

Provocation Tests in Nonimmediate Hypersensitivity Reactions to β -Lactam Antibiotics in Children: Are Extended Challenges Needed?



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What is already known about this topic? β -Lactam antibiotics are the most common trigger of reactions in children with most of them being nonimmediate (85.5%), but proven allergy after the allergological workup is low. There is no agreement on how to perform the provocation tests in these types of hypersensitivity reactions.

What does this article add to our knowledge? This study confirms that a delayed reaction can be triggered with a unique dose of the drug.

How does this study impact current management guidelines? In most of the cases, the provocation test would not need to be performed over several days, but more studies are needed before supporting this recommendation.

BACKGROUND: β -Lactam antibiotics are the most common trigger of reactions in children with most of them being nonimmediate (85.5%), but proven allergy after the allergological workup is between 7% and 10%. There is no agreement on how to perform the provocation tests in these types of hypersensitivity reactions.

OBJECTIVE: To determine whether or not repeated doses of the β -lactams are required to reproduce a nonimmediate reaction in children.

METHODS: This is a retrospective observational study. We included children under 14 years who were referred for a nonimmediate reaction to β -lactams. All patients underwent a 1-day hospital provocation and were kept under observation at home during the following days for at least the time elapsed between the first dose and the symptoms of the index reaction. If no reaction was triggered, the patient resumed the provocation at home with 2 daily therapeutic doses for an equal of interval time.

RESULTS: Ninety-seven patients were included in the study. A positive reaction was recorded in 14 of them (14.4%). The short hospital provocation triggered 3 immediate reactions and 8 delayed reactions. The home rechallenge developed 1 immediate reaction and 2 delayed reactions.

CONCLUSIONS: Nonimmediate reactions to β -lactams in children may be triggered with a 1-day provocation test. We suggest to perform a 1-day provocation test followed by an observational period of at least the time interval of the index reaction. If this challenge is negative, an extended home provocation could subsequently be carried out. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:265-9)

Key words: β -Lactams; Antibiotics; Infants; Children; Provocation tests; Challenge tests; Delayed reactions; Nonimmediate reactions; Diagnosis

β -Lactam antibiotics are the most frequently prescribed drugs in childhood due to their effectiveness against respiratory infections, the most frequent ones in this age group. They also trigger the most reactions in children, although the incidence of these reactions is approximately half that in the adult population,¹ and much lower in the case of exanthemas.² Proven allergy after the allergological workup is between 7% and 10%¹⁻³ and 30%⁴ of the children with a history suggestive of β -lactam hypersensitivity. Most reactions are nonimmediate (85.5%); that is, they appear at any time as from 1 hour after the initial drug administration⁵ and are manifested mostly as rashes (75%).¹ The overestimation of the diagnosis may be due to the appearance of nonspecific reactions (vomiting, abdominal pain) or to symptoms of the underlying disease (viral exanthema) as well as to possible drug interactions with viral infections.⁵ It is important to confirm the diagnosis to avoid the use of inappropriate, more expensive, or unneeded broad spectrum antibiotics.

Skin tests, including epicutaneous and intradermal tests with delayed readings, are not useful for diagnosing nonimmediate reactions to β -lactams in children.^{1,6} This fact has been confirmed by several studies,^{3,7,8} and some authors recommend the provocation test (PT) without performing previous skin

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Abbreviations used

DHR- Drug hypersensitivity reactions
 EHomPT- Extended home provocation test
 HosPT- Home provocation test
 HosPT- Hospital provocation test
 MPE- Maculopapular exanthema
 PT- Provocation test
 SD- Standard deviation
 SS-LS- Serum sickness-like syndrome

tests,⁹ being generally a risk-free exploration^{1,7} in the case of mild reactions.

The delayed reactions frequently appear several days after starting treatment with the β -lactam antibiotic; there is concern about how PTs should be performed in terms of the time interval between the doses and the need or not to repeat the therapeutic dose over several days after the first challenge. Some authors recommend an extended provocation during several days, according to the index case,¹⁰ having detected positive provocations up to 11 days after receiving 2 daily doses of the drug, but without checking whether that same delayed reaction had been triggered with a single dose. So far, the recommendations of the different consensus statements have not echoed this strategy.^{5,11}

We must remember that drug hypersensitivity reactions (DHRs) belong to type B adverse drug reactions according to the classification of the World Health Organization.⁵ These types of reactions are unpredictable, and the symptoms triggered are different from the pharmacological effects of the drug. They are reproducible, disappear when the drug is discontinued, are independent of the dose, and, in some cases (eg, with the use of abacavir, carbamazepine, and allopurinol), they are associated with the presence of certain HLA alleles.⁵ Certainly, some reactions are somewhat more dose dependent (eg, nonsteroidal anti-inflammatory drugs), requiring a higher dose of the drug to trigger the symptoms; there is no agreement on the necessity to repeat the last dose over several days. These characteristics of the DHRs would be applicable to both immediate and delayed reactions. These latter reactions are probably mediated by a type IV hypersensitivity mechanism that requires a few days or weeks for the onset of the reaction; it would seem reasonable that no more than 1 therapeutic dose has to be required to trigger the symptoms, even if the reaction is manifested after a prolonged time interval, which could also be shortened when the patient is re-exposed.

Indeed, the European Network of Drug Allergy and the European Academy of Allergy and Clinical Immunology recommended years ago^{12,13}: "In case of previous non-immediate reactions, the starting dose should not exceed 1:100 of the therapeutic one and the time-interval between each dose should vary from 3 days to one week, depending on the time-interval between drug intake and adverse reactions reported in clinical histories." However, there are numerous reports in which these recommendations are not followed, perhaps because they are too time consuming, but, instead, propose repeating the therapeutic dose of the drug at home over the same days that had elapsed from the first dose of the drug to the appearance of symptoms,¹³ or for 2 days,¹ 5-6 days,^{14,15} or 10 days.¹⁶

The 2014 International Consensus on allergy to drugs⁵ admits the lack of agreement in the recommendation whether to administer a single therapeutic dose or to apply any of the

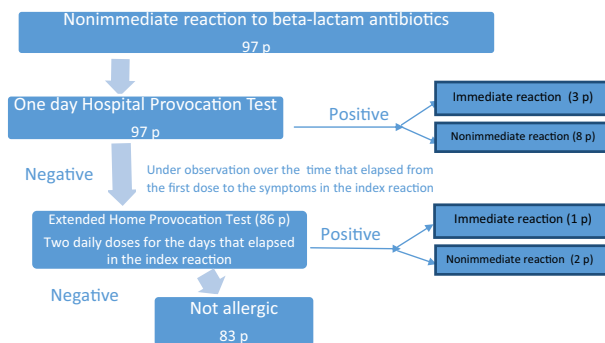


FIGURE 1. Algorithm for the allergologic workup of nonimmediate reactions to β -lactams in children and results of the provocation tests. p, patients.

forementioned approaches, with repeated doses over several days.

Since July 2014 and to avoid administering unnecessary doses of the β -lactam antibiotic to the children who could possibly react to a single day PT, the study protocol for this delayed reaction in children was modified in our clinic. Since then, the challenge was carried out with increasing doses of the drug involved up to the therapeutic dose during the first day of the study, and kept under home observation at least the same days that it took to trigger the reaction according to the clinical history. If the provocation did not trigger any reaction, then it was repeated with daily therapeutic doses at home for at least the same days that elapsed from the first dose of the drug to the appearance of the symptoms according to the clinical history.

We present the results obtained with this new diagnostic protocol in children with delayed reactions to β -lactam drugs to determine whether or not repeated doses of the drug are required to reproduce a nonimmediate reaction to β -lactams in children.

METHODS

This is a retrospective observational study. We included patients younger than 14 years of age who were referred to our allergy service for study from July 2014 to December 2017 for having presented a nonimmediate reaction to β -lactam antibiotics, and whose parents or guardians signed the consent for the study. Because of the existence of an overlap between immediate and nonimmediate reactions in the classification proposed by the International Consensus on Drug Allergy,⁵ only those patients whose symptoms had begun at least 6 hours after the first dose of the drug were included. Patients who subsequently tolerated the drug implicated in the reaction were excluded from the study.

All patients underwent a PT at the Hospital (HosPT). The final dose was one-third of the daily therapeutic dose (50 mg/kg of body weight) of phenoxymethylpenicillin, amoxicillin, or amoxicillin-clavulanic acid (100/12.5 mg), and the cumulative dose was 65% of the daily dose. The challenge started with one-fourth of that dose, followed by one-half and the full mentioned dose, at 30-minute intervals. For a child weighing 25 kg, the doses would be approximately 100, 200, and 400 mg at 30-minute intervals. Then, they were kept under observation for 2 hours, and they were instructed to contact the service or go to an emergency department in the case of a later reaction and to provide a picture of the possible cutaneous reaction. If no reaction appeared over the recorded time elapsed from

TABLE I. Characteristics of the patients and original reactions

Patients and reactions	Characteristics
Age, mean (SD)	5.2 (3.1)
Sex	51 male/46 female
Drugs	
AX	55.7%
AX/CL	39.2%
CEFUX	3.1%
Others	2%
Time to study, mean (range; SD)	18.2 mo (0.2-120; 27.1)
Interval time from first dose, mean (range; SD)	3.8 d (0.3-10; 2.5)
Symptoms	
MPE	46.4%
U	34%
U/A	8.2%
FDE	2.1%
SS-LS	2.1%
Others	7.2%
Number reactions, mean (range; SD)	1.3 (1-3; 0.6)

AX, Amoxicillin; AX/CL, amoxicillin/clavulanic acid; CEFUX, cefuroxime; FDE, fixed drug eruption; MPE, maculopapular exanthema; SD, standard deviation; SS-LS, serum sickness-like syndrome; U, urticaria, U/A, urticaria/angioedema.

the first dose to the appearance of the symptoms, the patient was instructed to resume the provocation at home (HomPT) immediately after the interval, in the form of 2 daily doses (400 mg bid in the previous example) over the number of days it took for the reaction to appear, being advised to report the appearance of a reaction in the same way previously indicated (Figure 1). Therefore, the total duration of the workup was variable for each patient.

To determine the existence of any factor associated with the appearance of these reactions, the different variables were analyzed by the χ^2 test or the Fisher exact test in the case of the qualitative variables (sex, symptoms, drug, personal or family atopic background, drug allergy, history of more than 1 reaction with any β -lactam drugs) and by the Mann-Whitney *U* test for quantitative variables (age, time interval between dose and reaction, duration of symptoms, number of previous reactions) because they did not follow a normal distribution.

RESULTS

Ninety-seven patients, 51 boys and 46 girls, were included in the study, with a mean age of 5.2 years (1-14 years) (standard deviation [SD] 3.1). The drugs most frequently involved were amoxicillin (55.7%) and amoxicillin-clavulanic acid (39.2%) (Table I). In 27 (27.8%) patients, more than 1 reaction was reported in the clinical history.

The average time from the reactions to consultation was 17.8 months (from 15 days to 10 years). Although this time was longer in the group that reacted as compared with the one that did not (average 19.7 months vs 10 months), it was not statistically different.

The average time interval from the first dose of the drug to the reaction, according to clinical history, was 3.8 days and ranged from 8 hours to 10 days (Table I); thus, the complete workup took from 1 day in those who presented the reaction between 6 hours and 1 day from the first dose of the antibiotic up to 20 days (10 days of home observation and 10 days of extended

home provocation test [EHomPT]) in those who reported a time interval of 10 days. Twenty patients (20.6%) needed only 4 days or less and 73 patients (75.2%) 10 or fewer days.

The most frequent manifestation was maculopapular exanthema (MPE) (46.4%) followed by urticaria (34%), and the lesions persisted for an average of 2.8 days (from 2 hours to 15 days).

After the PTs, a positive reaction was recorded in 14 of the 97 patients (14.4%). There were 3 immediate reactions and 8 delayed reactions triggered with the HosPT. The immediate reactions were manifested after 1 to 3 hours of the first dose of the drug, 2 in the form of mild urticaria, and 1 as a fixed drug eruption (Table II). Late reactions after the HosPT manifested after an average of 1.8 days (SD 55.9) in the range of 6 hours to 7 days, mostly in the form of MPE (Table II).

After the EHOMPT there were 3 reactions. It is important to note that the first of these patients had started with a febrile respiratory infection 1 day before starting the EHOMPT and, after 1 day, presented a rash similar to the one mentioned in the clinical history, although it appeared earlier.

The second patient presented urticaria accompanied by vomiting 30 minutes after taking the first home dose of amoxicillin-clavulanic acid. The reaction was mild and promptly resolved with antihistamines.

The other patient presented a serum sickness-like syndrome (SS-LS) 4 days after starting home treatment, manifested with a macular rash, fever, arthralgia, and neutrophilia (14.193 neutrophils/mL). Previously, he reported 2 episodes of very mild urticaria after 2 to 3 days of starting a course of amoxicillin or amoxicillin-clavulanic acid and another episode of urticaria and mild arthralgia after finishing a course of amoxicillin-clavulanic acid, although he had also suffered another similar episode without being treated with β -lactam antibiotic.

Using Fisher's exact test, no association was detected between the involved drug or the symptoms and the positive hospital or HomPTs. Reactions to the PTs were more frequently triggered in boys than in girls ($P = .04$) and in those who had suffered more than 1 reaction with a β -lactam antibiotic ($P < .01$). Using the Mann-Whitney *U* test, no significant differences were detected between children who did or did not have a reaction in age, time elapsed from the index reaction to the allergological workup or from the first dose to the symptoms, and duration of symptoms. The average number of previous reactions was significantly higher in those who reacted to the PTs ($P < .01$).

DISCUSSION

The aim of our study was to determine if repeated doses of the β -lactam antibiotic were required to trigger nonimmediate hypersensitivity reactions to these drugs in children. To this end, a hospital challenge with the drug was performed in 1 day, keeping the patient under observation at home for at least the time interval from the first dose until the symptoms in the original reaction, to detect the cases in which the reaction could be triggered with a single dose.

If this first provocation was negative, a second home provocation was carried out, with repeated doses over an equal interval. Some authors¹⁷ have studied the effect of an extended challenge over 7 consecutive days, but without allowing this observation period after a single therapeutic dose. In this study, 12% of the positive reactions occurred during subsequent days of treatment after the short provocation on the first day, but this protocol does

TABLE II. Positive reactions after hospital provocation tests

N	Sex	Age (y)	Drug	Latency (d)	Symptoms	Num reactions	HosPT latency (h)	HosPT symptoms
Immediate reactions								
1	M	1.5	AX	3	Erythema	2	1	Urticaria
2	M	7.5	AX/CL	3	MPE + AE	2	1	Urticaria
3	M	14	AX/CL	2	FDE	3	3	FDE
Delayed reactions								
1	F	6.5	AX	5	Urticaria	3	72	MPE
2	F	3	AX	1	MPE	2	6	MPE
3	M	11	AX/CL	7	MPE	2	168	MPE
4	M	13	AX/CL	3	MPE	3	8	MPE
5	M	3	AX/CL	5	Urticaria	2	9	Urticaria
6	M	3	AX	3	Urticaria	1	24	MPE
7	M	7	AX/CL	1	Urticaria	1	7	Urticaria
8	M	2	AX	9	U-AE	2	48	U-AE

AX, Amoxicillin; AX/CL, amoxicillin/clavulanic-acid; FDE, fixed drug eruption; HosPT, hospital provocation test; MPE + AE, maculopapular exanthema and angioedema; U-AE, urticaria/angioedema.

TABLE III. Positive reactions after extended home provocation tests

N	Sex	Age (y)	Drug	Latency (d)	Symptoms	Num reactions	HomPT latency (h)	HomPT symptoms
1	F	5	AX/CL	10	MPE	3	24	MPE (+viral infection)
2	M	3	AX/CL	7	Urticaria	1	0.5	Urticaria + vomiting
3	M	5	AX/CL	3-8	Urticaria/SS-LS	3	96	SS-LS

AX, Amoxicillin; AX/CL, amoxicillin/clavulanate; HomPT, home provocation test; MPE, maculopapular exanthema; SS-LS, serum sickness-like syndrome.

not allow one to rule out that late reactions may have occurred without the need to repeat the doses of the drug; something similar could be stated from the study of Ponvert et al.⁸

In our case series, reactions to the β -lactam antibiotic were triggered with a similar rate to some studies in children with nonimmediate reactions⁸ but more frequently (14.4%) than in most others.^{1,9}

The most frequently involved drugs, the symptoms, and the time interval between the first dose and the reaction do not differ much from those offered by other studies.^{1,7,18}

The symptoms were concordant with the original reaction in 10 of 14 positive reactions in the PTs. The time interval was shorter, that is, the reaction was triggered earlier compared with the original one in 9 cases, being in 4 cases an immediate reaction (3 in the HosPT and 1 in HomPT). These cases could be new sensitizations or errors in the clinical history referred by the parents. No patient reacted with a longer time interval than the one mentioned in the clinical history.

There were 8 patients who presented a delayed positive test with a single therapeutic inpatient dose, between 6 hours and 7 days after the HosPT, most of them as MPE. This observation confirms the idea that, at least in a majority of patients, a hypersensitivity delayed reaction with the drug may not require repeated doses to trigger a reaction. These 8 patients were spared unnecessary antibiotic exposure, approximately 24 total doses, and we do not know if these unnecessary doses would have caused more severe symptoms in the patients, as they would have received a higher cumulative dose of the antibiotic.

Although in some patients the completion of the workup was longer than in other reported protocols, some of our patients (20.6%) needed fewer days as compared with other studies¹³⁻¹⁵ and most of them (75.2%) needed 10 days or less.

There were 3 reactions with the HomPTs, but there would be reasons to exclude home reactions as true nonimmediate hypersensitivity reactions.

In the first case (Table III), because the home reaction coincided with a febrile respiratory infection, it could be due to the interaction of the drug with a viral process. In the second case, as previously mentioned, the reaction was immediate, presenting with urticaria and vomiting 30 minutes after the first home dose. The symptoms and the time interval suggest that the reaction was induced with this first home dose and not with the doses of the HosPT given 7 days before and, therefore, that it would probably be a new sensitization to the drug. In this case, the HomPT induced mild anaphylaxis that resolved promptly, but we have to keep in mind that there is a risk of systemic reactions and consider whether the first dose of the home provocation should be performed in the hospital.

In the third case, the patient manifested fever, arthralgias, and MPE 10 days after the HosPT and 4 days after starting the EHomPT doses. The question remains as to whether this reaction was due to the home or to the HosPT because the time interval in the case of SS-LS is between 1 and 3 weeks.¹⁹ In this case, the home observation period should have been longer, about 3 weeks, to avoid this confusion.

Neither the previous symptoms nor the implicated drug or the demographic characteristics of the patients (except the gender) were predictors for the appearance of delayed reactions to β -lactam antibiotics in children. Only the male sex and the history of having suffered more than 1 previous reaction with any β -lactam antibiotic was associated with the appearance of immediate or late reactions in the HosPT. Some authors also reported more reactions in boys than in girls³ but others did not.¹⁸ These differences in gender are difficult to explain.

Twenty seven patients reported more than 1 reaction with a β -lactam antibiotic; 11 of them reacted in the PTs (40.7%). This rate is significantly higher than that of those who had only 1 previous reaction to the drug (4.2%). These results are in accordance with the study reported by Rubio et al.²

We conclude that, in nonimmediate reactions to β -lactams in children, the only predictor associated with true hypersensitivity reactions is the previous history of more than 1 reaction with a β -lactam antibiotic. There may be delayed reactions, hours or several days later, with 1-day PT, and probably all the patients could be diagnosed with a 1-day PT, although more studies are necessary to confirm this hypothesis. Until then, it would be advisable to carry out a 1-day short provocation followed by an observation period of at least the time interval reported in the index reaction. If negative, an EHomPT should subsequently be carried out.

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