Received: 9 January 2022 | Revised: 29 April 2022 | Accepted: 17 May 2022

DOI: 10.1111/pai.13809

ORIGINAL ARTICLE

WILEY

Simplifying the drug provocation test in non-immediate hypersensitivity reactions to amoxicillin in children: The experience of a tertiary care allergy unit

Giulia Liccioli[1] | Mattia Giovannini[1] | Jean-Christoph Caubet[2] | Simona Barni[1] | Lucrezia Sarti[1] | Paola Parronchi[3] | Manuela Capone[3] | Leonardo Tomei[1] | Francesca Mori[1]

[1]Allergy Unit, Department of Pediatrics, Meyer Children's University Hospital, Florence, Italy

[2]Pediatric Allergy Unit, Department of Child and Adolescent, University Hospitals of Geneva, Geneva, Switzerland

[3]Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy

Correspondence
Mattia Giovannini, Allergy Unit, Department of Pediatrics, Meyer Children's University Hospital, Viale Pieraccini 24, 50139 Florence, Italy.
Email: mattiag88@hotmail.it

Funding information
This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Editor: Marina Atanaskovic-Markovic

Abstract

Background: Mild non-immediate reactions (NIR) to beta-lactams (βLs) are the most common manifestation of adverse drug reactions in children, and the drug provocation test (DPT) remains the gold standard for diagnosis. However, there are still controversies about the protocol that should be used, especially regarding the administration of doses and the DPT length.

Objective: This study aimed to evaluate a pediatric population with a history of mild NIR to amoxicillin (AMX) or to amoxicillin-clavulanic acid (AMX/CL) who underwent a diagnostic workup including a DPT with the culprit drug, to understand if a graded DPT or, instead, a single full dose could be the most appropriate way of administration in clinical practice.

Methods: The data of children were retrospectively analyzed for a 5-year period, with demographic and clinical characteristics collected. We reported the allergy workup and the results of the DPT performed with the administration of incremental doses and a prolonged DPT at home for a total of 5 days.

Results: Three hundred fifty-four patients were included. Overall, 23/354 (6.5%) DPTs were positive: 11/23 patients showed a reaction after 2–8 h after the last dose on the 1st or 2nd day (1 reacted 30 min after the last dose), 1/23 reacted with urticaria 30 min after the first dose, 11/23 reacted at home on the 5th day of the DPT.

Conclusion: This paper indirectly suggests that a single therapeutic dose administered on the 1st day of a DPT could be safe in the diagnostic workup of mild NIR to AMX/CL. Moreover, this could be less time-consuming as patients would spend less time in the hospital, also considering the public health restrictions imposed during the COVID-19 pandemic.

Abbreviations: AMX, amoxicillin; AMX/CL, amoxicillin–clavulanic acid; DPT, drug provocation test; IDTs, intradermal tests; LTT, lymphocyte transformation tests; NIR, non-immediate reactions; PT, patch test; βLs, beta-lactams.

Giulia Liccioli and Mattia Giovannini joint first coauthors.

KEYWORDS
beta-lactams, children, drug allergy, drug provocation test, incremental dose, non-immediate reactions

1 | INTRODUCTION

Beta-lactams (βLs) are the main elicitors of hypersensitivity drug reactions in children. Most of the reactions are non-immediate (NIR) with delayed appearing urticarial rashes or mild maculopapular exanthemas as the most common manifestations.

In these types of reactions the diagnostic approach proposed in 2016 by Gomes et al, consists of a direct drug provocation test (DPT) by skipping skin tests.[1,2]

Despite the widely demonstrated safety of performing a direct DPT without previous skin testing in mild NIR to βLs, to date, there are many controversies about the best protocol that should be used for the DPT (which remains the gold standard for the diagnosis), especially regarding the number of doses to be administrated and the length of the DPT itself.[3–7]

Several studies report the results of a single day versus a prolonged DPT in terms of sensitivity and negative predictive value (NPV). Indeed, the most recent papers seem to demonstrate a slightly higher diagnostic sensitivity of the extended protocols. In addition, a prolonged DPT results in increased confidence in the future use of the same drug when compared with a single-day DPT. On the other hand, a prolonged DPT is questioned because of its impact on the gut microbiota and the potential risk of increasing antibiotic resistance.[1,3,8–24] So far there is no agreement on the best protocol to be used that reaches the best compromise between safety, time consumption, and potential side effects. Today it is a matter of debate the way of administering the first dose of antibiotic during the DPT, in particular, if it would be better to fraction or not the drug dose (calculated according to the bodyweight).

In the literature, most of the studies focused on NIR report the results of graded DPTs using incremental doses of the antibiotics administered with different and non-standardized protocols,[1,15,16,23,25–31] describing how most of the reactions occur after the last dose on the first day or on subsequent days of DPT at home (Table 1). Only a few studies use a single-dose protocol for DPT.[20,24,32–34] Table 2 summarizes the few studies where the first dose was administered all at once.

This study aimed to evaluate the results of the diagnostic workup of a selected population of children with a history of mild NIR to amoxicillin (AMX) or to amoxicillin–clavulanic acid (AMX/CL) and who underwent a DPT with the culprit drug. In particular, we focused on the clinical characteristics of the reactions that occurred and on the timing of the onset of signs and symptoms during DPT. By analyzing the results of our study, we intended to discuss whether it is time to change the way to perform DPT in case of mild NIR and, in particular, whether a single full dose could be equally safe and effective in the diagnostic workup of such reactions.

Key Messages

In mild, non-immediate reactions (NIR) to beta-lactams in children, a direct drug provocation test (DPT) has been demonstrated to be safe, but there are controversies about the protocol that should be used (administration of incremental doses and length). This article reports the results of DPT performed with incremental doses and then a prolonged 5-day DPT, showing that all the patients but one reacted after some hours from the last dose administered. Most of the reactions occurred in children who reported a time latency within 6 h from the last drug intake. So, because clinical history alone is not a reliable tool for establishing a diagnosis, it should be taken into account for risk stratification to choose the investigation strategy best tailored to the individual patient ensuring a safe and more effective approach. This paper indirectly suggests the possibility that a single therapeutic dose, fully administered on the first day of DPT could be safe in the diagnostic workup of mild NIR, being also more realistic and less time-consuming than starting with fractionated incremental doses.

Moreover, we analyzed in detail the role of clinical history, in particular, for the reactions occurring within 6 h from the last drug intake that commonly remain in the "gray zone," and we discussed whether a graded approach would be better in terms of safety for these subtypes of reactions.

2 | METHODS

All children with a history of mild NIR to AMX or AMX/CL who underwent a DPT with the culprit drug at the Allergy Unit of Meyer Children's University Hospital, a tertiary care pediatric hospital, were retrospectively enrolled starting from 1 January 2016 to 31 August 2021. Patients with chronic urticaria, poorly controlled asthma, and severe cutaneous adverse reactions (i.e., drug reaction with eosinophilia and systemic symptoms, Stevens–Johnson syndrome/toxic epidermal necrolysis, acute generalized exanthematous pustulosis) were excluded from the study. Data were analyzed starting from the first visit together with the review of the clinical history and the description of the suspected drug reaction (often with the help of photographic documentation shown by the parents).

TABLE 1 Studies where the drug provocation test (DPT) was performed with incremental doses, using various protocols

Studies performing drug provocation tests with fractionated/incremental doses					
Study	**Number of children**	**History of reaction**	**Protocol**	**Positive DPT**	**Timing of reaction in case of IR after the fractionated doses**
Mori et al. (2015)[1]	200	38 IR 152 NIR 10 undefined	1/10 – 2/10 – 7/10	3/36 IR (8.3%) 14/141 NIR (9.9%)	All reacted >1 h after the last dose (7/10)
Labrosse et al. (2018)[16]	130	130 NIR	1/100 – 1/10 – full dose	6/130 (4.6%)	Not reported
García Rodríguez et al. (2019)[23]	97	97 NIR	1/4 – 1/2 – full dose every 30 min	3/14 IR (21.4%) 11/14 NIR (78.6%)	**2 reacted 1 h after the administration of the 2nd dose**
Kulhas Celik et al. (2020)[15]	365	365 NIR	Graded (not specified)	10/365 (2.7%)	**4 reacted after the 1st dose**
Ponvert et al. (2011)[25]	1431	162 IR 1269 NIR	Graded (1 – 10 mg, then incremental)	177/1087 NIR (16.7%)	Not reported
Zambonino et al. (2014)[26]	783	66 IR 717 NIR	1/4 – 1/4 – 1/2	51/717 NIR (7.1%)	65% of children reacted within 6–24 h, but the timing is not reported
Atanaskovic-Markovic et al. (2016)[27]	1026	1026 NIR	1/100 – 1/10 – full dose	19/1026 (1.8%)	All reacted at home
Mill et al. (2016)[28]	818	Both IR and NIR	1/10 – 9/10	48/818 (5.8%)	17 reacted within 1 h[a] 31 reacted after 1 h
Vezir et al. (2016)[29]	119	119 NIR	Graded (not specified)	4/119 (3.4%)	**1 reacted after the 3rd dose**
Pouessel et al. (2019)[30]	91	91 NIR	1/10 – 9/10	3/13 IR (23%) 10/13 NIR (77%)	3 reacted during hospitalization, but the timing is not specified

Note: Only studies including non-immediate reactions (NIR) are reported. IR immediate reaction. Reactions that occurred during the fractionated doses are listed in bold.

Abbreviations: IR immediate reaction; NIR non-immediate reaction.

[a]In this paper, the number of children with a history of IR or NIR is not specified. Indeed, the 17 reactions that occurred within 1 h could not be related to a previous index IR or NIR.

TABLE 2 Studies where the drug provocation tests (DPT) were performed with a single dose given all at once

Studies performing drug provocation tests with a single-dose all at once				
Study	**Number of children**	**History of reaction**	**Positive DPT**	**Timing of reaction**
Prieto et al. (2021)[20]	194	194 NIR	24/194 (12.4%)	No IR
Allen et al. (2020)[24]	136	102 NIR	3/102 (3%)	No IR
Caubet et al. (2011)[32]	88	88 NIR	6/88 (6.8%)	1 reacted after 30 min
Jaoui et al. (2019)[33]	446	446 NIR	39/456 (8.6%)	No IR
Wang et al. (2020)[34]	53	49 NIR or unknown	0	No positive DPT

Note: Only studies including non-immediate reactions (NIR) are reported.
Abbreviation: IR, immediate reaction.

TABLE 3 Clinical characteristics of the studied population

Characteristics	Total ($N = 354$)
Gender, male: *n* (%)	179 (50.6%)
Age at reaction (years): mean (SD)	4.8 (±3.7)
Suspected drug: *n* (%)	
Amoxicillin	34 (9.6%)
Amoxicillin-clavulanic acid	320 (90.4%)
Previous tolerance of suspected drug: *n* (%)	213 (60%)
Personal history of atopy (inhalant or food allergy): *n* (%)	69 (19.5%)
Cutaneous manifestation of the index reaction: *n* (%)	
Delayed urticaria	172
Maculopapular exanthema	61
Macular exanthema	33
Papular exanthema	23
Angioedema	14
Unspecific	14
Other type (scarlatiniform, morbilliform)	4
Combination of more than a type of rash	33
Latency period between index reaction and DPT (years): Mean (SD)	2.5 (±2.9)

Abbreviations: DPT drug provocation test; SD standard deviation.

We collected the demographic features and clinical characteristics of the patients enrolled. A reaction was defined as "non-immediate" when it occurred >1 h after the last drug intake and up to 48 h after the last dose.

Patients sent to our Allergy Unit underwent an allergy workup according to the European Network for Drug Allergy guidelines for NIR.[2]

Delayed intradermal tests (IDTs) with standard concentrations were performed by injecting 0.03 ml of the drug into the volar surface of the forearm with readings at 20 min and then at 24, 48, and 72 h. The drug concentration used for IDTs for AMX/CL was 20 mg/ml IDTs were considered positive at late reading when infiltration, induration, and increased diameter of the papule >5 mm appeared after >24 h.

All children underwent a DPT with the culprit drug. The DPT was performed as already described in a previous paper by our group.[1] On the first day, an open DPT to AMX or AMX/CL (1/10–2/10–7/10 of the therapeutic dose [25 mg/kg] administered every 30 min) was performed until the cumulative dose was reached or a reaction occurred. Patients were observed for 2 h after the last drug intake, and in the case of negative DPT, the drug was administered in a single full dose on the second day (25 mg/kg). Starting from the 2nd day, patients received another full dose after 12 h at home, and then, daily therapeutic doses of the culprit (25 mg/kg 2 times a day) were continued at home for a total of 5 days; parents were advised to stop the treatment in case of any reaction and to contact our unit and their own pediatrician, taking photographic documentation in the case of a cutaneous rash occurring.

Only in the case of positive DPT, a limited number of patients were evaluated at least 4 weeks after the reaction and underwent further investigations including repeated IDTs, patch tests (PT), and/or lymphocyte transformation tests (LTT).

PTs were freshly prepared with AMX/CL (intravenous solution at 200 mg/ml concentration) at 5% and 20% in petrolatum and applied

on the children's backs for 48 h. Readings were performed after 15 min and 24, 48, and 72 h after removal of the strips. Petrolatum alone was used as a negative control. PT was defined as positive when an infiltrate with vesicles was detected. The reading results' criteria are identical to those used for contact allergy.[35]

LTT was performed following the procedure previously described by our group.[36] Antigens used were: penicillin 2.5–0.5–0.1–0.02 mg/ml; ampicillin 2.5–0.5–0.1–0.02 mg/ml; AMX 1–0.5–0.1–0.02 mg/ml; and AMX/CL 0.5–0.1–0.02–0.004 mg/ml.

Qualitative data were expressed as counts and percentages; quantitative data were expressed as mean value ± standard deviation (SD).

3 | RESULTS

A total of 354 patients were included, 179 males (50.6%) and 175 females (49.4%). The mean age at reaction was 4.8 years (SD ± 3.7 years).

All the characteristics are reported in Table 3. In 34/354 (9.6%), the suspected drug was AMX; in 320/354 (90.4%) AMX/CL was incriminated; and 213/354 (60%) children had taken the suspected drug with tolerance in the years preceding the index reaction. Sixty-nine out of 354 (19.5%) patients had a personal history of atopy (inhalant or food allergy). All the children reported a skin eruption: 172/354 (48.6%) had delayed urticaria, 61/354 (17.2%) had maculopapular exanthema, 33/354 (9.3%) had macular exanthema, 23/354 (6.5%) had papular exanthema, 14/354 (4%) had angioedema, in 14/354 (4%), the rash was undefined on the basis of the reported history, in 4/354 (1.1%) other types of rashes (e.g., scarlatiniform and morbilliform), and the remaining 33/354 (9.3%) had a combination of more than a type of rash. Regarding gastrointestinal involvement, 2 children had mild abdominal pain, 1 had diarrhea and 1 had vomiting. No one suffered from respiratory signs and symptoms. As for associated clinical manifestations, 1 reported asthenia and 1 sweating. The mean latency between the index reaction and the allergy workup with DPT was 2.5 years (SD ± 2.9).

Delayed IDTs were negative in all but one child with a positive late reading (papule diameter of 6 mm). In this case, despite this result, due to the history of mild reaction, we proceeded anyway with the DPT, which was positive with a mild maculopapular exanthema. Overall, 23 out of 354 (6.5%) DPT resulted positive, 2 to AMX and 21 to AMX/CL.

Eleven out of 23 reacted during the first or second day of DPT at the hospital setting within 2–8 h of receiving the last dose (only 1/11 reacted about 30 min after the last dose). Eleven out of 23 reacted at home 24–48 h after the last dose on the fifth day of the therapy course. Finally, only 1 out of the 23 with a positive DPT (4.3%) reacted with urticaria after 30 min from the first administration of 1/10 of the therapeutic dose (Table 4). In this case, for a more confident diagnosis, the DPT was repeated in the Allergy Unit 6 months later with the same outcome.

Fourteen out of 23 patients (60.8%) showed at the DPT the same cutaneous manifestations described in their history, exhibiting concordance between the index reaction and the one elicited at the DPT with the culprit.

TABLE 4 Characteristics of the patients with positive drug provocation test (DPT) and reaction timing

Characteristics of the positive DPT	Total ($N = 23$)
Gender, male: *n* (%)	11 (47.8%)
Culprit drug	
Amoxicillin	2 (8.5%)
Amoxicillin-clavulanic acid	21 (91.5%)
Personal history of atopy (inhalant or food allergy): *n* (%)	2 (8.5%)
Timing of reaction	
On the fifth day of DPT at home, after 24–48 h since the last dose	11
On the first or second day of DPT at the hospital setting, after 2–8 h since the last dose (only 1/11 started the reaction about 30 min after the last dose)	11
On the first day of DPT at the hospital setting, 30 min after the first administration of 1/10 of the therapeutic dose	1

Abbrevition: DPT, drug provocation test.

However, the remaining children had skin rashes similar to those reported at the first visit (considering that in some cases, the manifestations were difficult to classify because of poor details), and there were no other associated clinical manifestations or systemic involvement. All the reactions were mild and required treatment with only antihistamines (7/23) or either improved without any therapy (16/23).

In addition, because in patients with a history of reaction within 2–6 h of the dose an overlapping between IR and NIR may exist,[5] we also analyzed and reported the number of positive DPTs in both groups (reaction in 2–6 h vs. more than 6 h). In particular: 17/23 (74%) positive DPTs occurred in patients with a history of reaction 2–6 h (2 out of 17 were the children reacting respectively after 1/10 of the dose and after 30 min from the last dose); 6/23 (26%) positive DPTs occurred in patients with a history of reaction after more than 6 h. Of those 6 cases, 5 showed a NIR >6 h during the DPT course therapy, in concordance with the index reaction; 1 out of 6 had a reaction >2 h from the dose.

After the positive DPT, the children were evaluated again during a follow-up at our Unit. In particular, 16 out of 23 underwent LTT, with positive results in 6/16 (37.5%). One patient had a PT with the culprit and resulted negative.

4 | DISCUSSION

In this paper, we retrospectively analyzed the results of the allergy workup in children with mild NIR to AMX or AMX/CL.

So far, several studies have shown the poor diagnostic performance of skin testing (i.e., delayed reading of IDTs) in these types of reactions and recently, a European Academy of Allergy and Clinical Immunology (EAACI) position paper and a report from an EAACI

task force suggested skipping skin tests in cases of mild NIRs to βLs in adults and children.[5,37] Our results confirm the poor utility of skin tests in NIR to AMX or AMX/CL, supporting the practice of skipping such in vivo tests. We showed that only 1 patient out of 354 had a positive IDT, and this positivity was confirmed by a DPT with the culprit drug. Even though this child underwent the DPT, the reaction was mild, and a confident diagnosis of hypersensitivity was reached. We additionally reported the results of LTT as an in vitro test in a few patients with NIRs to AMX or AMX/CL. LTT seems to have a higher sensitivity than skin testing, but the former is not the focus of this paper and in the literature few studies have been published on this topic in children, leaving this method restricted to be a research tool.

So, a DPT remains the gold standard for a confident diagnosis. Recently, the largest study on the direct DPT in mild reactions to βLs in children has been published. This multicentric study shows the safety of skipping the intradermal test by performing a graded oral DPT directly, even if the duration of the DPT is not reported. In that paper 42 out of 1914 (2.2%) children had a mild immediate reaction (IR) to DPT, with 3 of these patients (7%) reacting to the first dose of the DPT, however, it should be taken into account that the children included in the study were also those with history of IR.[4]

In terms of the number of patients, prevalence of positive DPT and timing of reactions, our results are very similar to the recent paper of Petersen et al.[17] where the incidence of positive DPT was 6.7% (22/305), and none of the children reacted on the first 1/10 of the full dose.

Several authors have recently studied the way of administering the first drug dose. So far, in NIR to βLs, it seems to be safe to administer the first dose of antibiotic in a single dose.[20,24,32–34] In our study, we fractionated the dose as recommended by the EAACI position paper.[5]

As reported above, only one patient reacted 30 min after the first fractionated dose (1/10) with mild urticaria. In this case, the timing and the type of the clinical manifestation appeared more related to an IR rather than a NIR, suggesting that maybe the history reported by parents at the first visit was not so reliable, as the index reaction was reported to have occurred 2 h after the dose at the 8th day of the therapy course.

For that reason, we correlated the positivity of all DPT performed with the time latency of the index reaction, and we observed that most of the positive DPT occurred in those patients who had a history of reactions within 6 h from the last drug intake. This finding underlines that clinical history should be collected correctly at the beginning. In the case of our child, the DPT was repeated a few months later, showing the same type of reaction, suggesting that he could have had an IgE-mediated hypersensitivity to AMX/CL since the beginning. Actually, the "one size fits all approach" theory is not the right one for each patient, and, in particular, based on our results, the graded DPT protocol should be the appropriate one in the case of patients with a history of reactions occurring up to 6 h from the last drug assumption. More attention should be paid to these cases because an overlap between IR and NIR could not be excluded. On the contrary, only six children with a history of NIR (>6 h from the last drug intake) did not pass the DPT with the culprit. All reacted after the last dose (7/10) of the graded DPT with mild NIR. Regarding the type of reaction, our study is in agreement with the literature showing that most of the reactions during DPT have the same clinical characteristics as the index reaction. Moreover, we could speculate that, for those patients, one dose of the culprit administered all at once could be safe and less time-consuming than a graded DPT.

Regarding the duration of DPT, several studies focused on the risks-benefits of a short versus a prolonged protocol. By performing a single day DPT, the percentage of positivity ranges between 0% and 7.7%, with a NPV of 89.1% and 94.9% in the only studies published so far.[28,38] The percentage of self-confident future intake of the tested drug varies between 22% and 76%.

By performing a prolonged DPT, the NPV calculated is almost comparable to that described with a single day DPT (over 90% in all the studies published),[16,32,39–42] but the percentage of confirmatory diagnosis is higher, ranging between 2% and 17.2% with a greater percentage of patients/parents (52%–100%) who feel more confident about using the tested drug again in case of necessity,[18] Finally, in the study by Exius et al.[4] the NPV of the DPT has been confirmed at 85.3% after a 5-year follow-up.

Our study supports the evidence that a prolonged DPT increases the diagnostic value of the DPT for NIR. Indeed, among our patients, 11 out of 23 reacted at home, showing that at least 47.8% of these children would not have received a correct diagnosis of non-immediate hypersensitivity to AMX/CL if we had applied a single-day protocol. This finding is comparable to that reported by Fransson et al.[19] even though it includes adult patients. On the other hand, exposing 354 patients to prolonged treatment with potential impact on the gut microbiota only led to the identification of 11 more children who developed a mild reaction. So far, more studies are needed to reach a final conclusion comparing the risk for a future mild reaction to the same drug in patients with a missed diagnosis to the potential risk for an increase in antibiotic resistance.

For that reason, a more personalized approach is suggested by the recent literature. Iammatteo et al.[43] propose risk-based algorithms for the evaluation of βLs allergy in pediatric and adult populations based on a description of the historical reaction. In particular, regarding children <18 years of age with a history of mild (limited to the skin) NIRs (more than an hour after exposure), the authors suggest a direct single-day DPT with one full dose or graded DPT (10%–90% of the therapeutic dose). However, it must be emphasized that we can administer a full dose only in patients with a clear history in terms of latency and symptom severity and we should consider a graded DPT for those reacting between 1 and 6 h after receiving the last drug dose.[43] This study confirms the great importance of collecting a clinical history of reaction in as much detail as possible, since the following allergy workup, with its risk-benefit evaluation, is based on it. Additionally, other factors such as the number of previous reactions, underlying diseases, genetic predisposition, and biomarkers should be taken into account. All of these factors need to be studied thoroughly to apply a personalized diagnostic approach to every single patient.

5 | CONCLUSION

This is the largest study published to date, investigating children with mild NIR to AMX and AMX/CL, which includes both in vivo and in vitro tests and compares the results critically with recent literature. This paper indirectly suggests the possibility that a single therapeutic dose administered on the first day of DPT could be safe in the diagnostic workup of mild NIR to AMX/CL occurring 6 h after the last drug intake, being also more realistic because the child would receive the full dose of the drug from the beginning of the DPT, as in real life. Moreover, this method could be less time-consuming as the patients and their caregivers would spend less time in the hospital, also considering the public health restrictions imposed during the COVID-19 pandemic.

AUTHOR CONTRIBUTIONS

Giulia Liccioli: Conceptualization (supporting); Data curation (lead); Formal analysis (lead); Investigation (supporting); Writing – original draft (lead); Writing – review & editing (supporting). **Mattia Giovannini:** Formal analysis (supporting); Investigation (supporting); Writing – original draft (supporting); Writing – review & editing (supporting). **Jean-Christoph Caubet:** Formal analysis (supporting); Writing – original draft (supporting); Writing – review & editing (supporting). **Simona Barni:** Formal analysis (supporting); Investigation (supporting); Writing – review & editing (supporting). **Lucrezia Sarti:** Formal analysis (supporting); Investigation (supporting); Writing – review & editing (supporting). **Paola Parronchi:** Formal analysis (supporting); Investigation (supporting); Writing – review & editing (supporting). **Manuela Capone:** Formal analysis (supporting); Investigation (supporting); Writing – review & editing (supporting). **Leonardo Tomei:** Formal analysis (supporting); Investigation (supporting); Writing – review & editing (supporting). **Francesca Mori:** Conceptualization (lead); Data curation (supporting); Formal analysis (supporting); Investigation (lead); Writing – original draft (supporting); Writing – review & editing (lead).

ACKNOWLEDGEMENT

Open Access Funding provided by Universita degli Studi di Firenze within the CRUI-CARE Agreement.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests to disclose in relation to this paper.

DATA AVAILABILITY STATEMENT

Aggregate analyses are available on reasonable request to the corresponding author.

ETHICAL APPROVAL

The code of the event report issued by Meyer Children's University Hospital is IR904-21–54120.

INFORMED CONSENT

Written informed consent was obtained from the children's parents for all procedures performed.

ORCID

Giulia Liccioli https://orcid.org/0000-0002-5216-0423
Mattia Giovannini https://orcid.org/0000-0001-9568-6882
Jean-Christoph Caubet https://orcid.org/0000-0001-5006-5724
Simona Barni https://orcid.org/0000-0001-5598-2740
Lucrezia Sarti https://orcid.org/0000-0001-8055-3788
Paola Parronchi https://orcid.org/0000-0002-9184-5089
Manuela Capone https://orcid.org/0000-0002-4690-9960
Leonardo Tomei https://orcid.org/0000-0002-7177-7939
Francesca Mori https://orcid.org/0000-0001-7483-0128

REFERENCES

1. Mori F, Cianferoni A, Barni S, Pucci N, Rossi ME, Novembre E. Amoxicillin allergy in children: five-day drug provocation test in the diagnosis of nonimmediate reactions. *J Allergy Clin Immunol Pract*. 2015;3:375-380.e1.
2. Gomes ER, Brockow K, Kuyucu S, et al. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. *Allergy*. 2016;71:149-161.
3. Atanaskovic-Markovic M. What is new in beta-lactam allergy in children? *Pediatr Allergy Immunol*. 2021;32:219-222.
4. Exius R, Gabrielli S, Abrams EM, et al. Establishing amoxicillin allergy in children through direct Graded Oral Challenge (GOC): evaluating risk factors for positive challenges, safety, and risk of cross-reactivity to cephalosporines. *J Allergy Clin Immunol Pract*. 2021;9:4060-4066.
5. Romano A, Atanaskovic-Markovic M, Barbaud A, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams — An EAACI position paper. *Allergy Eur J Allergy Clin Immunol*. 2020;75:1300-1315.
6. Blanca-López N, Zapatero L, Alonso E, et al. Skin testing and drug provocation in the diagnosis of nonimmediate reactions to aminopenicillins in children. *Allergy*. 2009;64:229-233.
7. Graham F, Tsabouri S, Caubet J-C. Hypersensitivity reactions to beta-lactams in children. *Curr Opin Allergy Clin Immunol*. 2018;18:284-290.
8. Atanaskovic-Markovic M, Tsabouri S. Exanthematous reactions to drugs in children. *Curr Opin Allergy Clin Immunol*. 2021;21:335-339.
9. Koosakulchai V, Sangsupawanich P, Wantanaset D, Jessadapakorn W, Jongvilaikasem P, Yuenyongviwat A. Safety of direct oral provocation testing using the Amoxicillin-2-step-challenge in children with history of non-immediate reactions to amoxicillin. *World Allergy Organ J*. 2021;14(7):100560.
10. Torres-Rojas I, Pérez-Alzate D, Somoza ML, et al. Patterns of response and drugs involved in hypersensitivity reactions to beta-lactams in children. *Pediatr Allergy Immunol*. 2021;32:1788-1795.
11. Goh SH, Chong KW, Chiang WC, Goh A, Loh W. Outcome of drug provocation testing in children with suspected beta-lactam hypersensitivity. *Asia Pac Allergy*. 2021;11:e3.
12. Confino-cohen R, Rosman Y, Meir-shafrir K, et al. Oral challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. *J Allergy Clin Immunol Pract*. 2017;5(3):669-675.
13. Iammatteo M, Alvarez Arango S, Ferastraoaru D, et al. Safety and outcomes of oral graded challenges to amoxicillin without prior skin testing. *J Allergy Clin Immunol Pract*. 2019;7:236-243.

14. Vila L, Garcia V, Martinez Azcona O, Pineiro L, Meijide A, Balboa V. Mild to moderate hypersensitivity reactions to beta-lactams in children: a single-centre retrospective review. *BMJ Paediatr Open*. 2019;3:e000435.
15. Kulhas Celik I, Guvenir H, Hurmuzlu S, et al. The negative predictive value of 5-day drug provocation test in nonimmediate beta-lactam allergy in children. *Ann Allergy, Asthma Immunol*. 2020;124:494-499.
16. Labrosse R, Paradis L, Lacombe-Barrios J, et al. Efficacy and safety of 5-day challenge for the evaluation of nonsevere amoxicillin allergy in children. *J Allergy Clin Immunol Pract*. 2018;6:1673-1680.
17. Petersen BT, Gradman J. Prospective study of 5-day challenge with penicillins in children. *BMJ Paediatr Open*. 2020;4:e000734.
18. Ratzon R, Reshef A, Efrati O, et al. Impact of an extended challenge on the effectiveness of β-lactam hypersensitivity investigation. *Ann Allergy, Asthma Immunol*. 2016;116:329-333.
19. Fransson S, Mosbech H, Kappel M, et al. The importance of prolonged provocation in drug allergy — Results from a danish allergy clinic. *J Allergy Clin Immunol Pract*. 2017;5:1394-1401.
20. Prieto A, Muñoz C, Bogas G, et al. Single-dose prolonged drug provocation test, without previous skin testing, is safe for diagnosing children with mild non-immediate reactions to beta-lactams. *Allergy*. 2021;76:2544-2554.
21. Hjortlund J, Mortz CG, Skov PS, Bindslev-Jensen C. Diagnosis of penicillin allergy revisited: the value of case history, skin testing, specific IgE and prolonged challenge. *Allergy Eur J Allergy Clin Immunol*. 2013;68:1057-1064.
22. Borch JE, Bindslev-Jensen C. Full-course drug challenge test in the diagnosis of delayed allergic reactions to penicillin. *Int Arch Allergy Immunol*. 2011;155:271-274.
23. García Rodríguez R, Moreno Lozano L, Extremera Ortega A, Borja Segade J, Galindo Bonilla P, Gómez Torrijos E. Provocation tests in nonimmediate hypersensitivity reactions to β-lactam antibiotics in children: are extended challenges needed? *J Allergy Clin Immunol Pract*. 2019;7:265-269.
24. Allen HI, Vazquez-Ortiz M, Murphy AW, Moylett EM. De-labeling penicillin-allergic children in outpatients using telemedicine: potential to replicate in primary care. *J Allergy Clin Immunol Pract*. 2020;8:1750-1752.
25. Ponvert C, Perrin Y, Bados-Albiero A, et al. Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. *Pediatr Allergy Immunol*. 2011;22:411-418.
26. Zambonino MA, Corzo JL, Muñoz C, et al. Diagnostic evaluation of hypersensitivity reactions to beta-lactam antibiotics in a large population of children. *Pediatr Allergy Immunol*. 2014;25:80-87.
27. Atanaskovic-Markovic M, Gaeta F, Medjo B, et al. Non-immediate hypersensitivity reactions to beta-lactam antibiotics in children – Our 10-year experience in allergy work-up. *Pediatr Allergy Immunol*. 2016;27:533-538.
28. Mill C, Primeau M-N, Medoff E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. *JAMA Pediatr*. 2016;170:e160033.
29. Vezir E, Dibek Misirlioglu E, Civelek E, et al. Direct oral provocation tests in non-immediate mild cutaneous reactions related to beta-lactam antibiotics. *Pediatr Allergy Immunol*. 2016;27:50-54.
30. Pouessel G, Winter N, Lejeune S, Thumerelle C, Deschildre A. Oral challenge without skin testing in children with suspected non-severe betalactam hypersensitivity. *Pediatr Allergy Immunol*. 2019;30:488-490.
31. Chiriac A-M, Rerkpattanapipat T, Bousquet P-J, Molinari N, Demoly P. Optimal step doses for drug provocation tests to prove beta-lactam hypersensitivity. *Allergy*. 2017;72:552-561.
32. Caubet JC, Kaiser L, Lemaître B, et al. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol*. 2011;127:218-222.
33. Jaoui A, Delalande D, Siouti S, et al. Safety and cost effectiveness of supervised ambulatory drug provocation tests in children with mild non-immediate reactions to beta-lactams. *Allergy*. 2019;74:2482-2484.
34. Wang LA, Patel K, Kuruvilla ME, Shih J. Direct amoxicillin challenge without preliminary skin testing for pediatric patients with penicillin allergy labels. *Ann Allergy, Asthma Immunol*. 2020;125:226-228.
35. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - Recommendations on best practice. *Contact Dermatitis*. 2015;73:195-221.
36. Mori F, Fili L, Sarti L, et al. Sensitivity and specificity of lymphocyte transformation test in children with mild delayed hypersensitivity reactions to beta-lactams. *Allergy*. 2020;75:2696-2699.
37. Blanca-Lopez N, Atanaskovic-Markovic M, Gomes ER, et al. An EAACI task force report on allergy to beta-lactams in children: clinical entities and diagnostic procedures. *Pediatr Allergy Immunol*. 2021;32:1426-1436.
38. Chiriac AM, Romano A, Ben Fadhel N, et al. Follow-up of patients with negative drug provocation tests to betalactams. *Clin Exp Allergy*. 2019;49:729-732.
39. Regateiro FS, Rezende I, Pinto N, Abreu C, Carreiro-Martins P, Gomes E. Short and extended provocation tests have similar negative predictive value in non-immediate hypersensitivity to beta-lactams in children. *Allergol Immunopathol (Madr)*. 2019;47:477-483.
40. Misirlioglu ED, Toyran M, Capanoglu M, Kaya A, Civelek E, Kocabas CN. Negative predictive value of drug provocation tests in children. *Pediatr Allergy Immunol*. 2014;25:685-690.
41. Tonson la Tour A, Michelet M, Eigenmann PA, Caubet J-C. 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. *J Allergy Clin Immunol Pract*. 2018;6:1321-1326.
42. Ponvert C, Weilenmann C, Wassenberg J, et al. Allergy to beta-lactam antibiotics in children: a prospective follow-up study in retreated children after negative responses in skin and challenge tests. *Allergy*. 2007;62:42-46.
43. Iammatteo M, Lezmi G, Confino-Cohen R, Tucker M, Ben-Shoshan M, Caubet JC Direct challenges for the evaluation of beta-lactam allergy: evidence and conditions for not performing skin testing. *J Allergy Clin Immunol Pract*. 2021;9:2947-2956.

How to cite this article: Liccioli G, Giovannini M, Caubet J-C, et al. Simplifying the drug provocation test in non-immediate hypersensitivity reactions to amoxicillin in children: The experience of a tertiary care allergy unit. *Pediatr Allergy Immunol*. 2022;33:e13809. doi:10.1111/pai.13809