

Mild to moderate hypersensitivity reactions to beta-lactams in children: a single-centre retrospective review

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ABSTRACT

Objective Beta-lactam (BL) antibiotics are the most reported drugs in hypersensitivity reactions in children. More than 90% of these children tolerate the suspected drug after diagnostic work-up. Skin tests (STs) show low sensitivity. Our aim was to assess the performance of drug provocation tests (DPTs) without previous ST in mild and moderate delayed reactions and to propose a new DPT protocol.

Design of the study Charts from 213 children under 15 years of age referred for suspected BL allergy from 2011 to 2013 were reviewed. Prick, intradermal and patch tests were performed with major determinant penicilloyl-polylysine, minor determinant mixture, amoxicillin (AMX), cefuroxime, penicillin G and AMX-clavulamate. Children with negative skin tests underwent DPT. After an initial full dose of antibiotic, DPT was carried on for 3 days at home in patients reacting within the first 3 days of treatment. If the reaction took place from day 4 on of treatment, patients took the antibiotic for 5 days.

Results We included 108 girls and 105 boys. Mean age at the time of reaction was 3.66±3.06 years. 195 patients (91.5%) reacted to one BL. 154 reactions (67.2%) were non-immediate. Mild to moderate skin manifestations were most frequently reported. AMX-clavulanate was the most frequently involved (63.4%). DPT confirmed the diagnosis of drug hypersensitivity in 17 (7.3%) cases. These 17 patients had negative ST.

Conclusion In mild and moderate cases of BL hypersensitivity, diagnosis can be performed by DPT without previous ST

INTRODUCTION

Although around 10% of parents report drug hypersensitivity in their children,^{1 2} after a careful evaluation, more than 90% of these children are able to tolerate the suspected drug.^{1 3-5}

In the paediatric population, antibiotics, mainly beta-lactam (BL) and especially amoxicillin (AMX),^{6 7} are the most commonly involved drugs, followed by non-steroidal anti-inflammatory drugs.^{1 3} Unlike adults, children usually experience mild non-immediate skin reactions, as maculopapular exanthema and non-immediate urticarial rash.⁸ Most of these benign skin reactions are not

truly allergic but related to the underlying infectious disease or due to the interaction between the antibiotic and the infectious agent.^{5 9}

An accurate diagnosis of antibiotic hypersensitivity not based only on clinical history is mandatory since antibiotic allergy labels imply the use of alternative antibiotics which may be more expensive, less effective and may contribute to an increase in antibiotic-resistant bacteria.¹⁰

According to the European Network for Drug Allergy, the diagnosis of immediate IgE-mediated reactions to BLs should be based on clinical history, skin tests (STs) (skin prick test [SPT] and intradermal tests [IDTs]), in vitro laboratory tests as serum specific IgE determination and drug provocation tests (DPTs).¹¹

For the diagnosis of non-immediate reactions, there are no standardised tests available. Although the pathogenic mechanism is unknown, it is believed to be T-cell mediated.¹² Late reading IDT or patch tests show very low sensitivity^{4-6 8}; therefore, in mild skin reactions, which are the majority, performing DPT without previous skin test work-up has been proposed.¹³ Even though considered the gold standard test for the diagnosis of drug allergy, DPT also lacks standardisation and there are concerns whether the number of days of drug administration may influence its outcome and the diagnosis of delayed hypersensitivity reactions.

We have retrospectively reviewed 213 paediatric patients evaluated for BL allergy in the Complejo Hospitalario Universitario A Coruña (CHUAC) between the years 2011 and 2013. Our aim is to assess the performance of DPT, with no previous skin test evaluation, in cases of mild and moderate delayed skin reactions regarding safety and diagnosis effectiveness as well as to propose a new DPT.

METHODS

Charts from 213 children under 15 years of age referred to the Pediatric Allergy Unit of CHUAC for suspected BL allergy from 2011 to 2013 were reviewed. Patients with severe non-immediate reactions (drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, generalised exanthematic pustulosis and Steven-Johnson syndrome) were excluded from the study.

Clinical data

Reactions were classified as immediate if they occurred within 1 hour after antibiotic intake and non-immediate if they occurred more than 1 hour after antibiotic intake.

Both types of reactions were graded as mild (no treatment required), moderate (patients responded readily to appropriate treatment and no hospitalisation was needed) or severe (reaction required treatment in hospital, was life threatening or resulted in death).

Patient involvement

Patients were not directly involved in the design of this study.

Skin tests

For immediate reactions, SPTs were performed with the major determinant penicilloyl-polylysine (Diater, Madrid, Spain), minor determinant mixture (Diater) and the suspected drug at the following concentrations: AMX (20 mg/mL), cefuroxime (2.5 mg/dL), penicillin G (10 000 IU/mL) and AMX-clavulamate (20 mg/mL). Children older than 12 years also underwent ID testing in case of negative SPT.

Readings were made 15 min after. STs were considered positive if weal diameter was ≥ 3 mm larger than the negative control (normal saline solution), with a flare. As positive control, we used histamine hydrochloride (ALK, Madrid).

Children reporting delayed reactions underwent SPT and if negative, IDT (if older than 12 years of age), and patch tests were performed at the concentrations above mentioned. Readings were made at 48, 72 and 96 hours.

Serum-specific IgE

For immediate reactions within the previous year to clinical evaluation, serum-specific IgE to the suspected drug, if available, was determined by ImmunoCAP (Uppsala, Sweden). Specific IgE levels over 0.35 kU/L were considered as positive.

Drug provocation tests

Children with mild and moderate immediate reactions whose skin tests were negative underwent open DPT with a full dose of the drug, calculated by weight, as follows: AMX, 50 mg/kg/dose; AMX-clavulanate, 50 mg/kg/dose; cefuroxime, 15 mg/kg/dose; cefaclor, 8 mg/kg/dose. They stayed for 1 hour of observation at the hospital setting.

In cases of severe immediate reactions, doses were fractionated: one-tenth, one-half and total dose, administered every 30 min, with 1 hour of observation.

Patients reporting non-immediate reactions received a full dose of the antibiotic calculated by weight and they were observed during 1 hour. Then daily therapeutic doses of the antibiotic were prescribed at home. If the reported reaction took place within the first 3 days of treatment, DPT was carried on for 3 days. If the reaction took place from day 4 on of treatment, the patient was asked to take the antibiotic for 5 days.

In case of a home reaction, parents were instructed to stop antibiotic and to contact us by phone as well as to visit their primary care physician.

If the patient or the family could not remember the interval between antibiotic intake and reaction, STs were performed as described above and if negative, DPT was carried on during 5 days, in case of negative ST.

DPT was considered positive if objective skin, respiratory and/or cardiovascular symptoms were observed.

In case of positive DPT with AMX, DPT with cefuroxime was performed in order to provide antimicrobial therapeutic alternatives given the high rate of tolerance to cephalosporins among patients with delayed hypersensitivity to AMX.^{14 15}

Diagnosis algorithm is shown in [figure 1](#).

Statistical analysis

A descriptive analysis was performed of all the variables under study, expressing quantitative variables as mean \pm SD, median and range, and qualitative variables as absolute frequencies and percentages.

The association between qualitative variables was analysed with the χ^2 test or Fisher's exact test. Means were compared with the Mann-Whitney U test or Kruskal-Wallis test based on the number of groups being compared after verifying the normality assumption by means of the Kolmogorov-Smirnov test. Statistical analysis was performed with the SPSS V.19.0 software. We defined statistical significance as a p value of less than 0.05.

RESULTS

Clinical results

From January 2011 to December 2013, charts from 213 children referred with suspected hypersensitivity reactions to BL antibiotics were reviewed. There were 108 girls (50.7%) and 105 boys (49.3%). Mean age at the time of the reaction was 3.66 \pm 3.06 years. Mean age at the time of the allergic work-up was 6.26 \pm 3.9 years. Demographic characteristics are summarised in [table 1](#).

Most children (195 patients, 91.5%) reacted to one BL. Seventeen children (8%) reacted to two different BL antibiotics and one child reacted to three different BL antibiotics. A total of 229 suspected hypersensitivity reactions to BL antibiotics were reported. One hundred and fifty-four reactions (67.2%) were non-immediate, 24 (10.5%) were reported as immediate and 51 patients

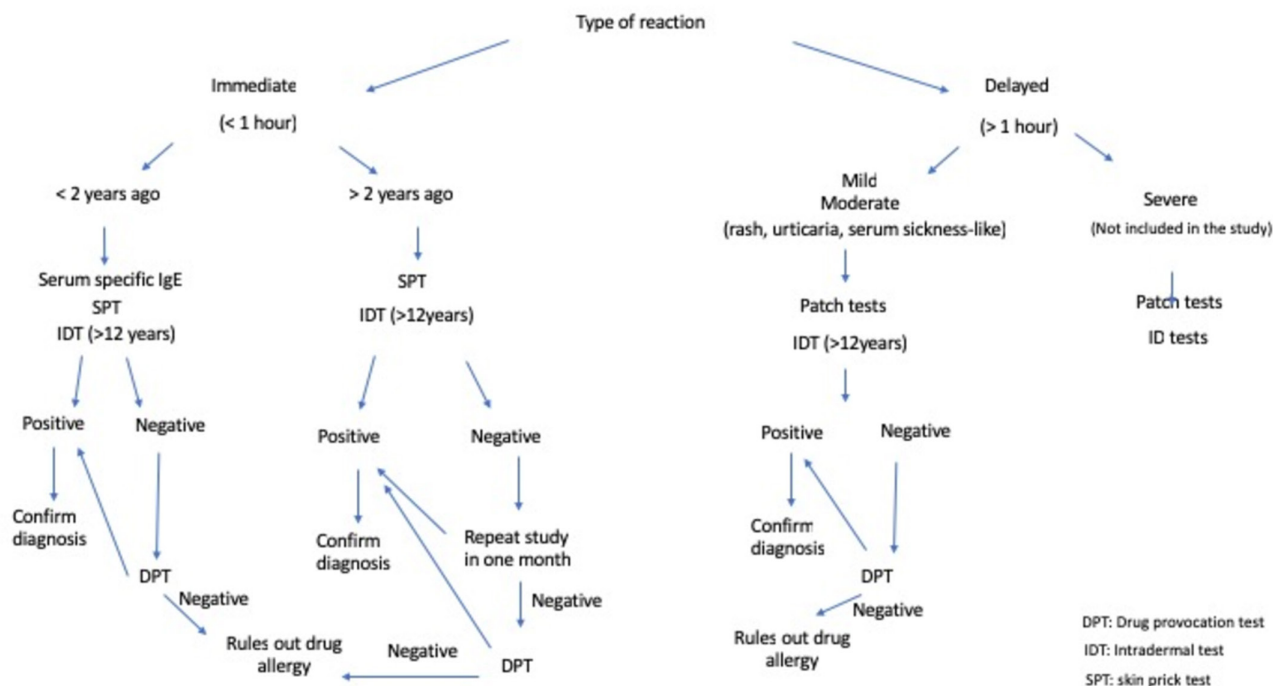


Figure 1 Diagnosis algorithm for hypersensitivity reactions to beta-lactams in children.

(22%) could not remember the interval between antibiotic intake and reaction. AMX–clavulanate was the most frequently implicated antibiotic (63.4%), followed by AMX alone (19.4%), cefuroxime (6.9%) and cefaclor (4.7%). Mild to moderate skin manifestations were most frequently reported: maculopapular exanthema in 52.2% of cases, urticaria in 33.6%, angioedema in 13.4% and 6.5% of patients developed serum sickness–like reaction.

Table 1 Demographic characteristics of children with suspected hypersensitivity reactions to beta-lactam antibiotics

	Number of reactions N=232
Age	6.26±3.87
Mean±SD (years) median (range)	5 (1–15)
Sex	
Female, n (%)	108 (50.7%)
Male, n (%)	105 (49.3%)
Personal history of atopy	63 (29.7%)
Rhinitis, n (%)	33 (15.5%)
Asthma, n (%)	35 (16.4%)
Atopic dermatitis, n (%)	18 (8.5%)
Food allergy, n (%)	2 (0.9%)
Family history of drug allergy	13 (6.1%)
Parents	6 (2.8%)
Grandparents	6 (2.8%)
Brothers	1 (0.5%)

No patient reported history of anaphylaxis. Delayed reactions took place after a mean of 3.5 ± 3.2 days of antibiotic intake.

These and other clinical characteristics are summarised in [table 2](#).

Testing results

Regarding ST, 32 children older than 12 years with non-immediate skin reactions underwent IDT. All IDTs were negative. Only 2 of 205 children who underwent patch testing yielded positive results. The involved antibiotic was amoxicillin in both cases and they reported a non-immediate reaction. These two patients were diagnosed as allergic to amoxicillin and they tolerated cefuroxime on DPT. One patient reporting an immediate reaction presented positive SPT with penicillin G and was diagnosed with BL allergy. Serum-specific IgE to the suspected drug was negative in patients referring immediate reactions. Results are showed with a flow chart in [figure 2](#).

DPT confirmed the diagnosis of drug hypersensitivity in 17 (7.5%) cases. All patients had delayed skin reactions. While DPT at home, 16 patients developed mild skin rashes that could be treated with antihistamines and one child developed generalised urticaria and oedema of knees, wrists and ankles suggestive of serum sickness, and needed treatment with oral steroids as well.

All patients reporting immediate reactions with negative ST tolerated the suspected antibiotic on DPT. ST and DPT results are summarised in [table 3](#).

Two patients (11.8%) with confirmed BL allergy reported family history of drug allergy. There were non-significant differences regarding family history of

Table 2 Clinical characteristics of children with suspected hypersensitivity reactions to beta-lactam antibiotics

	Number of reactions N=232
Age at reaction	
Mean±SD (years)	6.66±3.06
Median (range)	3 (1–14)
Type of reaction	
Delayed	154 (67.2%)
Not determined	51 (22%)
Immediate	24 (10.5%)
Symptoms	
Exanthema	121 (52.2%)
Urticaria	78 (33.6%)
Angioedema	31 (13.4%)
Serum sickness like	15 (6.5%)
Antibiotics	
Amoxicillin/clavulanate	147 (63.4%)
Amoxicillin	45 (19.4%)
Cefuroxime	16 (6.9%)
Cefaclor	11 (4.7%)
Cefixime	6 (2.6%)
Penicilin V	3 (1.3%)
Cefotaxime	1 (0.4%)

drug allergy between BL allergic and non-allergic children ($p=0.356$).

Eight patients (42.1%) of BL allergic patients presented personal history of atopy. There were non-significant differences regarding personal history of atopy between BL allergic and non-allergic children in our population ($p=0.189$).

For non-immediate hypersensitivity reactions, skin tests show very low sensitivity and are time consuming. Since 2014, we do not perform skin tests for the work-up of

Table 3 Outcome of skin tests and drug provocation tests performed for the diagnosis of beta-lactam hypersensitivity

Test	Positive n (%)	Negative n
SPT (n=229)	1 (0.4%)	228
IDT (n=32)	0	32
Patch test (n=205)	2 (0.9%)	203
DPT (n=226)	17 (7.5%)	226

DPT, drug provocation test; IDT, intradermal test; SPT, skin prick test.

delayed adverse reactions in our daily practice: after a careful clinical history, patients with mild and moderate non-immediate reactions to antibiotics undergo DPT as described previously.

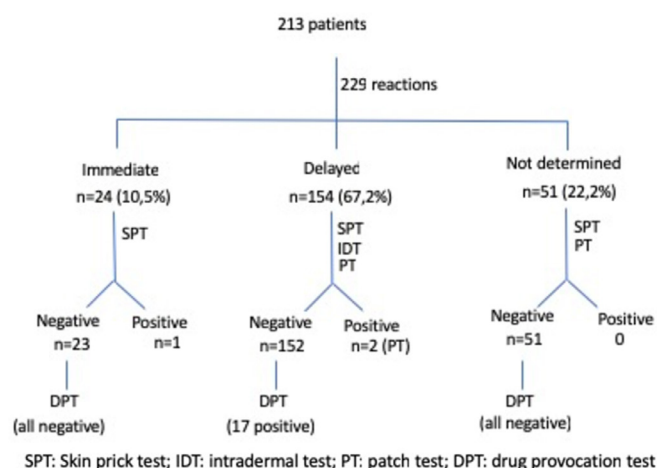
DISCUSSION

Delayed skin maculopapular or urticarial rashes are frequently reported in children receiving BL antibiotics. From that moment on, the majority of those children are labelled as ‘allergic to beta-lactams’ and they are prescribed alternative antibiotics that may be less effective and/or more expensive.¹⁰ Establishing an accurate diagnosis is associated with a more rationale use of antibiotics and also with lower rates of healthcare utilisation.¹⁶

Until recently, the diagnosis of non-immediate BL allergy was assessed by ST as IDT and patch tests, followed by DPT in those patients with negative ST results. This diagnostic work-up has been reconsidered since STs are not efficient for the diagnosis of mild and moderate non-immediate reactions to BLs in children, they are time consuming, and IDTs are painful and difficult to perform in small children. The reasons for the low sensitivity of ST are not well understood. It could be due to the use of a drug structure or conjugate that is not well recognised by the immune system since BLs are haptens that need to bind to proteins covalently to elicit an immune response.¹⁷

DPT confirmed BL hypersensitivity in 7.5% of cases in our population. These 17 patients, who presented delayed hypersensitivity reactions, showed negative ST. We assumed the diagnosis of BL allergy in those patients with positive ST. Recently, Caubet *et al*¹⁸ reported that 7 out of 11 patients with positive ID tests tolerated the suspected drug on DPT, yielding a positive predictive value for ST of 36% in that population. Vyles *et al*¹⁹ also reported that three children with positive ST to BLs tolerated the antibiotic on DPT. Given these observations, we wonder if the three patients with positive ST in our study (two with delayed reactions and one reporting immediate reaction) would have tolerated the suspected antibiotic on DPT.

Based on our findings, since 2014 we do not perform ST in children referred to us with non-immediate mild to moderate skin reactions related to antibiotics. Diagnostic

**Figure 2** Results based on diagnosis algorithm.

procedure has become simpler, less time consuming and it is safe. Up to date, we have not had severe reactions during DPT at home. Considering our results and based on our experience, we support previous reports proposing DPT-based protocols for the study of non-severe antibiotic hypersensitivity in children.^{11 20 21}

Even though DPT is considered the gold standard for the diagnosis of non-severe, non-immediate skin reactions, it is not standardised in children.

The duration of the DPT and the dose administered vary from one study to another. Although according to the members of the Task Force panel,¹² a full single therapeutic dose should be enough to diagnose delayed hypersensitivity reactions, there are concerns whether the number of days of drug administration may influence the outcome of DPT and therefore the diagnosis. There is the possibility that short DPT protocols would not identify all allergic children with delayed skin reaction. Mill *et al*¹⁵ studied 818 children with suspected AMX allergy. They performed a graded DPT with an only dose of antibiotic and found that 6% of patients reacted to it: 2% reacted within the hour after the last dose administered and 4% developed late reactions. Among those patients tolerating AMX on DPT, 10.9% requiring subsequent full treatment with AMX developed delayed skin reactions identical to the initial reactions.

Tonson la Tour *et al*²² reported high negative predictive value (96.7%) of a 2-day DPT but still, 4% of children with negative DPT reacted when re-treated at home with the suspected antibiotic.

Mori *et al*⁸ evaluated 200 children with suspected drug allergy. After ST, a 5-day DPT was performed. First dose was administered gradually, and if there were no adverse reactions, patients received daily therapeutic doses at home for 5 days. From the 17 patients (9.6%) who reacted on DPT, 14 did it on day 5. As they point out, shorter DPT would not identify 7.3% of late reactors leading to misdiagnosis.

What is known about the subject

- ▶ For diagnosis of non-immediate reactions there aren't standardised tests available. - Skin tests show low sensitivity. It has been proposed to perform only DPT for the diagnosis of non-severe hypersensitivity reactions.
- ▶ There are concerns whether the number of days of drug administration during DPT may influence its outcome.

What this study adds

- ▶ We conclude that performing drug provocation test (DPT) without previous skin tests in paediatric patients with non-severe delayed drug reactions is safe and effective.
- ▶ We propose a new drug provocation test protocol (3–5 days), based on the timing of the initial reaction.
- ▶ It supports the recommendation of DPT without previous skin tests for the diagnosis of non-severe beta-lactam allergy in children.

To minimise adverse reactions as diarrhoea or vomiting as well as the impact on bacterial microbiota and with the aim to diagnose the majority of true hypersensitivity reactions, we propose a different DPT protocol based on the timing of the initial reaction: for children reacting during the first 3 days of treatment, DPT lasts 3 days. In cases of later reactors (from day 3 on), DPT lasts 5 days. Based on this protocol, we found a similar prevalence of BL allergy to what has been previously reported by other authors.³⁻⁵

Regarding risk factors for BL allergy in children, Faitelson *et al*²³ recently found significant association between family history of drug allergy and Mill *et al*¹⁵ reported the same observation. Among patients diagnosed with BL allergy by DPT included in the present study, 11.8% (two patients) referred family history of drug allergy. We could not confirm the suggested association between family history of drug allergy and BL allergy in children.

On the other hand, although personal history of asthma and food allergy have been reported as significant risk factors for the development of AMX allergy²³ we found non-significant differences regarding personal history of atopy between BL allergic and non-allergic patients in our population.

The main limitation of this study to be considered is its retrospective design that, as previously reported, may overestimate the incidence of true allergy.²⁴

In summary, skin tests are not useful for the diagnosis of non-immediate hypersensitivity reactions to BLs in children. In cases of mild and moderate skin manifestations, DPT without previous ST is safe, effective and less time consuming. There would be interesting to unify the different DPT protocols with the aim to achieve an accurate diagnosis minimising the potential adverse drug reactions.

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