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SHORT COMMUNICATION

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Positive drug provocation with beta-lactam antibiotics in children: A single test may not be enough

Luis Moral[a]*, Sara Latorre[b], Teresa Toral[a], Nuria Marco[c], Francisco Canals[d], María José Forniés[e], María Cristina González[e], Belén García-Avilés[f]

[a]*Pediatric Allergy and Respiratory Unit, Dr. Balmis General University Hospital, Alicante Institute for Health and Biomedical Research (ISABIAL), Alicante, Spain*
[b]*Pediatrics Department, Dr. Balmis General University Hospital, Alicante, Spain*
[c]*Pediatrics Department, Vega Baja Hospital, Orihuela, Spain*
[d]*Pediatrics Department, Elche General University Hospital, Elche, Spain*
[e]*Pediatrics Department, Elda General University Hospital, Elda, Spain*
[f]*Pediatrics Department, Sant Joan d'Alacant University Hospital, Sant Joan d'Alacant, Spain*

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Abstract
Background: Drug provocation tests (DPTs) are considered the gold standard for diagnosing beta-lactam allergy. However, positive results tend to be mild and difficult to interpret. This study aimed to describe pediatric patients with a presumedly positive or inconclusive DPT, assess the decision to repeat the DPT, and describe its outcome.
Methods: Retrospective review of all presumedly positive or inconclusive DPTs performed in six pediatric allergy clinics from 2017 to 2019. We describe the interpretation of results, focusing on the decision to repeat the DPT and its outcome.
Results: Of 439 children challenged with a beta-lactam, 26 (5.9%) with a presumedly positive or inconclusive result were included in this study. Most were girls (n = 16, 61.5%), and the median age was 5 years (range 1–13). The initial DPT used amoxicillin (n = 13, 50.0%), amoxicillin-clavulanic acid (n = 12, 46.2%), or cefadroxil (n = 1, 3.8%). Reactions were early (n = 11, 42.3 %), delayed (n = 14, 53.8 %), or not registered (n = 1, 3.8 %), but mild in all cases. A second confirmatory DPT was proposed in 19 patients (73.1%) and performed in 17 patients (65.4%). Nine DPTs were performed from 1 day to 4 months after the first DPT, and the remaining eight took place 6 months to 2 years later. Fifteen children tolerated the drug in the second DPT: 88.2% of those reevaluated and 57.5% of the whole study group.
Conclusion: The positive predictive value of DPT may be lower than expected. Given the mildness of observed reactions, a second confirmatory DPT is warranted within a few weeks or months.

***Corresponding author:** Luis Moral, Pediatric Allergy and Respiratory Unit. Dr. Balmis General University Hospital. C/Pintor Baeza, 12. 03010 Alicante. Spain. *Email address:* lmoralg@gmail.com

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Introduction

Beta-lactam antibiotics (BLAs) are the drugs most commonly associated with hypersensitivity reactions in children. The drug provocation test (DPT) is considered the gold standard for diagnosis and helps rule out an allergy to BLA in most pediatric patients, resulting in a very low prevalence of proven allergy.[1-3] BLA allergy delabeling has important implications for the patient.[4] However, protocols for performing the DPT are heterogeneous, and there is marked interobserver variability in the interpretation of results.[5,6] The negative predictive value of the DPT with BLA is considered high.[7] The positive predictive value is also assumed to be high, but this may be affected by differences in interpretation, the presence of false positive reactions, and the low prevalence of true BLA allergy. This study aimed to describe the clinical characteristics of pediatric patients with a presumedly positive or inconclusive DPT for BLA hypersensitivity, assess the decision to repeat the DPT, and describe its outcome.

Materials and Methods

This retrospective observational study investigated patients aged up to 15 years who attended any of the six participating pediatric allergy clinics from January 2017 to December 2019. Patients examined for suspected BLA hypersensitivity with positive or inconclusive DPT were included in the study. The study was approved by the hospital's research ethics committee. Data collected included details of age, gender, BLA involved, clinical features of the initial suspicious reaction, details of the first DPT (DPT-1), and results of the tests performed after DPT-1, including, if applicable, a second DPT (DPT-2). The DPT consisted of the oral administration of the suspicious BLA, usually in three incremental doses of 1/100, 1/10, and the full dose of the drug, with 1-hour intervals between doses. In some cases, the DPT was continued at the patient's home for one or more days, as determined by the prescribing physician. For this study, the DPT was considered positive when signs or symptoms potentially related to the DPT were observed, including cases in which such an association could be deemed inconclusive. Reactions observed within the first 2 hours following administration of the BLA were considered immediate, whereas those appearing afterward were considered delayed. Exanthem and urticaria type reactions following the DPT were grouped because some cases met overlapping characteristics for both. The studies conducted following the positive DPT were decided by the attending physician, with the informed consent of the patients and their parents. When a DPT-2 was proposed, it was considered early if performed within the first 6 months following the DPT-1, and late if performed at least 6 months after.

Results

During the study period, 505 patients were evaluated for suspected BLA hypersensitivity, and 439 (86.9%) underwent a DPT (Figure 1). Of these, 26 (5.9%) had

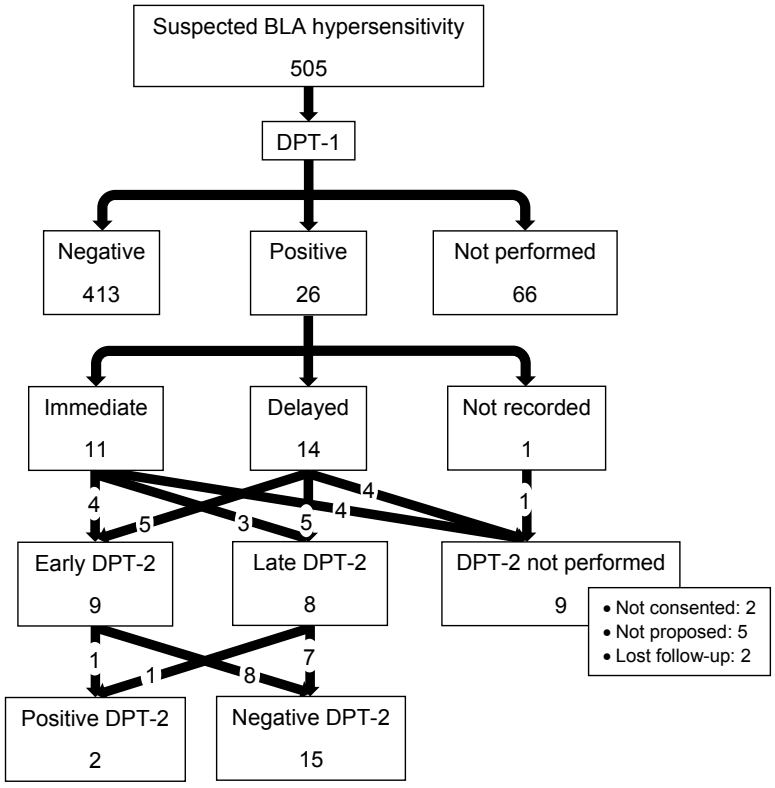

Figure 1 Flowchart of patients attended, drug provocation tests (DPT-1 and DPT-2) performed and outcomes.

a presumedly positive or inconclusive result and were enrolled in the study. Table 1 shows the main patient characteristics and reactions following the DPT. The patients' age ranged from 1 to 13 years (median 5), and most were girls (n = 16, 61.5%). The main reason for referral to the allergy clinic was the appearance of exanthem and/or urticaria/angioedema (n = 24, 92.3%) following administration of a BLA; no patient had anaphylaxis or other severe reactions. BLAs used for the DPT-1 were amoxicillin (n = 13, 50.0%), amoxicillin-clavulanic acid (n = 12, 46.2%), and cefadroxil (n = 1, 3.8%). Reactions following the DPT-1 were immediate in 11 patients (42.3%) (six with exanthem/urticaria, three with vomiting, and two with pharyngeal pruritus), delayed in 14 patients (53.8%) (all of them with exanthem/urticaria), and not recorded in one patient (3.8%). In all cases, the reaction observed was mild and easily resolved.

The flowchart of patients attended, DPTs performed, and outcomes is shown in Figure 1. Overall, a second DPT was performed in 17 of the 26 patients (65.4%), 15 of whom tolerated the BLA (88.2% of those reassessed with a DPT-2 and 57.7% of all the positive cases from DPT-1). Only two (11.8% of those reassessed with a DPT-2) had mild, delayed symptoms. An early DPT-2 was proposed in 11 patients, but it was only performed in 9 patients (two patients did not consent), yielding only one positive case (delayed exanthem). A late DPT-2 was proposed and performed in eight patients from 6 months to 2 years after DPT-1, again with only one positive case (delayed exanthem and vomiting). In five patients, the result of DPT-1 was taken as valid, and confirmatory tests were not considered. The remaining two patients did not attend the scheduled appointments. The results of DPT-2 in patients with immediate versus delayed reactions in DPT-1 (Table 2) were similar. Likewise, no differences were observed between patients for whom an early or a late DPT-2 was proposed. Disparate clinical decisions (regarding skin tests, specific IgE, frequency, and timing of DPT-2) after a positive DPT-1 were observed among the different pediatric allergy clinics (Table 1).

Discussion

As observed in other large pediatric series, only 5.9% of our patients who attended for suspected BLA allergy had a potentially positive DPT (1-3). However, more than half the patients with a positive or inconclusive DPT-1 tolerated the BLA in DPT-2, most of which were performed within 6 months of the DPT-1. These results challenge the positive predictive value of the DPT, which might be lower than usually assumed, which would in turn further reduce the true prevalence of hypersensitivity to BLAs in the pediatric population. We are aware of only three studies that conducted a DPT-2 with BLAs in pediatric patients, in all cases at least a year following the positive DPT-1, reporting tolerance in 50% to 89% of them.[3,8,9] Although the authors of these studies suggested a loss of hypersensitivity over time, none repeated the test at an early stage, which could lead to speculation regarding how many of those DPT-1 tests might have been false positives.

In adults, the main reason for a false positive in a DPT is the nocebo effect, which has been well characterized in blind, placebo-controlled challenges.[10-13] The nocebo effect can provoke not only subjective symptoms but also objective signs, mainly cutaneous. This effect is poorly documented in children and adolescents, but nocebo by proxy is another possibility to be considered.[14] In our series, two of the patients reported subjective symptoms and were not rechallenged, but probably they should have been. False positive reactions may also be due to the presence of pre-existing or concomitant symptoms or illnesses—usually cutaneous—which may concur, worsen, or become more apparent as a result of the special vigilance required for the test. However, there are limited reports of false positive drug-related reactions in pediatric patients.[15,16] It is often difficult to classify the result as positive or negative, and it is common to find mild, unspecific, inconclusive, or different reactions than the initially suspicious ones. In view of this, we have combined potentially positive and inconclusive results in this work, due to overlapping characteristics and inherently subjective classification of DPT results. Similar questions and problems to these have been considered regarding food challenges.[17-19]

Positive predictive values of diagnostic tests are known to be influenced by the prevalence of the tested condition in the population that is being tested.[20] Given the low prevalence of BLA hypersensitivity in children, the likelihood of a false positive DPT is significant for different reasons. Despite the limitations of our study, including its retrospective nature, small sample, and heterogeneous practices in participating clinics, we conclude that a positive BLA DPT should preferably be confirmed with a second DPT conducted within a few weeks or months. Since positive DPT rates for BLA are low, and reactions observed are rarely severe,[21] the excess work required to repeat the DPT may be largely compensated by the higher diagnostic accuracy and the potential for removing a false label and averting its negative consequences. Placebo-controlled tests may be a rare and last resort when the DPT is repeatedly inconclusive or a nocebo effect is suspected.

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Conflicts of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

Table 1 List of cases with description of studies performed and results.

Case	Sex, age†, and BLA involved	DPT-1: symptoms	Skin tests/specific IgE following DPT-1	Interval between DPTs, DPT-2 result
Clinic 1				
1	Female, 2, amoxicillin	Delayed exanthem	Not performed	4 months, NEGATIVE
2	Male, 2, amoxi-clav	Delayed exanthem	Not performed	1 month, NEGATIVE
3	Male, 3, cefadroxil	Immediate vomiting	Not performed	2 days, NEGATIVE
4	Female, 13, amoxicillin	Delayed exanthem	Not performed	1 month, NEGATIVE
5	Female, 13, amoxicillin	Immediate mild urticaria	Not performed	1 day, NEGATIVE
6	Female, 7, amoxi-clav	Immediate vomiting	Not performed	2 weeks, NEGATIVE
7	Male, 1, amoxicillin	Delayed generalized erythema	Weak positive prick test (3–4 mm) to PPL, MDM, and amoxi-clav. Negative to penicillin, amoxicillin, and cephalosporines Negative intradermal test (immediate and delayed) with all BLAs	Proposed in 2 months, but patient did not attend the test
Clinic 2				
8	Female, 2, amoxi-clav	Immediate vomiting	Not performed	1 month, NEGATIVE
9	Male, 13, amoxi-clav	Delayed exanthem and hand edema	Positive skin tests to amoxicillin (14 mm) and amoxi-clav (18 mm), late reading	Not proposed
10	Female, 5, amoxi-clav	Delayed urticaria	Negative skin tests	Patient fails to attend visit 1 year later
Clinic 3				
11	Male, 3, amoxicillin	Delayed urticaria	Negative skin tests and specific IgE	6 months, NEGATIVE
12	Female, 2, amoxicillin	Delayed pruritic exanthem	Negative skin tests and specific IgE	1 year, NEGATIVE
13	Male, 1, amoxi-clav	Immediate exanthem	Not performed	Patient fails to attend visit 1 month later
14	Female, 1, amoxicillin	Delayed exanthem	Negative skin tests and specific IgE	1 year, NEGATIVE
15	Female, 1, amoxicillin	Delayed urticaria	Negative skin tests and specific IgE	Proposed within 3 months, no consent
16	Female, 13, amoxicillin	Delayed urticaria	Negative skin tests and specific IgE	3 months, NEGATIVE
17	Female, 8, amoxicillin	Delayed localized erythema	Negative skin tests and specific IgE	1 year later, POSITIVE: pruritic exanthem in back and foot, and vomiting 3–4 hours after test
Clinic 4				
18	Male, 8, amoxicillin	Immediate urticarial exanthem	Negative skin tests and specific IgE	Not proposed
19	Female, 11, amoxicillin	Immediate pharyngeal pruritus	Not performed	Not proposed
20	Female, 11, amoxi-clav	Unspecified	Not performed	Not proposed
21	Male, 13, amoxicillin	Pharyngeal pruritus and immediate abdominal pain	Not performed	Not proposed
22	Male, 3, amoxi-clav	Delayed exanthem	Not performed	3 weeks, POSITIVE: generalized rash 8 hours after test
Clinic 5				
23	Female, 6, amoxi-clav	Immediate urticaria	Negative specific IgE	2 years later, NEGATIVE (amoxicillin)
24	Male, 1, amoxi-clav	Immediate palpebral edema	Not performed	Almost 2 years later, NEGATIVE (amoxicillin)
Clinic 6				
25	Female, 5, amoxi-clav	Immediate lip edema and sialorrhea	Negative skin tests and specific IgE	1 year, NEGATIVE
26	Female, 9, amoxi-clav	Delayed pruritic exanthem	Negative skin tests and specific IgE	6 months, NEGATIVE

† Age in years.

Amoxi-clav, amoxicillin with clavulanic acid; BLA, beta-lactam antibiotics; DPT-1, first drug provocation test; DPT-2 second drug provocation test; MDM, minor determinant mixture; PPL, penicilloyl-polylysine.

Table 2 Relationship between timing of reaction to DPT-1 and DPT-2 outcome, n (%).

DPT-2 outcome	Type of reaction in DPT-1	
	Immediate (n=11)	Delayed (n=14)
Positive	0 (0.0)	2 (14.3)
Negative	7 (63.6)	8 (57.1)
Patient refusal or nonattendance	1 (9.1)	3 (21.4)
Not proposed	3 (27.3)	1 (7.1)

Results from 25 patients are presented, excluding one case for whom the details of DPT-1 were not known and no DPT-2 was proposed.
DPT-1, first drug provocation test; DPT-2 second drug provocation test.

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