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Direct oral challenge for immediate and non-immediate beta-lactam allergy in children: A real-world multicenter study

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Abstract

Background: Allergy to beta-lactam antibiotics (BLA) is frequently suspected in children, but a drug provocation test (DPT) rules it out in over 90% of cases. Direct oral DPT (DODPT), without skin or other previous tests, is increasingly been used to delabel non-immediate BLA reactions. This real-world study aimed to assess the safety and effectiveness of DODPT in children with immediate and non-immediate reactions to BLAs.

Methods: Ambispective registry study in children (<15 years), attended between 2016 and 2023 for suspected BLA allergy in 15 hospitals in Spain that routinely perform DODPT.

Results: The study included 2133 patients with generally mild reactions (anaphylaxis 0.7%). Drug provocation test with the implicated BLA was performed in 2014 patients (94.4%): 1854 underwent DODPT (86.9%, including 172 patients with immediate

reactions). One hundred forty-five (7.2%) had symptoms associated with DPT, although only four reactions were severe: two episodes of anaphylaxis and two of drug-induced enterocolitis syndrome, which resolved rapidly with treatment. Of the 141 patients with mild reactions in the first DPT, a second DPT was considered in 87 and performed in 57, with 52 tolerating it without symptoms. Finally, BLA allergy was ruled out in 90.9% of the sample, confirmed in 3.4%, and remained unverified, usually due to loss to follow-up, in 5.8%.

Conclusions: Direct oral DPT is a safe, effective procedure even in immediate mild reactions to BLA. Many reactions observed in DPT are doubtful and require confirmation. Severe reactions are exceptional and amenable to treatment. Direct oral DPT can be considered for BLA allergy delabeling in pediatric primary care.

KEYWORDS
beta-lactam allergy, children, drug provocation test, safety

1 | INTRODUCTION

Suspected allergy to beta-lactam antibiotics (BLA) is a major health problem. About 5%–10% of the pediatric population has presented reactions suggestive of allergy, mainly skin rashes, related to the intake of an antibiotic.[1–5] Even in high-income countries, many of these patients are not adequately studied.[6] Children labeled as allergic to BLA are at risk of receiving less appropriate antibiotics and as a result, suffering side effects and having longer hospital stays.[7–13] From a community point of view, the use of second-line antibiotics may facilitate the emergence of bacterial resistance and increase healthcare costs.[14] Many adults with a penicillin allergy label acquired it in childhood, so its pernicious effects are prolonged throughout life.[15] Most reactions associated with the use of BLA appear during the course of treatment of an infectious disease, and they are usually mild and limited to the skin, in the form of a maculopapular rash or urticaria. Clearly immediate reactions, appearing within the first hour after taking the drug, are less frequent than late reactions, although reactions occurring up to 6 hours after taking the drug can be considered immediate.[16,17] Severe reactions that affect several organs or systems, whether immediate (anaphylaxis) or delayed (severe cutaneous adverse reactions, such as Stevens–Johnson syndrome or toxic epidermal necrolysis) rarely occur. Numerous studies have confirmed that an adequate study allows BLA-allergy delabeling in more than 90% of children with mild, immediate, and non-immediate reactions.[18,19] Many of these reactions may indeed result from the interaction between a viral infection, the drug, and a genetically predisposed host immune system, and be transient in nature.[20]

Although many patients are not referred for testing, suspected BLA allergy accounts for about 10% of patients seen in pediatric allergy clinics.[21] However, the cost associated with this care is offset by the high percentage of patients in whom it is ruled out.[22–24] No patient with suspected BLA allergy should be deprived of an adequate, cost-effective study that can benefit both them and the community.[25,26]

Key Message

This real-world, multicenter study reporting data from more than 2000 children confirms that direct oral drug provocation test is a safe and effective procedure for beta-lactam allergy (BLA) delabeling, even in immediate mild reactions. Severe responses to the test are exceptional (0.2%) and amenable to treatment. Many reactions observed in drug provocation tests are doubtful and require confirmation. These results reinforce the notion that direct oral drug provocation tests could be performed in non-specialized and primary care settings in most patients without risk factors, which would facilitate the convenient delabeling of BLA allergy in a larger number of children.

The study of BLA allergy has evolved over time.[27] Beta-lactam antibiotics anaphylaxis became very rare after the introduction of oral amoxicillin (AX) and the reduction in the use of parenteral penicillin.[28–30] Nevertheless, many guidelines still recommend a stepwise study starting with in vitro and skin tests. Negative results should then be verified with a drug provocation test (DPT), considered the gold standard for ruling out BLA allergy.[31–34] However, real-world practice varies widely between centers.[22,35] The possibility of performing a direct oral drug provocation test (DODPT) in low-risk children, without prior skin or other tests, was first proposed in Europe in the early 2010s.[36,37] Since then, an increasing number of studies have confirmed the usefulness and safety of this procedure in selected patients,[18,38] especially in the predominant group of children with mild, non-immediate skin reactions, whom current guidelines consider suitable candidates for DODPT,[16,17] reducing the inconvenience and costs of the procedure.[25,39] Although some controversy persists about the benefit of skin tests in the smaller group of children with immediate reactions, Mill et al.'s study of DODPT in

children with suspected AX allergy, including cases with a history of immediate reactions, suggests that DODPT could be performed in all patients with non-severe reactions, regardless of the time elapsed since intake.[40,41] Thus, this study aimed to assess the safety and effectiveness of DODPT for both immediate and delayed reactions to BLA in real-world clinical practice.

2 | METHODS

This ambispective, multicenter study collected data from a cohort of children seen in the specialized pediatric allergy units of the participating hospitals from November 2016 to March 2023. Children who presented with any suspected allergic reaction related to the administration of any BLA before the age of 15 years, or those in whom BLAs were avoided due to suspected allergy for any other reason, were included.

Case registration was initiated at the main study center, General University Hospital Dr. Balmis (Alicante, Spain), and at several nearby hospitals as they adopted the same updated protocol for studying children with suspected BLA allergy. Specifically, these clinical guidelines were revised in November 2016 to recommend the performance of DODPT in children presenting a non-severe, immediate, or non-immediate presumed allergic reaction over the course of oral BLA treatment. Over the following years, the rest of the participating hospitals were incorporated into the study, on the condition that pediatric patients with suspected non-severe reactions after administration of a BLA were generally studied by means of DODPT. In the case of patients with severe immediate reactions (anaphylaxis), or severe non-immediate cutaneous or systemic reactions (including Stevens–Johnson syndrome, toxic epidermal necrolysis, drug hypersensitivity syndrome/drug reactions with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis), or in episodes related to the administration of a BLA for parenteral use only, our guidelines call for an individualized case assessment and study, which might include skin tests (prick and/or intradermal tests with the involved BLA and/or other BLAs, or major and minor determinants of penicillin) or in vitro tests, at the discretion of the attending physician. Tests prior to DPT are also allowed in patients with mild skin reactions, if deemed appropriate based on the patient's or the family's individual circumstances. Before DPT, and regardless of the performance of other complementary tests, the parents must receive an adequate explanation of the study to be performed and sign their written informed consent. The mode and duration of DPT, performed at the hospital for 1 day, or continued at home over several days, are at the discretion of the attending physician. If no reaction attributable to the DPT is observed, allergy can be ruled out. If signs or symptoms possibly related to the test are observed, the attending physician defines the test result as either positive (drug allergy confirmed) or equivocal, and make the decision as to whether to repeat or extend the study to verify the doubtful result or to ensure tolerance to alternative BLA. Diagnosis of BLA allergy is also confirmed if skin or in vitro tests were positive and a DPT was then excluded.

Patient data were prospectively recorded in a database created for this study by completing the fields of a form that elicited no identifying patient data. In hospitals that joined the study late, retrospective collection of patient data was also allowed if they had been attended in the previous year, according to the same criteria as those recorded prospectively. The variables collected on the form are detailed in Table S1. In this study, only reactions occurring within the first hour after BLA administration were considered immediate.

Categorical variables are presented as frequencies (*n*) and percentages (%), and quantitative variables as the median and interquartile range (IQR). The Kolmogorov–Smirnov test was used to assess the normality of the distribution. The χ^2 test was used to compare categorical variables between groups, and the Mann–Whitney *U* test to compare continuous variables. All statistical analyses were carried out using SPSS V.22.0 (IBM Corp). *P* values of less than .05 were considered statistically significant.

The General University Hospital Dr. Balmis Ethics Committee approved the study, and this decision was endorsed by the ethics committees of all participating hospitals.

3 | RESULTS

Data were obtained from 2133 patients attended in 15 hospitals. No patient was excluded due to the presence of severe conditions or concomitant medications that could impede DPT performance. Table 1 summarizes the main characteristics of the patients included in the study, the suspected reactions and the drugs involved. The sample was predominantly made up of very young children: 41.0% of the patients were aged 1–3 years, and 63.1% were aged 1–6 years. AX, alone or associated with clavulanic acid (AX/C), was implicated in 2029 patients (95.1%). Differences between reactions occurring within 15 min and 15–60 min after BLA administration were minimal, so these data were pooled for analysis. Only 14 patients (0.7%) had symptoms suggestive of anaphylaxis; these patients are described in Table 2. Patients with a history of anaphylaxis were older (median 10 years vs. 4 years; $p < .001$), and anaphylaxis was more frequent among those who had the reaction in the first hour after drug administration (4.6% vs. 0.1%, $p < .001$), or related to parenteral BLA administration (9.4% vs. 0.5%, $p < .001$). Only one patient had a severe non-anaphylactic reaction (Stevens-Johnson syndrome) related to AX/C administration and underwent DPT with an alternative BLA, oral cefuroxime for 4 days, which was well tolerated.

Specific IgE against BLA were determined in 140 patients (6.6%). In 76 of these, this assay was requested by the pediatric allergist at the consultation (3.6%) while in the remaining 64, it was requested by another physician, generally their primary care pediatrician. Only one of the 140 patients had penicillin-specific IgE values higher than 0.35 kU/L, in whom the diagnosis was considered confirmed without performing DPT. BLA skin tests were performed in 193 patients (9.0%): in 153 before DPT and in 40 after positive or equivocal DPT. Skin tests were positive in 12 patients (6.2% of all those tested, Table 3): 7 of the 153 who were tested before DPT (4.6%) and 5 of

TABLE 1 Characteristics of included patients, suspected reactions, and beta-lactam antibiotics (BLA) involved ($N = 2133$).

Variable	*n* (%)[a]
Age in years, median [interquartile range]	4 [2–8]
Male sex	1092 (51.2%)
<1 year since the (last) reaction	1347 (63.2%)
Dose that coincided with the reaction	
First dose	306 (14.3%)
First day of treatment, but not first dose	321 (15.0%)
Second day of treatment	347 (16.3%)
After second day of treatment	781 (36.6%)
After the end of treatment	242 (11.3%)
Not remembered	128 (6.0%)
Others[b]	8 (0.4%)
Time elapsed between dose and reaction	
<15 min	65 (3.0%)
15–60 min	173 (8.1%)
1–2 h	235 (11.0%)
2–24 h	1040 (48.8%)
>24 h	143 (6.7%)
Unknown	477 (22.4%)
More than 1 episode with any BLA[c]	266 (12.5%)
Same BLA	214 (10.0%)
Different BLAs	60 (2.8%)
Type of reaction observed	
Anaphylaxis	14 (0.7%)
Typical urticaria/angioedema	660 (30.9%)
Looks like urticaria, but not typical	153 (7.2%)
Maculopapular rash	1072 (50.3%)
Serum sickness-like reaction (vasculitis/arthritis)	17 (0.8%)
Other ill-defined rashes: cutaneous, mucosal or angioedema	104 (4.9%)
Gastrointestinal manifestations	11 (0.5%)
Other nonspecific manifestations[d]	6 (0.3%)
Stevens-Johnson syndrome	1 (0.05%)
Unknown	95 (4.5%)
Parenteral route of administration	32 (1.5%)
Antibiotic involved[e]	
Amoxicillin	1321 (61.9%)
Amoxicillin-clavulanic acid	749 (35.1%)
Penicillin (G or V)	30 (1.4%)
Ampicillin	4 (0.2%)
Cloxacillin	2 (0.1%)
Piperacillin-tazobactam	1 (0.05%)
Any cephalosporin	93 (4.4%)
Cefixime	34 (1.6%)
Cefuroxime	34 (1.6%)
Cefaclor	10 (0.5%)
Ceftriaxone	6 (0.3%)
Cefotaxime	4 (0.2%)
Cefadroxil	4 (0.2%)
Cefazolin	1 (0.05%)
Cefminox	1 (0.05%)
Tolerated any BLA after the suspected reaction	269 (12.6%)
Same suspected BLA	17 (0.8%)
Amoxicillin, after suspected reaction with amoxicillin-clavulanic acid	37 (1.7%)
Different BLA	215 (10.1%)

[a]Unless otherwise noted.

[b]4 patients avoided BLA because of family history and/or previous positive skin tests, 2 appeared to have had some skin manifestation in the course of the disease before starting BLA treatment, 1 case had had a reaction during BLA treatment by the mother during breastfeeding, and 1 case did not take BLA because of urticaria on skin contact with BLA.

[c]Some patients have more than one episode with the same and with different BLAs, so the number of patients does not match the sum of cases with the same and with different BLAs.

[d]Convulsion, hypotonia, pallor, tremor, dyspnea, pharyngeal pruritus, palatal pruritus, ocular pruritus, and lacrimation.

[e]Some patients have more than one BLA involved, so the sum of antibiotics involved does not match the number of patients.

the 40 who were tested afterwards (12.5%). Altogether, the attending pediatric allergist ordered specific IgE tests and/or skin tests in 177 patients (8.3%), and this was followed by a DPT in 160 of them (Figure 1). Significant variability ($p < .001$) in the pretesting rate was observed between participating centers, ranging from 2.0% to 20.9%. Significantly more pretests ($p < .001$) were performed in children who: were older (median 8 years vs. 4 years), had the reaction after the first dose of treatment (18.3% vs. 6.6%), presented immediate reactions (24.8% vs. 7.3%), experienced two or more suspected episodes (15.0% vs. 6.6%), had anaphylaxis (85.7% vs. 7.8%) or serum sickness-like illness (35.3% vs. 7.9%), had typical episodes of urticaria versus maculopapular rashes (10.9% vs. 5.2%), received the BLA parenterally (43.8% vs. 7.8%), and presented a reaction related to a penicillin other than AX or AX/C (32.4% vs. 7.8%).

A total of 2014 patients (94.4%) underwent 2040 DPTs with the drug(s) involved in their reaction(s) (Figure 1): 1251 DPTs were performed with AX, 688 with AX/C, and 101 with other BLAs (penicillins and cephalosporins). These patients included six whose initial reaction was associated with AX/C but who showed tolerance to AX alone on DPT and did not receive the DPT with AX/C. The provocation test was performed intravenously in three patients, one with cefazolin and two with ceftriaxone, with no reactions observed in any of them. Table 4 summarizes the number of patients according to the performance of DPT and its outcome. Of the 2014 patients undergoing DPT, 1854 received a DODPT (92.1% of those undergoing DPT and 86.9% of the total cohort), including 172 patients with a history of immediate reaction in the first hour after BLA intake.

TABLE 2 Patients reporting symptoms of anaphylaxis related to the administration of a beta-lactam antibiotic (BLA).

Case	Sex	Age at: anaphylaxis–allergy evaluation	Risk factors	Timing of the reaction	Previous episodes	Route	Culprit BLA	Index reaction	S-IgE and skin tests	DPT	Conclusion
1	F	11 y–11 y	No	<15 min after 1st dose	Age 1 y, urticaria with AX-clav	Oral	AX-clav	Urticaria and bronchospasm treated with adrenaline and salbutamol	S-IgE <0.35 kU/L Intradermal AX and AX-clav 0 mm, cefuroxime 3 mm	Negative for AX-clav and cefuroxime	No allergy
2	M	14 y–14 y	No	15–60 min, 1st day (2nd dose)	No	Oral	AX-clav	Urticaria, malaise and chest tightness treated with corticosteroids and antihistamine	S-IgE <0.35 kU/L Negative skin tests	AX-clav not performed (medical decision). Negative for cefaclor and cefuroxime	Unresolved
3	F	3 y–8 y	Asthma and allergic rhinitis	15–60 min after the 1st dose	No	Oral	AX	Urticaria, angioedema and respiratory distress, treated with corticoid and antihistamine	S-IgE <0.35 kU/L Skin tests not performed	Negative for AX	No allergy
4	M	1 y–7 y	Allergic rhinitis, atopic cough, multiple food allergies	After 2nd day of treatment, timing not remembered	2 episodes of asthma exacerbation in the 1st year of life related to AX	Oral	AX-clav	Asthma exacerbation	S-IgE and skin tests not performed	Negative for AX-clav	No allergy
5	M	6 y–12 y	Allergic rhinitis	1–2 h after the 1st dose	Similar episode to index reaction with AX at age 5 y	Oral	AX-clav	Urticaria, angioedema and vomiting	S-IgE not performed Negative skin tests	Negative for AX-clav	No allergy
6	M	9 m–8 y	Asthma, atopic dermatitis, and egg allergy	15–60 min after the 1st dose	No	Oral	AX	Urticaria, angioedema and vomiting, treated with adrenaline, corticosteroids and, possibly, nebulized salbutamol	S-IgE <0.35 kU/L Skin tests not performed	AX not performed (family refuses) Negative for cefuroxime and penicillin V	Unresolved
7	M	12 y–12 y	Allergic rhinitis and strawberry allergy	15–60 min, 1st day but not the 1st dose	No	Oral	AX	Urticaria, angioedema and respiratory distress treated with corticosteroids and antihistamine	S-IgE <0.35 kU/L Skin tests not performed	Negative for cefuroxime, penicillin, and then AX	No allergy

(Continues)

TABLE 2 (Continued)

Case	Sex	Age at: anaphylaxis–allergy evaluation	Risk factors	Timing of the reaction	Previous episodes	Route	Culprit BLA	Index reaction	S-IgE and skin tests	DPT	Conclusion
8	M	13 y–13 y	Asthma and allergic rhinitis	30 min after the 1st dose	No	Oral	AX	Urticaria and respiratory distress treated with salbutamol	S-IgE not performed Negative intradermal with AX and cefuroxime. After AX DPT: BAT positive for AX and benzylpenicillin; negative for clav and cefuroxime	Anaphylaxis with AX, treated with salbutamol and antihistamine. Negative for cefuroxime	Allergy to AX
9	M	12 y–12 y	No	<15 min after 1st dose	No	IV	AX-clav (after 2 days on oral AX)	Urticaria, angioedema and bronchospasm, treated with adrenaline, corticosteroids, and antihistamine	S-IgE <0.35 kU/L Negative skin tests BAT positive to clav	AX-clav not performed (medical decision). Negative for cefuroxime and AX	Allergy to clav
10	M	8 y–9 y	No	≈ 60 min, 1st day but not the 1st dose	No	Oral	AX	Urticaria, angioedema and respiratory distress, treated with adrenaline and salbutamol	S-IgE <0.35 kU/L (previously ordered by his primary care pediatrician) Skin tests not performed	AX-clav not performed (medical decision). Negative for cefixime	Unresolved
11	F	13 y–13 y	Asthma and allergic rhinitis	<15 min after 1st dose	Age 12 y, urticarial rash after 7 days on AX-clav	IV	Cloxacillin	Dyspnea, throat and chest tightness, mild rash, treated with adrenaline and corticosteroids	S-IgE not performed Intradermal AX-clav and cloxacillin negative. BAT negative for AX, benzylpenicillin and clav. TTL positive for clav negative for AX and benzylpenicillin	Cloxacillin not performed (medical decision). Negative for cefuroxime	Unresolved
12	F	4 y–4 y	Asthma and atopic dermatitis	15–60 min after the 1st dose	No	Oral	AX	Urticaria and possible respiratory distress	S-IgE not performed Intradermal AX negative	Negative to AX	No allergy

TABLE 2 (Continued)

Case	Sex	Age at: anaphylaxis–allergy evaluation	Risk factors	Timing of the reaction	Previous episodes	Route	Culprit BLA	Index reaction	S-IgE and skin tests	DPT	Conclusion
13	F	7 y–9 y	Genitourinary malformation with persistent cloaca	15–60 min after the 1st dose	No	IV	Ceftriaxone	Perioperative episode of facial edema, bronchospasm, hypotension and oxygen desaturation	S-IgE not performed Intradermal cefotaxime, ceftazidime and aztreonam positive (ceftriaxone not tested)	Ceftriaxone not performed (medical decision). Negative for cefuroxime and cefixime	Allergy to ceftriaxone
14	M	5 y–5 y	Asthma and atopic dermatitis	More than 2 hours after the 2nd dose	No	Oral	AX-clav	Urticaria, angioedema and bronchospasm, treated with adrenaline, salbutamol and antihistamine	S-IgE not performed Indeterminate intradermal test with AX-clav, clav and cefotaxime; negative intradermal with penicillin, ampicillin and cefuroxime.	Negative for AX-clav	No allergy

Abbreviations: AX, amoxicillin; BAT, basophil activation test; clav, clavulanic acid; DPT, drug provocation test; F, female; IV, intravenous; M, male; m, months; S-IgE, specific IgE against beta-lactams; y, years.

TABLE 3 Description of patients with positive skin tests.

Sex and age	Suspected reaction	DODPT	Tests before DPT	DPT after skin tests	Results
Patients with skin tests performed before DPT					
Male, 9 years	Urticaria/angioedema within 15 min after administration of intravenous AX/C, occurring >1 year before study	No	Specific IgE <0.35 kU/L. Intradermal test negative to AX but immediate positive to AX/C	DPT AX, 1 day: immediate pharyngeal, facial and arm pruritus. Subsequent DPT with cefuroxime tolerated	Allergy to AX/C by positive skin test and DPT
Male, 11 years	Maculopapular rash 1–2 h after oral intake of AX/C, occurring <1 year before study	No	Delayed positive intradermal tests to AX, AX/C and clavulanic acid	DPT not performed with involved BLA, but negative to cefuroxime	Allergy to AX/C by positive skin tests
Male, 12 years	Maculopapular rash >2 h after administration of AX and of AX/C occurring <1 year before the study	No	Delayed positive intradermal tests to clavulanic acid, but negative to AX	Negative DPT with cefuroxime, then negative DPT with AX	Allergy to clavulanic acid by positive skin tests with tolerance to AX
Female, 12 years	Maculopapular rash >2 h after administration of AX/C occurring >1 year before the study	No	Immediate positive intradermal test to PPL. Specific IgE <0.35 kU/L	Negative DPT with cefuroxime, then negative 6-day DPT with AX/C	No allergy by negative DPT
Male, 7 years	Maculopapular rash 1–2 h after oral intake of AX/C, occurring <1 year before the study	No	Delayed positive intradermal tests to clavulanic acid, but negative to AX	Negative 2-day DPT with AX	Allergy to clavulanic acid by positive skin tests and tolerance to AX
Female, 11 years	Urticaria/angioedema more than 2 h after administration of AX/C, on more than one occasion, occurring <1 year before the study	DPT with 1 dose of AX/C after immediate negative skin test reading, but before late reading, resulting in an itchy rash after 24 h of intake	Delayed positive intradermal tests to clavulanic acid, but negative to AX	Negative DPT with AX	Allergy to clavulanic acid by positive DPT and skin test, with tolerance to AX
Female, 9 years	Perioperative anaphylaxis <1 h after intravenous administration of ceftriaxone <1 year ago	No	Immediate positive intradermal tests to cefotaxime, ceftazidime and aztreonam (ceftriaxone not skin tested)	Negative DPT with cefuroxime and with cefixime	Allergy (anaphylaxis) to ceftriaxone with positive skin tests
Patients with skin tests performed after a positive or doubtful DPT					
Male, 13 years	Unspecified reaction after AX/C; administration <1 year before the study	AX/C, maculopapular rash after 2 days of administration	Specific IgE <0.35 kU/L. Delayed positive intradermal tests to AX and AX/C	Negative DPT with cefuroxime	Allergy to AX/C by positive DTP and skin tests
Female, 9 years	Maculopapular rash >2 h after oral intake of AX/C, occurring <1 year before the study	AX/C, maculopapular rash after 3 days of administration	Delayed positive intradermal test to clavulanic acid, but negative to AX	Negative DPT with cefuroxime. Then negative DPT with AX	Allergy to clavulanic acid by DPT and skin test
Female, 4 years	Maculopapular rash >2 h after oral intake of AX/C, occurring <1 year before the study	AX/C, mild pruritus and maculopapular rash after 2nd dose administered at home	Delayed positive intradermal test to clavulanic acid, but negative to AX	Negative DPT with AX	Allergy to clavulanic acid by positive DPT with tolerance to AX

TABLE 3 (Continued)

Sex and age	Suspected reaction	DODPT	Tests before DPT	DPT after skin tests	Results
Male, 8 years	Urticaria/angioedema >2 h after administration of AX and of AX/C, occurring <1 year before the study	AX, late itchy generalized maculopapular rash after 1 dose	Delayed positive intradermal test to AX/C and to clavulanic acid (AX not tested)	Negative DPT with cefuroxime	Allergy to AX by positive DPT
Male, 1 year	Maculopapular rash >2 h after oral intake of AX, occurring <1 year before the study	AX/C, late intense erythroderma and mild pruritus after 1 dose	Positive prick test (3–5 mm) to PPL, MDM and AX/C; negative to penicillin, AX and cephalosporins	DPT with amoxicillin not performed due to lost follow-up	Allergy to AX/C by positive DPT

Abbreviations: AX/C, amoxicillin with clavulanic acid; AX, amoxicillin; DODPT, direct oral drug provocation test; DPT, drug provocation test; MDM, minor determinant mixture; PPL, penicilloyl polylysine.

Of the 1975 patients with available data, the DPT was performed on a single day in 939 children (47.5%), over 2 days in 338 (17.1%), 3–4 days in 232 (11.7%), 5 days in 371 (18,8%), and 6 to 10 days in 95 (4.8%). The duration of DPT varied widely among participating centers, reflecting local practices, but it was also significantly longer in patients with delayed reactions (in days of treatment before the reaction and/or in time from last dose to reaction), whereas the DPT was shorter in children who had a reaction immediately or in the first 1–2 days of treatment. The tests were also longer in those receiving AX alone than with AX/C or other BLAs.

Of the 2014 patients undergoing a DPT, 1863 tolerated the involved drug (87.3% of the total cohort and 92.5% of those who underwent DPT). Seven of these had a second suspected BLA to cephalosporins, which were not studied with a DPT; this suspicion was ruled out in two cases after reviewing the clinical history, and in the other five, the suspicion remained unverified. Signs or symptoms related to the DPT were observed in 145 (7.2%) children, but only four had a severe reaction (3 of them after a DODPT): two had episodes of anaphylaxis and two episodes compatible with drug-induced enterocolitis syndrome (Table S2). The remaining 141 patients had mild reactions that resolved without treatment or with antihistamines and/or oral corticosteroids, generally consisting of maculopapular, urticarial, or mixed rashes, mostly with delayed onset. A few patients also presented other manifestations such as joint swelling, vomiting, rhinoconjunctivitis, and cutaneous or oropharyngeal pruritus. In 87 (60.0%) patients with DPT-associated symptoms, the manifestations were equivocal (including three patients with lesions suggestive of mosquito bites), prompting proposal of a second DPT (Table 4). This DPT was performed in 57 patients (39.3% of those who had clinical manifestations in the initial DPT): 52 tolerated it without symptoms, while 5 again had mild skin reactions. In the other 30 patients, the DPT was not repeated, mainly due to the family's refusal or loss to follow-up. In the remaining 58 patients with a positive DPT, no confirmatory test was deemed necessary for a definitive diagnosis (Table 4).

Only 119 patients (5.6%) did not undergo DPT with the implicated drug (Table 4). The test was considered unnecessary in 23 because allergy was ruled out by the clinical history (generally because the drug had been tolerated after the supposed reaction). In 71, DPT was proposed, but the family refused or did not come to the follow-up visits, while in 16 patients, the physician ruled out DPT, generally because the episodes were severe or involved parenteral drugs, and a DPT with an alternative BLA was performed. In nine other patients, allergy was diagnosed without DPT: two had a new reaction after treatment with BLA despite a previous negative DPT, one presented an elevated specific IgE value, four had a positive skin test, and two had a positive basophil activation test.

Altogether, allergy to the implicated BLA was ruled out in 1938 patients (90.9% of the total cohort, 96.4% of those who completed the study): 1915 by negative DPT and 23 by clinical history (Figure 1 and Table 4). The diagnosis of BLA allergy was verified in 72 patients (3.4%): 63 by positive DPT and nine by other means. The diagnosis of BLA allergy could be neither verified nor ruled out

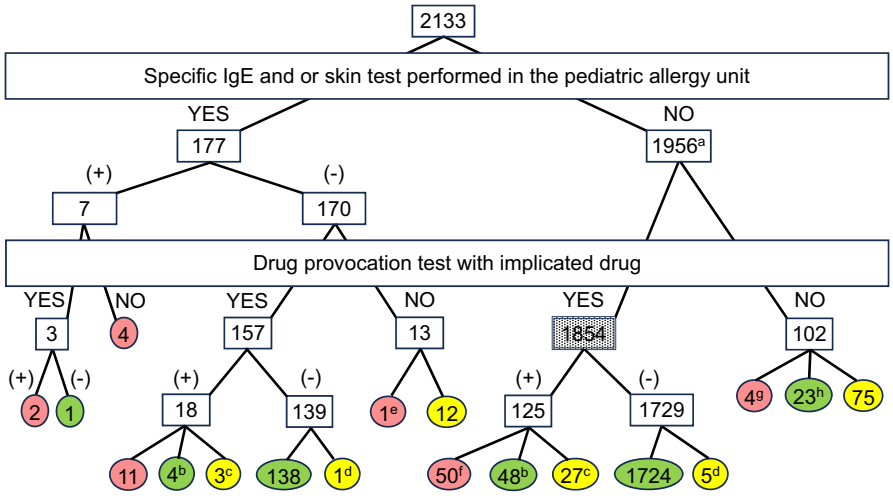

FIGURE 1 Simplified flowchart of patients attended according to the performance of DPT, with or without prior specific IgE and/or skin tests ordered in the pediatric allergy unit, and its outcomes. Patients receiving a DODPT ($n=1854$) are highlighted in a shaded square. Patients with a drug allergy diagnosis ($n=72$) are marked in red, patients with demonstrated drug tolerance ($n=1938$) in green, and those with unproven drug tolerance ($n=123$) in yellow. [a]Includes 53 patients with a specific IgE test ordered by another physician before being attended at the pediatric allergy unit: 49 had a DODPT performed, and 4 did not, including 1 patient with a positive test (>0.35 kU/L). [b]Patients with a first equivocal DPT and a second negative DPT performed. [c]Patients with a first equivocal DPT and a second DPT proposed but not performed. [d]The initial reaction was associated with AX/C, but DPT was performed (and passed) with AX but not with AX/C. [e]Diagnosis confirmed by a positive basophil activation test (BAT) (patient 9 in Table 2). [f]Includes 5 patients with a first equivocal DPT and a second positive DPT performed. [g]1 patient diagnosed by a positive specific IgE test ordered before referral to the pediatric allergy unit, 1 patient diagnosed by a positive BAT and 2 patients diagnosed due to a new reaction after treatment with BLA despite a previous negative DPT. [h]Allergy ruled out by clinical history.

TABLE 4 Classification of patients according to the performance of DPT and its result ($n=2133$).

BLA allergy study	*N* (%)	Result
DPT performed	2014 (94.4%)	
Tolerates drug in DPT[a]	1863 (87.3%)	Demonstrated tolerance
Tolerates AX but reaction had been with AX/C	6 (0.3%)	Tolerance not proven
Any sign or symptom associated to DPT	145 (6.8%)	
Considered for repeating DPT	87 (4.1%)	
• Tolerates BLA at second DPT	52 (2.4%)	Demonstrated tolerance
• Does not tolerate BLA at second DPT	5 (0.2%)	Diagnosed allergy
• Second DPT not performed	30 (1.4%)	Tolerance not proven
Second DPT not proposed	58 (2.7%)	Diagnosed allergy
DPT not performed	119 (5.6%)	
Allergy ruled out by clinical history	23 (1.1%)	Demonstrated tolerance
Allergy diagnosed without DPT (see text)	9 (0.4%)	Diagnosed allergy
Physician rules out DPT	16 (0.8%)	Tolerance not proven
Family refuses or does not come for DPT	71 (3.3%)	Tolerance not proven

[a]Among this group there were 5 patients with another suspected BLA allergy (cephalosporin) that was not studied by DPT, leaving tolerance unproven for the cephalosporin.

in 123 patients (5.8%): Six cases with a suspected reaction to AX/C because the DPT was performed with AX alone, 16 cases because the physician ruled out the DPT or it could not be performed with the drug involved and was performed with an alternative drug, 71 patients because of refusal or loss to follow-up and 30 patients because a DPT that had presented a doubtful result could not be repeated. In five patients with negative DPT, a cephalosporin allergy was also suspected but not tested. There was very strong association ($p<.001$) between diagnosis of allergy and older age (median 7 years vs. 4 years; a diagnosis of allergy was confirmed in 2.3% of children 0–6 years old but in 5.4% of children ≥7 years old), two or more episodes with the same drug (11.9% vs. 2.7%) or

with different BLAs (15.8% vs. 3.2%), and a history of anaphylactic reaction (30.0% vs. 3.5%). The type of rash was also significantly associated ($p < .001$) with a confirmed diagnosis (percentage of confirmed diagnoses: maculopapular exanthema 2.4%, non-typical urticaria 3.4%, typical urticaria/angioedema 5.1%, serum sickness-like reaction 20.0%). Original reactions occurring in the first 2 h after the administered dose had more commonly confirmed BLA allergy (6.0% vs 3.3%; $p = .01$). No significant association was observed with the rest of the variables recorded in our study, including the duration (in days) of DPT, even when breaking down immediate and delayed reactions.

4 | DISCUSSION

This study provides data from the largest cohort of children studied for suspected BLA allergy. Our patients are similar to those seen in other large published series in terms of the predominance of young children, who mostly presented with mild skin reactions while taking AX or AX/C.[40,42–48] Most patients underwent DODPT (86.9% of the total), including 172 children with a history of clearly immediate reactions, which few previous studies have described.[40,42,44] Other tests were requested prior to DPT in only 177 patients (8.3%), conditioned both by the usual practice in the different centers and by some patient factors, such as age, immediacy and severity of the reaction, or history of more than one suspected episode. However, a positive result was obtained in only seven previous skin tests and in only one specific IgE determination, which confirms their poor performance and doubtful positive predictive value.[31,49] As in most of the published pediatric series, our results showed tolerance to the drug involved in most cases (90.9%), while allergy was confirmed in only 3.4% and unverified in the remaining 5.8%. The probability of proving BLA allergy was higher in children with older age, more than one suspected episode, anaphylactic reactions, parenteral administration of BLA, and in immediate and serum sickness-like or urticarial reactions.

A major contribution of this study is the confirmation of the safety of DODPT in real-world conditions in a large number of patients in different centers, including children with a history of immediate reactions. DPT was also performed in eight patients with a history of anaphylaxis, resulting positive in only one. The test was safe even in patients with positive skin tests or a previous positive DPT. Only 4 of the nearly 2000 patients who underwent DPT (0.2%) had a severe reaction, which resolved adequately with treatment and just required several hours of monitoring, with only one overnight hospital admission. In two of these patients, the manifestations were suggestive of drug-induced enterocolitis syndrome, which is being increasingly reported since the first description in 2014.[50–54] The safety of DPT has been widely confirmed in recent studies,[19,55,56] and the newest guidelines recommend DODPT for children with a history of mild skin reactions (morbilliform rashes and urticaria) regardless of whether they were immediate or not.[17]

Our study has some limitations. Its multicenter, real-world design entailed a marked variability on some important details, such as the frequency of pre-DPT testing as well as the duration of DPT. The latter is a matter of some controversy, with discordant opinions and results in different publications.[57–59] In our study, as in others, we did not observe that the duration of the DPT appreciably influenced the results. Another important limitation, common to most studies of this type, is related to the quality of the data, generally obtained from parents, who often do not remember the exact type of reaction or the time elapsed between the treatment and the suspected reaction. The differentiation between immediate and non-immediate reactions can be arbitrary, both in the time of onset (between 1 and 6 h) and in their characteristics.[60] If the delineation between immediate and delayed reactions is not well defined, the report obtained from the parents can be uncertain, but DPT is equally safe in children with immediate and non-immediate mild reactions, DODPT seems the best option for all mild suspected reactions, regardless of the temporality. Another important limitation in our study—often overlooked in other series—is the absence of criteria for DPT positivity. The positive predictive value of open DPT has recently been called into question and may be lower than generally accepted.[61] In our study, clinical manifestations were observed during DPT in 145 patients, but the vast majority were mild and often equivocal, prompting the consideration of a second DPT on more than half of the occasions. Most of the patients who repeated the test tolerated the implicated drug well, while DPT was positive in only 8.8% of these cases. This finding calls into question the results of many of the tests that presented mild manifestations but were not verified with a new DPT, as well as the results of the published studies that do not specify how many of the reactions observed in the DPT were doubtful and how many DPTs were repeated.[62] Another limitation is the relevant proportion of patients (5.8%) who did not complete the study and in whom the result could not be verified, most of them due to refusal or loss to follow-up. Presumably, most would have tolerated BLA if the pending DPT had been performed, so that the prevalence of confirmed allergy to BLA could be less than 4% of the total cohort. Finally, another limitation of our study is the relatively low number of patients with immediate reactions, or with other BLAs different from amoxicillin (cephalosporins or other penicillins).

In conclusion, our study confirms the safety of DODPT and its effectiveness in ruling out BLA allergy in children with a history of mild reactions, including those that were immediate, with allergy confirmed in less than 5% of the patients. Most reactions observed during DPT are mild or equivocal, and repeat testing should be considered for confirmation. Very few reactions were severe, but all resolved adequately with the treatment administered, and only one required overnight hospitalization. These results open the door to considering performance of DODPT in non-specialized and primary care settings in most patients without risk factors, which would facilitate the delabeling of BLA allergy in a larger number of children, with important benefits for patients, their families, and health systems.[63,64]

AUTHOR CONTRIBUTIONS

Luis Moral was involved in conceptualization (lead), data curation (lead), formal analysis (lead), funding adquisition (lead), investigation (equal), supervision (lead), validation (lead), writing—original draft preparation (lead), and writing—review & editing (equal). **Teresa Toral, Candelaria Muñoz, Nuria Marco, Belén García-Avilés, Laura Murcia, María José Forniés, María Cristina González, Francisco Canals, Esther Bragado, Javier Martínez Olmos, Carlos García-Magán, José Domingo Moure González, Nuria Cortés, Magalí Giménez, Catalina Gómez, Ana Belén Rodríguez, Ana Moreno, José Manuel Lucas, Sergio Quevedo, Cristina Blasco, and Yolanda Aliaga** were involved in data curation (equal); investigation (equal); writing—review & editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest related to this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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