs, the analysis of the time required for inducing a positive DPT showed two response patterns. Up to a third of the cases were diagnosed on the first day, but over half the diagnoses required 6 or 7 days, which suggests that a 5-day protocol, as reported by some groups^{13,17,24}, will miss an important number of positive cases. Other studies have also supported periods longer than 5 days^{26,27}. In order to reconcile results from the different groups, responders with NIRs may fall into two broad groups, those responding early and those with a later response. This time interval is independent of the clinical entity induced (MPE or NIU), as shown in our work.

In NIRs, the role of selective responders to AX seems more relevant than in IRs, since 83% of cases with NIRs were selective in contrast with 63% of cases in IR. These data are similar to those reported in adults¹⁰.

One limitation of this study, as in other similar ones, is the lack of comparison between children showing a reaction at 2-3 days versus 5 days or longer. The low prevalence of allergy to BLs in children complicates this analysis. Also, we used patch testing, as done by other authors^{30,31} although there are studies suggesting that intradermal testing is more sensitive^{8,26}.

Summarizing, after prospectively evaluating a large series of children with DHRs to BLs, we confirmed the diagnosis in 8.3% of the children assessed for IRs and 11.4% of those assessed for NIRs. Overall, NIRs were more frequent and had a higher proportion of selective responders. Moreover, reactions to CLAV were exclusively NIRs.

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Table 1. Clinical characteristics of cases with confirmed IR by DPT

Patient	Age (years)	Sex	Clinical Entity	Clinical characteristics (symptoms induced, dose, time from I
1	7	F	ANA	Cough and wheezing, with facial erythema and 20% FEV ₁ decrease 10
2	3	F	URT	Facial erythema with eyelid angioedema and wheals on neck, 20 min a
3	6	F	URT	Pruritus on face, ears and back, followed by generalized wheals and lip
4	1	F	URT	Wheals in chest and face with pruritus 45 min after a cumulative dose
5	3	F	AE	Eyelid angioedema with pruritus 45 min after a cumulative dose of 30

F: female; M: male; ANA: anaphylaxis; URT: urticaria; AE: angioedema; AX: amoxicillin; PV: penicillin V.

Table 2. Clinical characteristics of cases with confirmed NIR by DPT

Patient	Age (years)	Gender	Clinical entity	Clinical characteristics (symptoms induced, dose, time from DPT to reaction)
1	2	F	MPE	Generalized MPE 6 h after taking 150 mg AX (1 st day). Good tolerance
2	4	F	MPE	MPE on chest and legs with facial and retroarticular erythema and pruritus
3	15	F	MPE	Facial erythema and pruritus followed by MPE on chest 3 h after taking
4	10	M	MPE	MPE on chest and abdomen after taking 250 mg of AX every 8 h (2 nd day)
5	5	M	MPE	Isolated wheals on back after taking 250 mg of AX every 8 h (6 th day).
6	1	M	MPE	MPE on trunk, abdomen, and legs accompanied with pruritus 4 h after taking
7	9	F	MPE	MPE on abdomen, legs, and back accompanied with pruritus 8 h after taking
8	12	F	MPE	Pruritus and generalized MPE after taking 500 mg of AX every 8 h (4 th day)
9	6	M	MPE	MPE on chest and neck with pruritus after taking 250 mg of AX every 8 h
10	11	M	MPE	Wheals on face, abdomen, shoulders and legs with pruritus 8 h after taking
11	1	M	MPE	Pruritus and MPE on abdomen and chest after taking 125 mg of AX every 8 h
12	1.5	F	MPE	MPE on neck, back, arms and legs 1.5 h after taking 200 mg of PV (1 st day)
13	15	F	MPE	MPE on chest and back with pruritus 2 h after taking 500 mg of PV (1 st day)
14	5	F	MPE	MPE on abdomen, legs, and chest after taking 200 mg of cexime every 8 h
15	0.5	M	MPE	Maculopapulae on abdomen and neck with facial erythema after 100 mg of AX
16	4	F	URT	Wheals with pruritus on chest, abdomen and legs after 250 mg of AX every 8 h
17	3	F	URT	Generalized wheals with pruritus after taking 150 mg of AX every 8 h (6 th day)
18	6	M	URT	Pruritus followed by wheals on legs and buttocks, and facial erythema after taking
19	8	M	URT	Generalized pruritus with wheals on the back after taking 250 mg of AX every 8 h
20	6	F	URT	Pruritus and wheals on legs and arms after taking 250 mg of AX every 8 h
21	4	F	URT	Generalized wheals with pruritus after taking 250 mg of AX every 8 h (7 th day)
22	1	F	URT	Wheals on abdomen, back, face and legs after taking 125 mg of AX every 8 h
23	4	M	URT	Urticaria with pruritus on back that generalized after taking 250 mg of AX every 8 h
24	7	F	URT	Generalized wheals on abdomen, buttocks and back after taking 250 mg of AX every 8 h
25	12	F	URT	Systemic pruritus with wheals on abdomen and legs 1.5 h minutes after taking
26	5	M	URT	Skin pruritus followed by wheals on arms that extended to abdomen, chest and neck
27	4	F	URT	Facial erythema and wheals on abdomen after taking 250 mg of AX every 8 h
28	1.5	M	URT	Wheals on legs and neck, extended to chest 1.5 h after taking 125 mg of AX every 8 h
29	2	F	URT	Generalized wheals on chest, abdomen and legs after taking 100/12.5 mg of AX every 8 h
30	13	F	URT	Generalized pruritus with wheals on elbows, knees, and legs after taking 250 mg of AX every 8 h
31	5	F	URT	Wheals on abdomen and neck, with joint pain after taking 250 mg of ceftriaxone every 8 h
32	2	M	URT/AE	Facial and eyelid angioedema with wheals on back, abdomen and arms after taking
33	3	F	URT/AE	Generalized erythema and lips angioedema after taking 125 mg of AX every 8 h
34	11	M	URT/AE	Systemic pruritus with facial erythema, eyelid angioedema and wheals on chest and neck
35	4	M	URT/AE	Wheals on abdomen, face, and neck with eyelid angioedema after taking 250 mg of AX every 8 h
36	15	M	URT/AE	Erythema and pruritus on face followed by wheals on arms and lips angioedema

F: female; M: male; PV: penicillin V; AX: amoxicillin; AX-CLAV: amoxicillin-clavulanic acid; MPE: maculopapular exanthema; URT: urticaria; URT/AE: urticaria/angioedema.

FIGURE LEGENDS

Figure 1. Allergological evaluation algorithm.

Figure 2. Time from drug provocation test (DPT) to reactions in children with nonimmediate drug hypersensitivity reactions.

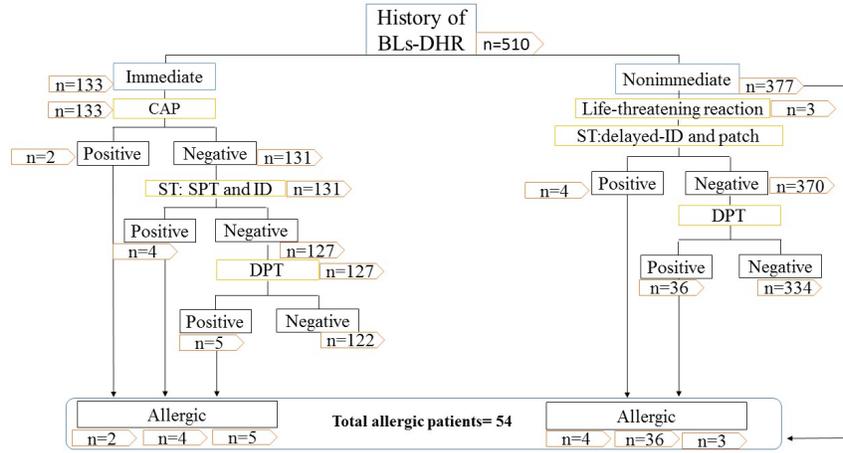


Figure 2. Time from drug provocation test (DPT) to reactions in children with nonimmediate drug hypersensitivity reactions

