

Natural History of Benign Nonimmediate Allergy to Beta-Lactams in Children: A Prospective Study in Retreated Patients After a Positive and a Negative Provocation Test



Aude Tonson la Tour, MD^a, Marine Michelet, MD^b, Philippe A. Eigenmann, MD^c, and Jean-Christoph Caubet, MD^c
Geneva, Switzerland; and Toulouse, France

What is already known about this topic? Although it has been shown that the sensitivity to beta-lactams (BL) decreases over time in patients with an immediate hypersensitivity, data are lacking regarding the natural history of nonimmediate hypersensitivity to BL.

What does this article add to our knowledge? Our results showed that the vast majority of children (89%) with benign nonimmediate BL allergy become tolerant after 3 years. From another point of view, the negative predictive value of the drug provocation test (DPT) using a 2-day protocol was 96.7%.

How does this study impact current management guidelines? Our data strongly suggest that a follow-up DPT is safe and useful to assess tolerance acquisition in children with nonimmediate BL allergy. In addition, our data support the use of a 2-day protocol DPT.

BACKGROUND: The drug provocation test (DPT) is considered as the gold standard to diagnose drug allergy and is particularly important in the diagnosis of nonimmediate beta-lactam (BL) allergy in children. The natural history of BL allergy remains unknown.

OBJECTIVE: Our main aim was to evaluate the natural history of nonimmediate BL hypersensitivity and the long-term tolerance acquisition, and our secondary objective was to determine the negative predictive value (NPV) of the DPT following a 2-day protocol.

METHODS: Children developing a benign rash while treated by BL were prospectively recruited at the Emergency Department of the Geneva University Hospital from 2006 to 2011 and challenged with the incriminated BL (initial diagnostic drug provocation test [idDPT]) following a 2-day protocol. In case of a positive idDPT, the patients underwent a follow-up drug provocation test (fuDPT) 3 years later. In case of a negative

idDPT, we sent a questionnaire to assess tolerance of a subsequent treatment with the incriminated BL.

RESULTS: Among the 18 children with a positive idDPT, 16 children (89%) had a negative fuDPT and 2 children developed a benign exanthema. Among those 16 children, 11 tolerated a subsequent treatment with the incriminated BL without any reaction, suggesting natural antibiotic tolerance acquisition. From another point of view, we found that the NPV of the DPT following a 2-day protocol was excellent at 96.7%.

CONCLUSIONS: Our data strongly suggest that a fuDPT is safe and useful to assess tolerance acquisition in children with a confirmed benign nonimmediate BL allergy. In addition, our results support the use of a short DPT protocol (2 days), which led to a high NPV of 96.7% in our population, with a favorable benefit-risk balance. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1321-6)

Key words: Beta-lactam nonimmediate allergy; Drug provocation test; Negative predictive value

^aDivision of Pediatric Emergency, University Hospital of Geneva, Geneva, Switzerland

^bDivision of Pediatric Allergy, University Hospital of Toulouse, Toulouse, France

^cPediatric Allergy Unit, University Hospitals of Geneva, Geneva, Switzerland

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Corresponding author: Jean-Christoph Caubet, MD, Hôpitaux Universitaires de Genève, Département de Pédiatrie, 6 rue Willy-Donzé CH-1211 Genève 14, Switzerland. E-mail: jean-christoph.caubet@hcuge.ch.

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Drug hypersensitivity reactions, particularly to beta-lactams (BL), represent a well-known major public health problem in children associated with a substantial morbidity and mortality.^{1,2} The estimated prevalence in children ranges between 2.5% and 10.2%.³ However, most of the studies overestimated the true prevalence due to incomplete diagnostic allergy workup not including a drug provocation test (DPT). This overdiagnosis is mainly due to the fear of life-threatening reactions during DPT, thus avoiding this procedure. This leads to unnecessary drug restriction, which contributes to increased

Abbreviations used

BL- Beta-lactams

DPT- Drug provocation test

fuDPT- Follow-up drug provocation test

idDPT- Initial diagnostic drug provocation test

NPV- Negative predictive value

resistance to antibiotics in the general population and high medical costs.

Exanthemas occurring during BL treatment are relatively common in children, ranging between 1% and 5%.⁴ It has been shown that most of these benign skin rashes (ie, without symptoms suggestive of anaphylaxis or systemic reactions) are due to infectious diseases, or to interactions between drugs and infectious agents, rather than to real BL allergy.^{5,6} According to recent international guidelines, the diagnosis of nonimmediate BL allergy (ie, occurring more than 1 hour after the last dose) in children is mainly based on a DPT, considered as the gold standard.^{7,8} In addition, previous studies have shown that skin tests have a poor diagnostic value in nonimmediate benign reactions.^{5,9,10} However, the DPT is not standardized in children, and there are a large variety of protocols currently used not only among various countries, but also among various centers in a given country. Particularly, the duration (number of days) of the DPT to diagnose a nonimmediate reaction is still a matter of debate.⁸ There is a need for studies to determine the optimal duration of the DPT for nonimmediate reactions in children. In addition, the natural history of patients with a confirmed benign nonimmediate allergy to BL remains unknown. Only few studies, mainly performed in the adult population, have suggested a decreased sensitivity to BL over time, as shown by skin tests or *in vitro* tests becoming negative.^{11,12} However, studies including a follow-up DPT (fuDPT) in patients with confirmed BL allergy are currently lacking in the literature, particularly in the pediatric population.

The primary objective of this prospective follow-up study was to evaluate the natural history of nonimmediate BL allergy in children by performing a fuDPT 3 years after a positive initial diagnostic DPT (idDPT). In addition, a follow-up phone call visit was performed to evaluate long-term tolerance in case of subsequent treatments with BL if this fuDPT was negative. Our secondary objective was to determine the negative predictive value (NPV) of the DPT following a 2-day protocol by means of a questionnaire evaluating the tolerance of the incriminated BL after a negative idDPT.

METHODS

Patients and study setting

The current study is a follow-up of a previously published prospective study. Inclusion and exclusion criteria are described elsewhere.⁵ This study was approved by the Ethics Committee of the Geneva University Hospitals, Switzerland.

Briefly, children developing a benign rash while treated by BL were sequentially recruited at the Emergency Department of the Geneva University Hospital from 2006 to 2011. They were then challenged with the incriminated BL (idDPT) 2 months after the initial reaction. To increase the study's statistical power, additional children with a history of benign skin eruption during a BL treatment and challenged at our outpatient's clinic were prospectively

included (without any restriction regarding the delay from the initial reaction).

Then, depending on the result of this idDPT, positive or negative, children were divided into 2 groups.

Assessment of the natural history of BL allergy

In the case of a positive idDPT, the patients underwent a second DPT 3 years later with the culprit BL antibiotic (fuDPT). The DPT was performed by administering an initial dose of 10% of the whole dose (calculated by weight), and if this dose was well tolerated, the remaining 90% of the dose was given 30 minutes later. To identify reactions that may occur only at a higher dose, we used an initial dose of 25 mg/kg for amoxicillin, 23 mg/kg for cefprozil, and 23 mg/kg for cefaclor (which correspond to 150% of the usual therapeutic dose adapted to the weight). All patients were observed at least 1 hour after the last dose under strict hospital surveillance with full resuscitation backup. Then, the incriminated BL was prescribed for 48 hours at the standard therapeutic dose (50 mg/kg/day for amoxicillin, 45 mg/kg/day for cefaclor, and 30 mg/kg/day for cefprozil), to limit unnecessary exposure to a higher dose with potential side effects. In case of reactions, children were advised to stop treatment, to take oral antihistaminic, and to contact the research team to identify delayed reactions.

DPT was considered positive if any objective symptoms suggestive of an allergic reaction occurred during the treatment or within 48 hours after the last dose.

Finally, we organized a follow-up phone call visit for patients with a negative fuDPT to determine the tolerance of a subsequent full treatment for an infectious illness with the incriminated BL.

Questionnaire to assess the NPV of DPT

In case of negative idDPT, we sent a questionnaire to patients/parents and/or to their primary care physician, including questions about subsequent treatments and the tolerance to the culprit antibiotic. If the antibiotic was not tolerated, the patients were asked to describe the reaction.

Of note, the initial choice of a 2-day protocol for the idDPT was based on preliminary data suggesting that only a minority of allergic children will react after 2 days, and the potential side effects of a prolonged antibiotic treatment were taken into account.

RESULTS

fuDPT in patients with a BL allergy, confirmed by a positive idDPT

Characteristics of the included patients with a diagnosis of BL allergy as confirmed by a positive idDPT are shown in Table I. Eighteen patients with a positive idDPT have been included, 10 from the initial study (56%) and 8 recruited prospectively at our outpatient allergy clinic (44%). The reactions observed during the idDPT were maculopapular exanthema ($n = 9$, 50%), urticaria ($n = 8$, 44%), and vomiting/asthenia ($n = 1$, 6%). Although the initial reaction was nonimmediate (>1 hour), 5 children (28%) developed a reaction within the first hour after administration of the first challenged dose. None of the patients presented reactions after the third dose at home. The incriminated antibiotics were amoxicillin ($n = 10$, 55%), amoxicillin-clavulanic acid ($n = 6$, 33%), cefaclor ($n = 1$, 6%), and cefprozil ($n = 1$, 6%). The idDPT was performed at a median of 3 months after the initial reaction (range, 1 and 132 months).

To investigate the natural history of these BL allergies, a fuDPT was organized. The mean time elapsed between the

TABLE I. Characteristics of patients with an initial positive DPT (idDPT) and who benefited from a follow-up DPT (fuDPT) for assessing natural tolerance acquisition

Patient	Gender	Age at first reaction (y)	Culprit antibiotic	Initial nonimmediate reaction	idDPT symptoms	Delay (between challenge and symptoms at idDPT)		Time between idDPT and fuDPT (y)	fuDPT results	
						<1 h	>1 h			
1	M	4	Amoxicillin	Macular exanthema	Maculopapular exanthema, vomiting		X	3.5	Negative	
2	M	17	Amoxicillin	Nonspecific exanthema	Maculopapular exanthema		X	6.5	Negative	
3	F	9	Amoxicillin + clavulanic acid	Nonspecific exanthema	Urticaria	X		2.3	Negative	
4	M	8	Amoxicillin	Urticaria	Macular exanthema		X	5.5	Negative	
5	F	8	Cefaclor	Macular exanthema	Urticaria	X		Unknown	Negative	
6	M	8	Amoxicillin + clavulanic acid	Urticaria	Vomiting, asthenia		X	4.2	Negative	
7	M	7	Amoxicillin	Nonspecific exanthema	Urticaria			7.5	Negative	
8	M	8	Amoxicillin + clavulanic acid	Macular exanthema	Maculopapular exanthema		X	3.6	Negative	
9	F	5	Amoxicillin	Nonspecific exanthema	Urticaria	X		6.1	Negative	
10	M	2	Amoxicillin + clavulanic acid	Nonspecific exanthema	Urticaria		X	3.2	Positive	Urticaria 1 h after first dose
11	F	6	Amoxicillin	Urticaria	Maculopapular exanthema		X	3	Negative	
12	F	7	Cefprozil	Maculopapular exanthema	Maculo-papular exanthema		X	3	Negative	
13	F	Unknown	Amoxicillin + clavulanic acid	Papular exanthema	Urticaria		X	1.5	Negative	
14	F	6	Amoxicillin + clavulanic acid	Micropapular exanthema	Maculopapular exanthema		X	3.4	Negative	
15	F	14	Amoxicillin	Urticaria	Urticaria		X	3	Negative	
16	M	6	Amoxicillin	Maculopapular exanthema	Maculopapular	X		2.7	Negative	
17	M	5	Amoxicillin	Nonspecific exanthema	Urticaria	X		6.1	Positive	Urticaria 4 h after first dose
18	F	4	Amoxicillin	Macular exanthema	Maculopapular exanthema		X	5.1	Negative	

DPT, Drug provocation test.

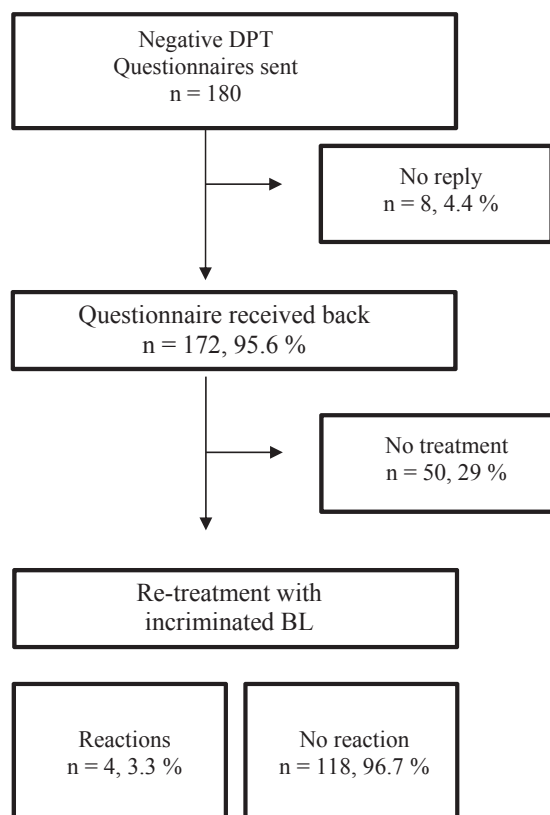


FIGURE 1. Follow-up questionnaires of patients with a negative DPT. BL, Beta-lactams; DPT, drug provocation test.

idDPT and the fuDPT was 3.5 years (range, 1.5 to 7.5 years). Among the 18 patients with a first positive idDPT, only 2 patients (11%) developed a benign generalized urticaria after receiving the first dose of the fuDPT (appearing 1 hour and 4 hours after the first dose, respectively).

Moreover, all the 16 patients with a negative fuDPT benefited from a follow-up phone call visit. Among them, a majority (11/16, 68.8%) received a subsequent regular treatment (8-10 days) with the incriminated BL without any reaction. Three patients did not need antibiotic treatment during the study period and 2 patients could not be contacted by phone.

Follow-up questionnaires of patients with a negative idDPT

A questionnaire has been sent to 180 patients with a negative idDPT as well as to their primary care physicians. One hundred and seventy-two patients responded to the query (95.6%). One hundred and twenty-two patients (71%) were treated again with the initially suspected BL or another BL. Fifty children (29%) did not require an antibiotic treatment during the study period. Among the 122 patients who were treated with the incriminated BL, only 4 (3.3%) reported an isolated generalized maculopapular exanthema after amoxicillin ($n = 1$, 25%), cefaclor ($n = 2$, 50%), and penicillin G ($n = 1$, 25%). However, the last patient had received amoxicillin-clavulanic acid few years later without any reaction. Based on these results, the NPV of a 2-day DPT, 96.7%, was excellent in our population. These results are shown in Figure 1.

DISCUSSION

To assess the natural history of nonimmediate BL allergy, we systematically performed a fuDPT in children with a confirmed benign nonimmediate BL allergy (positive idDPT) recruited prospectively. We found that the vast majority of BL allergic children ($n = 16/18$, 89%) were tolerant at follow-up (mean of 3.5 years; range, 1.5-7.5 years). To our knowledge, this is the first long-term prospective follow-up study evaluating the natural history of benign nonimmediate allergy to BL in children by performing systematically a rechallenge several years after an initial positive allergic workup. In addition, our data confirmed an excellent NPV of 96.7% for DPT following a 2-day protocol suggesting a low rate of resensitization and/or a few number of unidentified patients with this short protocol.

Tolerance acquisition is well known to occur naturally in children with food allergy, particularly milk and egg allergy with the vast majority of children becoming tolerant at 5 years of age.¹³ Regarding the natural evolution of drug allergy, data are rather limited. Nevertheless in immediate hypersensitivity to BL, it has been shown that the sensitivity of skin tests as well as of *in vitro* tests (specific IgE or basophils activation test) decreases over time.^{11,12,14} However, in the absence of DPTs in most of studies, it remains unclear if this decrease of sensitivity is associated with BL tolerance.^{11,12} In addition, data are lacking regarding the natural history of nonimmediate hypersensitivity. The strength of our study is the prospective inclusion of children with a confirmed BL allergy based on a positive idDPT and the realization of a systematic fuDPT. Our results showed that the large majority of children (89%) with a confirmed benign hypersensitivity to BL became tolerant after a mean of 3.5 years (range, 1.5-7.5 years), as shown by a negative fuDPT following a 2-day protocol. However, some authors have highlighted the possible risk of resensitization (ie, conversion of negative allergic workup to positivity) in patients with a history of immediate reaction, retested after a negative fuDPT.¹⁵ In other words, this means that although our patients had a negative fuDPT, they could react during a subsequent treatment because of the potential risk of being resensitized during this fuDPT.¹⁶ Some authors found a significant proportion of patients reacting to retest (23%) and suggest to perform a booster protocol.^{17,18} However, several studies, including mainly adults with immediate hypersensitivity, have shown a lower percentage of patients reacting to retest attributed to resensitization, ranging between 0% and 16%.^{16,19-22} Of note, most of these studies evaluated the risk of resensitization based on skin testing alone, without a DPT to confirm or exclude an allergy. In children, few studies have assessed the risk of resensitization, but the risk appears to be low, similar to the adult population.²³⁻²⁵ This phenomenon appears to occur mainly in patients with immediate reactions, but can occur also with nonimmediate reactions.^{15,25} Thus, further large studies are still needed to determine the utility of a boost test in the pediatric population. One limitation of our study is the lack of systematic retest after a negative fuDPT. However, to evaluate BL tolerance in our population of children initially diagnosed as BL allergic by a positive idDPT and who had a negative fuDPT several years later, we organized a follow-up phone call visit. Among those who had thereafter received a regular treatment with the incriminated BL several years after the fuDPT, all tolerated a full course of antibiotic, clearly showing that our patients acquired complete tolerance. Ponvert et al²⁵ found that

among 6 children who reacted after a negative fuDPT, 5 (83.3%) had a subsequent negative allergic workup including a DPT, suggesting that most reactions during subsequent treatment are most likely in relation to the underlying infection itself. These data reporting patients with negative DPT, but reacting when receiving the antibiotic during a concomitant infection, implicate viral infection acting as a cofactor in drug allergy. It is also important to note that these reactions were mild and no severe reaction was reported during these large studies. Taken together, these data strongly support the fact that a majority of children with nonimmediate penicillin allergy become tolerant. Further studies are needed to determine the optimal interval for the fuDPT, particularly if tolerance acquisition can occur earlier than 3 years.

Several other factors may affect the proportion of children reacting after a negative DPT. Indeed, a positive reaction after a negative DPT may be due to the resensitization effect or the need of a cofactor such as viral infection as discussed above, but may also be due to a false-negative DPT related to the inappropriate duration of the DPT. DPT is considered as the gold standard and is particularly important to diagnose benign nonimmediate reactions in children. Indeed, it has been shown that approximately 90% of children developing a benign nonimmediate exanthema will have a negative DPT, ideally performed 2 months after the initial episode.⁸ However, its procedure is currently not standardized; particularly the optimal duration (number of days) is not well defined.^{5,8} Thus, there is a large variation in the DPT protocols used to diagnose nonimmediate reaction to BL, especially for the duration of the test ranging from 1 dose to protocols lasting 10 days.^{5,9,26,27} Despite the limited number of pediatric studies, it has been suggested that most BL allergic children will react after the first challenge dose, and that longer protocols will only lead to identification of a low additional number of allergic patients.^{5,8-10,28} However, data are currently lacking in the literature for standardization of protocols, and prevent proper guidance for an optimal DPT duration.⁸ On the basis of a questionnaire sent to 122 children with a negative idDPT following a 2-day protocol, we found an excellent NPV of 96.7%. It is noteworthy that this proportion of patients is similar to numbers reported by others.²⁹ However, Mori et al²⁷ recently found that 26.6% (4/14) of children reacted after 5 days. But it is important to note that they had to perform 177 DPTs following a 5-day protocol, with only 4 children reacting after 5 days (2.2%). In addition to differences in the population studied (ie, particularly the age of the population, the number of antibiotic treatments previously received, and the genetic background), the delay between the initial reaction and the allergic workup might explain the discrepancies with our findings. One limitation of our study is the fact that the idDPT was performed during only 2 days, and the patients did not receive a full course of treatment for the DPT. In consequence, the exact number of patients who would have reacted after 2 days remains unknown and has been evaluated based on the rate of positive DPT during a subsequent treatment. Thus, other confusion factors (such as concomitant infection or the resensitization effect) might have affected our results. In addition, among the 172 patients who responded to the questionnaire, 50 did not receive the suspected BL during the study period. Although most of those patients simply did not need an antibiotic treatment during this period, we cannot exclude that some of those patients and/or their physicians preferred to avoid the

drug because of the fear of severe reactions. This entailed a selection bias. However, no difference in baseline clinical characteristics of those patients has been noted, and we did not expect a different proportion of allergic patients in this group of patients who were not retreated. Large multicentric prospective studies are required to determine the optimal length of DPT, taking into account the risk-benefit analysis of prolonged exposition to the antibiotic and the risk of developing a mild reaction.

In conclusion, our data showed that a fuDPT is safe and useful to assess tolerance acquisition in children with a confirmed benign nonimmediate BL allergy. Our results are in line with previous studies in adults suggesting loss of BL allergy over-time.^{11,12} The role of viruses in drug allergy requires further investigation, as it might play a central role and could explain natural tolerance acquisition. Indeed, as shown for Epstein-Barr virus, viruses might lead to transient immunostimulation that might be a necessary cofactor to develop a drug reaction, and as the virus-induced immune response decreases over time, the drug could be tolerated at a later timepoint.³⁰ The DPT is the gold standard and is particularly important to diagnose benign nonimmediate allergy, but also to assess tolerance acquisition. Our data support the use of a short protocol (2 days), which led to a high NPV of 96.7% in our population, with a favorable benefit-risk balance. Indeed, antibiotic exposition is limited with this protocol with a low impact on intestinal flora, and the limited number of patients who reacted during a subsequent treatment developed only a mild reaction. Using this protocol will lead to a decrease in the number of children falsely labeled as “penicillin-allergic,” associated with decreased antibiotic resistance, and direct impact on patients’ health.

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