

Diagnostic value and safety of penicillin skin tests in children with immediate penicillin allergy

Ilknur Kulhas Celik, M.D.,¹ Irem Turgay Yagmur, M.D.,¹ Ozge Yilmaz Topal, M.D.,¹ Muge Toyran, M.D.,² Ersoy Civelek, M.D.,² Betul Karaatmaca, M.D.,¹ and Emine Dibek Misirlioglu, M.D.²

ABSTRACT

Background: The first-line method in the diagnosis of patients who describe an immediate reaction after penicillin intake is a skin test (ST) with penicillin reagents.

Objectives: We aimed to determine the safety and diagnostic value of penicillin STs in the diagnosis of immediate reactions to penicillins in pediatric patients.

Methods: The study included pediatric patients with suspected immediate reaction to penicillin who were subjected to STs by using a standard penicillin test kit as well as suspected penicillin and the drug provocation tests (DPT) with the suspected penicillin at our clinic.

Results: A total of 191 patients (53.9% boys) with a median age of 6.83 years (interquartile range, 4.2–12 years) were included in the study. The time from drug intake to the onset of reaction was ≤ 1 hour in 138 patients (72.3%) and 1 to 6 hours in 53 patients (27.7%). Penicillin allergy (PA) was confirmed by diagnostic tests in 36 of the 191 patients (18.8%). In multivariate logistic regression analysis, the history of both urticaria and angioedema (odds ratio [OR] 27.683 [95% confidence interval {CI}, 3.143–243.837]; $p = 0.003$) and anaphylaxis (OR 56.246 [95% CI, 6.598–479.489]; $p < 0.001$) were the main predictors of a PA diagnosis. Although ST results were positive in 23 patients (63.8%), 13 patients (26.2%) had positive DPT results despite negative ST results. The negative predictive value (NPV) of STs was calculated 92.2% (155/168). None of our patients experienced immediate or delayed systemic and/or local reactions in relation to the STs.

Conclusion: A history of urticaria with angioedema and anaphylaxis were the main predictors of true PA in children with suspected immediate reactions. STs with penicillin reagents are safe for use in children. Although STs have a high NPV, DPT is the gold standard for diagnosis. DPTs should be performed as the final step of the diagnostic evaluation of PA in patients with negative ST results.

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One of the most common causes of drug hypersensitivity reactions (DHR) in children is β -lactam antibiotics (BLA).¹ The prevalence of self-reported amoxicillin allergy is 1.4% and 1.2% for other penicillin allergies (PA) in children.² However, confirmed cases of suspected penicillin DHRs in children are much lower.^{3–5} Patients with suspected antibiotic allergy usually have longer hospitalization times and are prescribed more-expensive and broad-spectrum antibiotics.^{6–8} Therefore, patients with suspected DHRs to penicillin should be evaluated to confirm true PA.

Immediate reactions (IR) occur within the first hour of administration of the suspected drug but may occur

up to 6 hours and are mostly mediated by drug-specific immunoglobulin E (IgE) antibodies. Some IRs are mediated by non-IgE-mediated mast-cell activation. IRs typically involve urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms, or anaphylaxis.⁹ Non-immediate DHRs occur >1 hour after the administration of the causative drug and are often mediated by T cells. They mostly manifest as a maculopapular rash. The guidelines recommend skin testing (ST) as the first-line method for diagnosing IRs to BLAs.^{10,11} If a non-immediate cutaneous reaction is mild, then a drug provocation test (DPT) can be performed without a previous ST.¹ STs for DHRs to BLAs comprise the major and minor determinants of penicillin, penicillin G, and any other suspected BLAs.¹² ST without benzylpenicilloyl-poly-L-lysine (PPL) and minor determinant mixture (MDM) may miss a BLA allergy diagnosis in 20% of the cases. However, this concern is still under debate.¹³

The negative predictive value (NPV) of STs is high but some reactions have developed after DPT in patients with suspected PA who have negative ST results.^{14–17} The frequency of systemic reactions related to STs with penicillin reagents in children has been

From the ¹Division of Pediatric Allergy and Immunology, Ankara City Hospital, Ankara, Turkey; and ²Department of Pediatric Allergy and Immunology, Health Sciences University, Ankara City Hospital, Ankara, Turkey
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Address correspondence to Ilknur Kulhas Celik, M.D., Division of Pediatrics Allergy and Immunology, Ankara City Hospital, postal code:06800, street no:1604 Ankara, Turkey

E-mail address: dr.ilknur-46@windowslive.com

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reported to vary between 0.3 and 1.2%.¹⁸ The aim of this study was to determine the NPV and safety of STs performed by using penicillin reagents in children with a history of IRs to penicillins.

METHODS

The study was designed as cross-sectional and included patients who presented to our pediatric allergy clinic between January 2013 and December 2019, with a history of IRs to penicillins and who had undergone STs with a standard penicillin test kit (Diater Pharmaceutical Laboratory, Madrid, Spain) and suspected penicillin and DPTs with the suspected penicillin. The study was approved by the ethics review committee of Ankara City Hospital (EC E1-20-338). Written informed consent was obtained from the parents or legal guardians of patients.

Allergy Workup

The initial drug allergy workup started with the standardized European Network of Drug Allergy questionnaire.¹⁹ A detailed history was taken. If the history was consistent with drug hypersensitivity, then STs and DPTs were performed. The reactions suggested that IgE-mediated reactions, such as urticaria, angioedema, bronchospasm, and anaphylaxis, were classified as immediate when they occurred within the first 6 hours of drug administration. Patients who had a mild cutaneous reaction (such as maculopapular exanthem) after 1 hour of drug intake and suggesting T-cell mediated reaction were excluded from the study.

For patients who had a reaction with phenoxymethylpenicillin (pen-V) or benzylpenicillin (pen-G) and negative ST results with PPL, MDM, and pen-G, we performed a DPT with pen-V or pen-G. For patients who had a reaction with aminopenicillins or other penicillins and negative ST results with PPL, MDM, pen-G, and aminopenicillins or other penicillins, we performed DPT with suspected aminopenicillin or other penicillins.

Prick and Intradermal Testing

Patients were subjected to skin-prick test (SPT) with the classic penicillin test kit (including PPL and MDM), pen-G (10,000 IU/mL), amoxicillin-clavulanate (20 mg/mL), and the suspected penicillin. If SPTs results were negative, then the patients had an intradermal test (IDT) with the classic penicillin test kit, pen-G, and the suspected penicillin. We used classic penicillin reagents available in the Diater DAP kit. Amoxicillin-clavulanate (intravenous form) was used for ST until June 2019, because there were no separate preparations of amoxicillin and clavulanate in our country. After June 2019, we used amoxicillin and clavulanate separately (Diater DAP kit). Medications that

could affect the STs or DPTs were stopped 1 week before testing.^{13,20}

All of the drugs were initially tested on the forearm skin by using the prick method, and reactions were considered positive when a wheal with a diameter > 3 mm than the negative control with surrounding erythema was present 20 minutes later. When prick tests yielded negative results, 0.02 mL of the relevant agent was injected intradermally on the forearm skin. The diameter of the injection papule (wheal) was measured immediately after injection. Readings were taken 20 minutes after the injections. Results were considered positive when the size of the initial wheal increased by ≥ 3 mm in diameter accompanied by erythema.^{9,20} Positive controls for prick tests were carried out with histamine at 10 mg/mL; 0.9% NaCl was used as the negative control. When a ST yielded a positive result, the patient was considered to be hypersensitive to the tested drug, and the procedure was ceased.

DPT

An incremental DPT protocol was used. The therapeutic single and daily doses of the drug were calculated according to age and weight of the patient. The European Network of Drug Allergy guidelines for DPTs were carefully followed.²¹ The DPT involved administering the suspected drug in divided doses (generally 3–4 doses) every 30 minutes until reaching a cumulative dose close to the daily dose of the drug. The test was discontinued in the event of any reaction. The DPT was performed as open. After the last dose had been administered without a reaction, the patient was kept under surveillance for at least 2 hours.

Statistical Analyses

Statistical analyses were performed by using the SPSS v.22 statistical software package for Windows (IBM, Chicago, IL). Continuous variables were expressed as means and standard deviations for data with a normal distribution and as medians and interquartile ranges (IQR) for non-normally distributed data. The χ^2 test was used to compare nonparametric data; the Mann-Whitney *U* test was used for comparisons among non-normally distributed continuous variables and independent samples *t*-test for normally distributed continuous variables. A value of $p < 0.05$ was considered statistically significant. A logistic regression analysis was performed to determine the predictors of PA confirmation, in univariable analysis values of ≤ 0.20 were included in the multivariable analysis. The results are given as odds ratio and 95% confidence interval.

RESULTS

A total of 206 patients (52.6% boys) with suspected PA underwent STs by using the penicillin test kit. Fifteen of these patients had STs by using a penicillin test kit and also the suspected drug, with negative results. However, DPT with the suspected drug could not be performed for these patients because parental consent was not available. These patients were excluded from the study. A total of 191 patients (53.9% boys), with a median (IQR) age of 6.83 years (4.2–12 years), who had completed an allergy workup were included in the study. Amoxicillin-clavulanate was the most commonly implicated drug ($n = 129$ [67.5%]). Suspected drugs are shown in Table 1.

Urticaria was the most common presented symptom ($n = 89$ [46.6%]) (Table 2). The time from drug intake to the onset of reaction was ≤ 1 hour in 138 patients (72.3%) and 1 to 6 hours in 53 patients (27.7%). The median (IQR) value of time elapsed between the original clinical reaction to penicillin and allergy workup was 5.37 months (2.95–15.15 months). Of the patients, 154 (80.6%) had a reaction to aminopenicillins, 36 (18.9%) had a reaction to pen-V and pen-G, and 1 patient had a reaction to piperacillin-tazobactam.

Patients Who Reported Reactions to Aminopenicillins

Among 191 patients, 154 (80.6%) reported a reaction to aminopenicillins. Allergy was confirmed with diagnostic tests in 33 patients (21.4%), of whom 21 (63.6%) had positive ST results. A total of 127 patients were subjected to STs with PPL plus MDM plus pen-G plus amoxicillin-clavulanate (intravenous). Although ST results were positive in 7 patients (5.4%), 10 patients (7.8%) had positive DPT results, despite negative ST results. Eight patients were subjected to standard amoxicillin and clavulanate antigens separately. Although ST results were positive in one patient, the other patient had positive DPT results, despite negative ST results.

Table 1 Culprit drugs of the study patients

Culprit drug	No. (%)
Amoxicillin-clavulanate	129 (67.5)
Penicillin G	29 (15.2)
Amoxicillin	6 (3.1)
Penicillin V	7 (3.7)
Ampicillin-sulbactam	13 (6.8)
Ampicillin	2 (1)
Amoxicillin-clavulanate + cefixime	2 (1)
Amoxicillin-clavulanate + cefuroxime	1 (0.5)
Amoxicillin-clavulanate + ceftriaxone	1 (0.5)
Piperacillin-tazobactam	1 (0.5)

SPT results were positive in four patients (19%) for the following: PPL in one patient, Pen-G in one patient, and amoxicillin-clavulanate in two patients. Seventeen patients (81%) had positive positive IDT results for the following: amoxicillin-clavulanate in five patients, MDM in six patients, PPL in two patients, clavulanate in one patient, Pen-G in two patients, and ampicillin-sulbactam in one patient. The DPT results were positive despite negative ST results in 12 patients (40%), of whom, 10 had positive DPT results with amoxicillin-clavulanate and two had positive DPT results with pen-V. Isolated cutaneous symptoms developed in all the patients who had positive DPT results: urticaria in 11 patients and urticaria with angioedema in one patient.

Patients with Reactions to Pen-V and Pen-G

There were 36 patients who had a DHR to pen-V and pen-G, and allergy was confirmed in two of them (5.5%). One of them tested positive on IDT with PPL and the other tested positive on DPT with pen-V. One patient with a positive DPT result developed urticaria during the DPT.

Patients with Reactions to Other Penicillins

One patient had a reaction to piperacillin-tazobactam. This patient tested negative on STs with penicillin determinants but positive on IDT with piperacillin-tazobactam. The results of diagnostic tests of patients are summarized in Fig. 1. In the current study, STs were positive in 23 of 36 patients (63.8%), with PA confirmed with diagnostic tests. Among patients with positive ST results, PPL and MDM positivity was detected in 10 patients (43.5%). Although ST results were positive in 23 patients (63.8%), 13 patients (26.2%) had positive DPT results despite negative ST results. The NPV of STs was calculated as 92.2% (155/168). None of our patients experienced immediate or delayed systemic and/or local reactions in relation to STs. Moreover, mild-to-moderate cutaneous symptoms developed in patients who had DPT results, and none had a serious systemic reaction.

Predictors of PA Diagnosis

PA was confirmed by diagnostic tests in 36 patients (18.8%). Patients with confirmed PA were significantly more likely to develop a reaction within the first hour of drug intake, to present with urticaria with angioedema, and to have anaphylaxis than patients with unconfirmed PA ($p < 0.05$) (Table 2). In the univariate logistic regression analysis, a history of urticaria with angioedema, only urticaria, anaphylaxis, concomitant allergic disease, and a reaction within the first hour of drug intake were associated with confirmation of a PA. In the multivariate logistic regression analysis, a history

Table 2 Comparison of the patients with confirmed allergy vs the patients with unconfirmed allergy

	Unconfirmed Allergy (<i>n</i> = 155)	Confirmed Allergy (<i>n</i> = 36)	<i>p</i>
Gender <i>n</i> (%)			0.6
Girls	84 (54.2)	19 (45)	
Boys	71 (45.8)	17 (55)	
Age at onset of reaction, median (IQR), y	6.5 (4.16–11.6)	7.62 (5–12.5)	0.5
Age at DPT, median (IQR), y	7.5 (5–13.3)	8.6 (5.7–12.8)	0.5
No. doses taken before a reaction, median (IQR)	2 (1–4)	1 (1–3)	
Interval between the last dose and the reaction, median (IQR), min	60 (15–120)	30 (11.2–60)	0.16
Interval between ST and reaction, median (IQR), mo	5.8 (3–15.8)	4.2 (2–13)	0.16
Time between the last dose and the reaction, <i>n</i> (%)			0.013
<1 hr	106 (68.4)	32 (88.9)	
1–6 hr	49 (31.6)	4 (11.2)	
Eosinophil count (mm ³), median (IQR),	100 (100–300)	150 (25–375)	0.62
IgE level, (IU/ml) median (IQR),	31 (13–140)	54 (25–370)	0.17
Presence of allergic disease, <i>n</i> (%)	32 (20.6)	14 (38.8)	0.059
Presenting reaction, <i>n</i> (%)			
Anaphylaxis	13 (8.3)	14 (38.9)	<0.001
Undefined rash	35 (22.5)	1 (2.8)	0.049
Urticaria	77 (49.6)	12 (33)	0.97
Urticaria + angioedema	15 (9.6)	9 (25)	0.001
Angioedema	8 (5.1)	0	0.25
Other symptoms	7 (4.5)	0	0.59

IQR = Interquartile range; DPT = drug provocation test; IgE = immunoglobulin E.

of urticaria with angioedema, only urticaria, anaphylaxis, and a reaction within the first hour of drug intake were predictors of confirmation of a PA (Table 3).

DISCUSSION

In our study, a PA was confirmed in 36 patients (18.8%), and 23 of the 36 patients (63.8%) tested positive on STs. Among patients with positive ST results, positivity was detected with PPL and MDM in 13 patients (56.5%), amoxicillin-clavulanate in 7 patients (30.4%), ampicillin-sulbactam in 1 patient (4.3%), clavulanate in 1 patient (4.3%), and piperacillin-tazobactam in 1 patient (4.3%). The first-line method for diagnosing IRs to β -lactams is ST.^{10,11} Results of previous studies suggest that STs without PPL and MDM may miss a diagnosis of allergy in 20% of the participants.¹³ In our study, PPL and MDM positivity was present in 10 patients (43.5%) with positive STs.

There is a wide range of confirmation rates in studies that evaluated children with suspected immediate BLA allergy and reported confirmation rates between 13.6% and 58.3%.^{3,14,15} In addition, there are patients with negative ST results but who tested positive on DPT,

and their prevalence also varies among studies.^{3,14,15,22} Ponvert *et al.*¹⁴ confirmed BLA allergy in 50 of 162 children (30.9%) who developed DHRs within the first hour after exposure to BLAs. They did not use PPL and MDM, and 43 of 50 patients (86%) tested positive on STs. In our study, the patients who had reactions within the first 6 hours of drug intake, especially within the first hour, had ST positivity in 63.8% of the patients whose PAs were confirmed by STs. The majority of our patients were diagnosed by using STs but not all. Although we used PPL and MDM in the current study, both the rate of confirmed allergies and the rate of ST positivity were lower than those reported by Ponvert *et al.*¹⁴

Atanasković-Marković *et al.*¹⁵ confirmed allergy by using STs (including major and minor determinants) or DPT in 682 of 1170 children (58.3%) who developed a DHR within the first hour after exposure to penicillin and/or cephalosporin. They found a low number of patients with negative ST results and positive DPT results among patients with confirmed allergy.¹⁵ In our study, the rate confirmation of drug allergy by diagnostic tests was lower and the number of patients with positive DPT results despite negative ST results was higher in comparison with corresponding figures

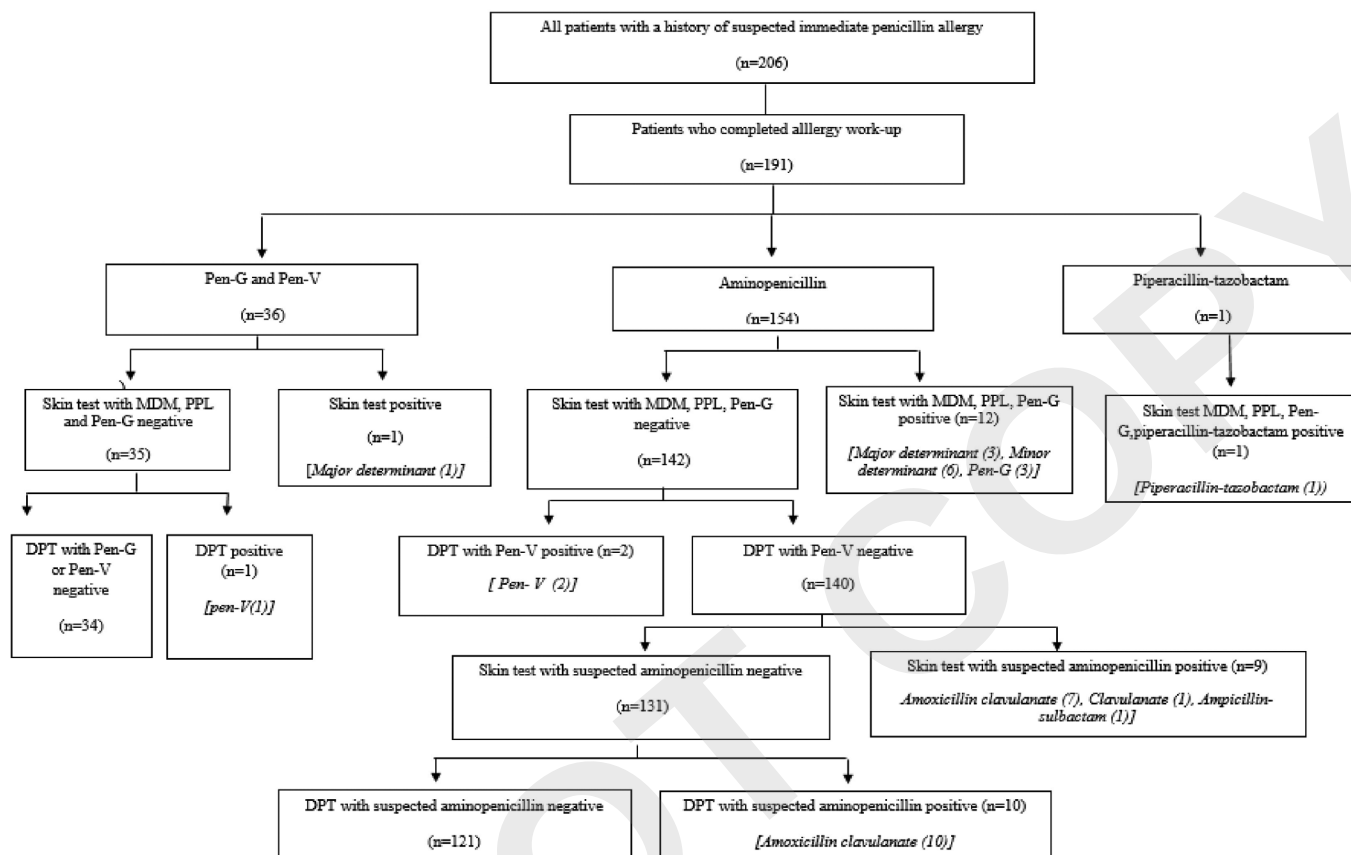


Figure 1. Diagnostic test results of all the patients.

reported by Atanasković-Marković *et al.*¹⁵ In one study, Zambonino *et al.*³ confirmed allergy in 9 of 66 patients (13.6%) who experienced a DHR within the first hour after receiving a BLA when using the same PPL and MDM as in our study, and found DPT positivity in five of these nine patients, despite negative ST results. Compared with the study by Zambonino *et al.*,³ a higher rate of confirmed allergies and a higher ST positivity rate in patients with confirmed allergy were found in our study.

Recently, Solensky *et al.*¹⁶ conducted a study in adult patients with a history suggestive of IgE-mediated PA by using a different penicillin kit with major and minor determinants, and reported an NPV of 97.7% for penicillin STs. In the present study, we found that the NPV of STs was 92.2% (155/168). The NPV of STs is high in studies that involved both children and adults. However, some patients can develop a reaction after negative ST results, and the number of these patients is different among

Table 3 Predictors of a penicillin allergy diagnosis with diagnostic tests

Parameters	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Gender	0.945 (0.457–1.954)	0.878		
Concomitant allergic disease	0.409 (0.188–0.887)	0.021	0.487 (0.195–1.216)	0.123
Allergic disease in family	0.764 (0.262–2.228)	0.621		
Age <10 y	0.719 (0.323–1.602)	0.419		
Age <5 y	1.471 (0.661–3.272)	0.343		
Reaction start time <1 hr	0.270 (0.091–0.807)	0.013	3.294 (1.011–10.739)	0.048
Urticaria	1.974 (0.922–4.227)	0.077	8.092 (1.008–64.959)	0.049
Urticaria + angioedema	0.321 (0.128–0.809)	0.022	27.683 (3.143–243.837)	0.003
Anaphylaxis	0.144 (0.060–0.346)	<0.001	56.246 (6.598–479.489)	<0.001

OR = Odds ratio; CI = confidence interval.

studies.^{3,14,15,22} Differences in methodologies used for patient selection, test procedures, and populational variances may have affected the results.

Although the NPV of penicillin STs is high in some studies,^{16,23} limited studies are available on the positive predictive value of penicillin STs in children.²⁴ This is because DPT cannot be performed in patients with positive ST results due to ethical reasons.²⁵ Although low positive predictive value and sensitivity were reported for ST results in children with non-serious immediate hypersensitivity reactions to BLAs, adequate information is not available in patients with severe IRs.²⁶ Mill *et al.*²⁷ evaluated 818 pediatric patients (median age, 1.7 years) with a history of isolated mild cutaneous reactions with amoxicillin and reported that 17 of the children (2.1%) developed an IR with DPT. It was reported that only 1 of the 17 children who experienced IRs had a positive ST result and, therefore, sensitivity of the ST was poor. We had patients who reported anaphylaxis as well as those with benign immediate hypersensitivity reactions, and we did not perform DPT due to ethical concerns for the patients with positive ST results. Thus, we could not estimate the positive predictive value of the STs.

In comparison with adults, children have a lower prevalence of systemic reactions associated with STs.¹⁸ Ponvert *et al.*¹⁴ reported that systemic reactions in relation to STs developed in 2.6% of patients who underwent STs and that all of these reactions were mild or moderate. Atanasković-Marković *et al.*¹⁵ observed no systemic reactions related to STs in patients who reported IRs to penicillin and/or cephalosporin. In our study, none of the patients developed systemic reactions during STs, which is consistent with the low rate of systemic reactions reported in the literature. However, in our study, we could not evaluate all the patients with a history of penicillin anaphylaxis because we only performed tests in those who accepted diagnostic tests; this was a limitation of the data.

IRs have a higher confirmation rate than non-IRs with BLAs in children.¹⁸ Ponvert *et al.*¹⁴ reported that the confirmation rate of BLA allergy was significantly higher in the children who had IRs than in the children who had non-immediate reactions (non-IRs). In addition, they found that the confirmation rate of BLA allergy was higher in the children who reported anaphylaxis.¹⁴ In the present study, we found that a history of having both urticaria and angioedema, anaphylaxis and a reaction within first hour of drug intake were predictors of confirmation of PA. Both the study by Ponvert *et al.*,¹⁴ and our findings showed that patients who had a reaction within the first hour of drug intake and a history of anaphylaxis had higher confirmation rates. We evaluated a large pediatric patient group. All of our patients were tested with a standard penicillin test kit. However, there were some

limitations of our study. Our study was a retrospective study and only a small number of our patients (5.7%) with suspected amoxicillin-clavulanate or amoxicillin allergy could be tested with standard amoxicillin and clavulanate antigens separately.

CONCLUSION

PA was not confirmed in 81.2% of our patients, which indicated the importance of allergy assessment to avoid labeling patients with a suspected history as “allergic to antibiotic.” In addition, although the majority of the patients without true PA could be detected with STs before DPT, the NPV of STs was not 100%. Our findings showed that, although STs with penicillin determinants were safe for use in children and had a high NPV, DPT remained the gold standard method for the diagnosis of PA.

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