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Oral Challenge without Penicillin Skin Tests in Children with Suspected Beta-Lactam Hypersensitivity

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Abstract

Objective A misdiagnosed "penicillin allergy" is a common problem in childhood. Recently, skipping skin tests (STs) and performing a direct oral challenge test (OCT) have become an increasingly common approach in children with suspected β-lactam (BL) allergy. In our study, we aimed to evaluate the safety and efficacy of OCT without using ST in children who had a history of hypersensitivity reactions with BL antibiotics.

Materials and Methods We retrospectively evaluated direct OCT outcomes in children with both nonimmediate and immediate-type reaction history with BL antibiotics. STs were not performed before the challenge test. The patients were monitored for 4 hours after the challenge and continued using the drug in two divided doses for 3 days at home.

Results In this study, 72 patients were included, with median age of 7 years (interquartile range: 4; min: 1 year to max: 16 years), and of these, 56% were male. Forty-five subjects (63%) reported immediate-type adverse reactions. The most common clinical manifestation was urticaria/angioedema (51%, *n*: 37) and maculopapular exanthema in 46% (*n*: 33) of patients, respectively. The most commonly suspected drug was 71% amoxicillin-clavulanate. A 3-day OCT without preceding ST was performed in all patients. Only three patients (4.2%) showed a positive response to the oral drug challenge test. None of these reactions observed was more severe than index reactions.

Conclusion Performing OCT without STs is a safe and convenient method to exclude BL hypersensitivity in the pediatric age group.

Keywords
- β-lactam hypersensitivity
- child
- oral challenge
- skin tests
- drug allergy

Introduction

Antibiotic allergy is an immunoglobulin E (IgE), IgG, and T lymphocyte-mediated immune response to a drug in susceptible individuals.[1] Immediate-type reactions are usually induced by an IgE-mediated mechanism and occur within the first hour after drug administration.[2,3] These reactions usually present as urticaria, angioedema, rhinitis, bronchospasm, or anaphylaxis. Nonimmediate-type reactions develop at least 1 hour after drug administration and are often induced by a T-lymphocyte-dependent reaction. They typically present as a macular or papular rash.[4–6] Serum sickness, acute generalized exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms, Stevens–Johnson syndrome, and toxic epidermal necrolysis are rarer but more severe late-type reactions.[7]

In children, hypersensitivity reactions, especially to penicillin and cephalosporin, are frequently reported. However,

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the percentage of confirmed reactions as drug allergies is very low. Approximately 10% of children report having a history of penicillin hypersensitivity, but approximately 90% of those may tolerate penicillin.[8–10] These people are misdiagnosed with "penicillin allergy." The use of broad-spectrum antibiotics in patients identified with "penicillin allergy" is associated with higher costs and increased antibiotic resistance.[11] The current step-wise approach for the diagnosis of drug allergy is based on the clinical history and tests, including specific IgE (sIgE) levels, basophil activation tests, skin tests (STs), and drug challenge tests.[12,13] Drug challenge tests use as a "gold standard" to establish the diagnosis of drug hypersensitivity reaction.[14] Challenge test duration can be 1, 3, 5, 7, or 10 days. Multiday challenges also have the potential to decrease patient anxiety and penicillin avoidance, but this will need to be weighed against the downside of increased antimicrobial exposure. As the duration of provocation increases, the risk of antibiotic resistance develops.[15,16]

STs for diagnosis of drug allergy require trained personnel and are time consuming and painful for children. In addition, positive predictive values of these tests in children are also low.[17,18] On the other hand, in drug allergy, skin testing is the most widely used method to determine sensitization. STs are relatively safe when compared with provocation tests, especially in patients with a history of severe reactions.[12]

Current studies have shown that in patients with benign rashes associated with β-lactam (BL) allergy is safe to administer direct oral drug challenge tests without skin testing. The currently available data show that if a reaction develops in these challenge tests, the severity is usually similar or milder than the index reaction.[19–22]

In our study, we aimed to evaluate the safety and efficacy of a direct oral challenge test (OCT) without using STs in children who had a history of hypersensitivity reactions associated with BL antibiotics.

Materials and Methods

Patients and Study Design

In this study, we evaluated the records of pediatric patients (aged 1–18 years), who underwent an oral drug challenge test because of a suspected hypersensitivity to BL antibiotics (penicillin and cephalosporin) at a tertiary pediatric allergy department, between January 2015 and January 2020. Patients' demographic data, detailed history of the suspected hypersensitivity reaction, and provocation test results were recorded.

Diagnosis of Drug Allergy

Our clinic does not have commercial kit penicillin allergenic determinants produced for penicillin skin testing. Therefore, serum-specific sIgE for penicillin G and V are required first in patients presenting with suspected BL hypersensitivity. Those with an sIgE level below 0.35 kU/L are considered negative and those with a higher sIgE level are considered positive. ST with the suspect drug is applied to patients with positive sIgE levels. Patients who show a positive reaction in the ST are considered allergic and drug challenge test with the culprit drug is not performed. In patients with negative ST, OCT is performed according to the European Network for Drug Allergy guideline recommendations.[23] In patients with negative sIgE levels, STs are skipped and OCT is performed (►**Fig. 1**).

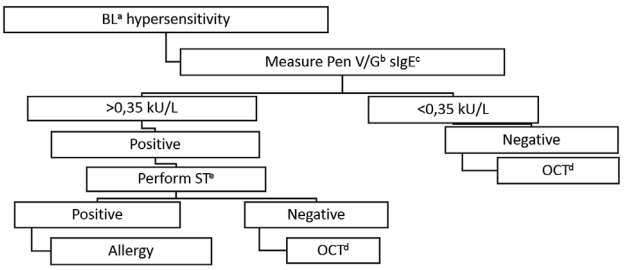


Fig. 1 Diagnostic approach in β-lactam hypersensitivity. [a]BL, β lactam, [b]Pen V, penicillin V, Pen G, penicillin G; [c]sIgE, specific immunoglobulin E, [d]OCT, oral challenge test, [e]ST, skin test.

Reactions occurring in the first hour after drug intake were considered immediate reaction; reactions that developed 1 hour or more after drug intake were considered nonimmediate reactions.

Oral Challenge Test

The challenge was performed with the daily therapeutic dose of the drug by a physician with full resuscitation backup. If the suspected drug was ceftriaxone, OCT was performed with amoxicillin, amoxicillin–clavulanic acid, and cefuroxime on different days, respectively. We performed OCT with amoxicillin and amoxicillin-clavulanic acid to find an alternative medicine, not to clarify the cephalosporin hypersensitivity in ceftriaxone hypersensitivity. The suspected drug was administered at divided doses every 30 minutes, until the full therapeutic daily dose was reached, in maximum five doses. Patients were monitored for acute reactions for 4 hours in the clinic, continued to use the drug in two divided doses for 3 days at home, and came to the clinic the next day. Patients were informed to stop taking the BL and call the clinic should any adverse reaction develop at home.

The present study was approved by the ethics committee of Dokuz Eylul University in light of the Helsinki Declaration (approval number; 2020/15–37). Written informed consent form was collected from parents.

Results

In this study there were 72 patients. Their median age was 7 years (interquartile range: 4; min: 1 year to max: 16 years). Characteristics of patients are shown in ►**Table 1**. Forty-five subjects (63%) reported immediate-type reactions (mean 39 minutes ± 19.2), 27 subjects (37%) reported nonimmediate-type reactions (mean 4 hours ± 2.2 hours). The most frequent clinical manifestations were urticaria/angioedema, maculopapular exanthema (MPE), and anaphylaxis (►**Table 2**).

The most frequently suspected drugs were reported as amoxicillin-clavulanic acid, ceftriaxone, and penicillin. The

Table 1 Characteristics of the patients

Sex, *n* (%)	
Girls	32 (44)
Boys	40 (56)
Age (y)	
Median (IQR)	7 (4)
Family history of drug allergy, *n* (%)	5 (6.9)
Aeroallergen sensitivity in the skin test, *n* (%)	13 (18.1)
Time between reaction and last dose (min), median (IQR)	
Immediate-type (63%; *n*: 45)	30 (30–60; 30)
Nonimmediate-type (37%; *n*: 27)	270 (135–345; 210)
Dose of administration, median (IQR)	3 (3)
Time between reaction and test (wk), median (IQR)	4 (17)

Abbreviation: IQR, interquartile range.

Table 2 The culprit drug and reported clinical manifestation

	n (%)	PEN	AMC	SAM	CRO	CFM	CXM
Anaphylaxis	2 (3)	0 (0)	0 (0)	0 (0)	2	0 (0)	0 (0)
Urticaria	37 (51)	3 (8)	27 (73)	0 (0)	7 (19)	0 (0)	0 (0)
MPE	33 (46)	4 (12)	24 (73)	1 (3)	1 (3)	2 (6)	1 (3)
Total	72 (100)	7 (10)	51 (71)	1 (1)	10 (14)	2 (3)	1 (1)

Abbreviations: AMC, amoxicillin–clavulanic acid; CFM, cefixime; CRO, ceftriaxone; CXM, cefuroxime; MPE, maculopapular exanthema; PEN, penicillin; SAM, ampicillin–sulbactam.

characteristics of the drug administration route and the type of allergic reaction are summarized in ►**Table 3**. The rate of immediate reactions was higher in patients who were administered parenteral medication ($p = 0.009$).

There was no significant difference between the patients with immediate and nonimmediate-type reaction regarding sex, eosinophil count, and serum total IgE levels ($p > 0.05$). The time between the reaction and admission to the allergy clinic was shorter in patients with immediate-type allergic reaction ($p = 0.03$). sIgE to penicillin G or V were negative in all patients. OCT was positive in only three patients (4.2%). Two patients had urticaria and one patient had angioedema. None of the reactions observed in the OCT were more severe than the index reactions. The symptoms regressed in a short time with oral antihistamine and no systemic reaction developed. Findings from patients with positive challenge test are summarized in ►**Table 4**.

In 95.8% of the patients (*n*: 69), no reaction was observed in the challenge test. Two patients who had a history of anaphylaxis with ceftriaxone had a positive intradermal (ID) reaction with ceftriaxone (ID test dose: 2 mg/mL, 1:100 concentration).[12] Therefore, an intravenous challenge test was not performed. OCT was performed with amoxicillin, amoxicillin–clavulanic acid, and cefuroxime, respectively, without skin testing to find alternative drugs. No reaction was observed in OTC.

Discussion

In our study, we presented the results of OCT in patients with both nonimmediate and immediate-type reaction history with BL antibiotics. The OCT was negative in 95.8% of the patients and positive in only 4.2% of the patients. None of the reactions which were observed in the challenge test were more severe than the index reaction. Nowadays, performing direct OCT with no prior STs in mild nonimmediate reactions to BLs is being challenged, especially in the childhood age group. Some guidelines have also started to include this approach in their recommendations.[23–26] Recently, consistent results have

Table 3 Frequency of reactions by route of drug administration

Oral, *n* (%)	**59 (82)**
Immediate	32 (54)
Nonimmediate	27 (46)
Parenteral, *n* (%)	18 (18)
Immediate[a]	12 (92)
Nonimmediate	6 (8)

[a]Administered parenteral medications were ampicillin-sulbactam (*n*: 1), penicillin (*n*: 2), and ceftriaxone (*n*: 9).

Table 4 Characteristics of the patients with positive oral challenge tests

	Index reaction	Culprit drug	Oral challenge result
1	Immediate type/urticaria	AMC	AMC: 1st day 30 minutes after the last dose, urticaria
2	Immediate type/urticaria	AMC	AMC: 1st day 5 minutes after the 2nd dose, angioedema on lips
3	Immediate type/urticaria	AMC	AMC: 1st day 10 minutes after the 3rd dose, urticaria

Abbreviation: AMC, amoxicillin–clavulanic acid.

been obtained for the adult age group.[20] In our study, we confirmed those results. However, there were no patients with a history of anaphylaxis with oral BL antibiotics in our study; therefore, no comment could be made for this patient group. In addition, the single-center and retrospective design of the present study are limitations. Therefore, it would not be appropriate to generalize our results to the whole population. Our data should be supported by large cohort studies involving heterogeneous patient groups.

Previous studies showed that mild and moderate MPEs were considered of low risk, particularly in children.[22] Mild MPE was defined as "a more or less widespread rash, with less than a week of duration, without systemic involvement" and moderate MPE, those with more than a week of duration, without systemic symptoms.[25] Many studies in the literature suggesting direct OCT were conducted on low-risk patients.[20,22,27] Therefore, it is not yet appropriate to apply the direct OCT approach for BL hypersensitivity for all patient groups. It is currently recommended to perform STs first, especially in high-risk patients.[25] However, studies involving patients with both immediate and nonimmediate-type reaction history, similar to our patient group, suggest that this algorithm may also change.[21,28]

In childhood, exanthems are usually triggered by viral and bacterial infections.[23] In clinical practice, it is an important problem whether the source of these rashes is related to the current infection or to the drugs used. Viral infections are the most common cause of maculopapular or urticarial eruptions, independent of medication.[19] The rate of exanthema in viral infection is highly variable depending on the virus.[29] In children, rashes are less commonly caused by BL hypersensitivity than in adults.[30] In addition, diagnostic procedures, such as intradermal STs for BL hypersensitivity, are painful and less tolerated in this age group. STs require trained personnel, are time-consuming, and also, the sensitivity and even the positive predictive value of these tests in children are far from optimal. Recently, skipping STs and performing direct OCT has become an increasingly common approach in children with suspected BL hypersensitivity.[23] Graded dose OCT protocols were also designed for direct OCT. In the study conducted by Mill et al on 818 patients, with both immediate and nonimmediate-type reactions with amoxicillin, graded OCT without other previous tests were performed. The authors showed that 94% of patients tolerated the amoxicillin challenge, 2% had a mild immediate reaction and 4% had a nonimmediate reaction. Not differently from other known series, in all cases, the positive reactions to the challenge were mild, with only skin manifestations.[21]

Clearly positive in vitro tests (e.g., serum-specific IgE assays) can be useful for avoiding OCT, especially in subjects who experienced severe reactions like anaphylaxis.[25] Therefore, we used it in patients with BL hypersensitivity before performing OCT. In diagnosing penicillin hypersensitivity, 97.4% specificity and 19.3% sensitivity are reported for penicillin sIgE.[31] However, it should be kept in mind that the sensitivity of these tests is affected by many factors, such as the time interval between reaction and test and the severity of the reaction.[25]

In a study evaluating the long-term follow-up of patients who received direct OCT, concerning safety, 4.6% of the patients reported an allergic reaction after the reuse of penicillins. Most of them reported a delayed benign rash.[32]

In the article by Nisticò et al to evaluate the real incidence of drug hypersensitivity in a large pediatric population and the validity of a short diagnostic algorithm, only 6.4% resulted positive to drug provocation test of 107 patients. After the challenge, 64 patients took the culprit drug again within 1 year, and only two reported a drug reaction.[33]

Rashes that occur during infections in the pediatric age group put clinicians in a challenging situation regarding diagnosis. Most children are diagnosed with penicillin hypersensitivity without appropriate tests because physicians are afraid of more severe reactions. This penicillin hypersensitivity label also persists into adulthood. During infections, they cannot be treated with antibiotics that have optimal antimicrobial coverage.

If further studies support these findings, direct OCT could be performed without STs in the diagnosis of children with suspected hypersensitivity reactions to BLs. However, it is still controversial which patient group should undergo direct OCT and which OCT protocol and dose should be chosen.

In conclusion, the application of the direct OCT protocol is gaining acceptance among clinicians. Our findings suggest that OCT can reduce the number of patients with a misdiagnosis of drug allergy and prevent unnecessary drug eliminations.

Conflict of Interest
None declared.

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