

Frequency of selective immediate responders to aminopenicillins and cephalosporins in Turkish children

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ABSTRACT

Background: Beta-lactam antibiotics (BLA) are the most commonly prescribed antibiotics and are responsible for the majority of immediate hypersensitivity reactions to drugs in children. Cross-reactivity is important in hypersensitivity to BLAs because these drugs all share a common beta-lactam structure and some share similar side chains.

Objective: The aim of this study was to evaluate the clinical characteristics of patients who are diagnosed with immediate-type BLA hypersensitivity and frequency of patients with side chain hypersensitivity, "selective responders."

Methods: The study included patients who were diagnosed with immediate-type BLA hypersensitivity between January 2011 and May 2016 in a pediatric allergy outpatient clinic. The patients who had negative penicillin test (minor determinant mixture, benzylpenicilloylpoly-L-lysine, penicillin G) results and could tolerate penicillin V and/or BLAs with dissimilar side chains but had positive skin and/or provocation test results with the suspected drug were diagnosed as selective responders.

Results: During the study period, 357 patients (55.2% girls) were admitted to our clinic with suspected immediate-type BLA hypersensitivity. Parents of 11 patients did not give consent for an allergy workup with the suspected drug. Forty-five of the patients were diagnosed (45/346 [13%]) based on skin test or drug provocation test results. The most common susceptible agent was amoxicillin-clavulanate. Of the patients, 71.4% with a reaction to sulbactam-ampicillin /or amoxicillin-clavulanate and 93.7% with a reaction to cephalosporin were classified as selective responders.

Conclusion: Among children with immediate BLA hypersensitivity, selective responders constituted an important group. Most of the patients with reactions to aminopenicillin and cephalosporins safely tolerated penicillin V and BLAs with dissimilar side chains after negative allergy workup results.

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Beta-lactam antibiotics (BLA) are the most commonly prescribed antibiotics and are responsible for the majority of immunoglobulin E (IgE) mediated hypersensitivity reactions.¹ The antigenic determinants are β -lactam ring and side R chains.² Cross-reactivity is important in hypersensitivity to BLAs because they all share a common β -lactam structure and may have similar side chains. Specific IgE against R chains may cause selective sensitization to aminopenicillins or cephalosporins.^{1,2} Patients with immediate allergic reactions to BLAs can be classified as "selective responders" to only a group of BLAs with similar R chains because of hypersensitivity to side R chains.^{3,4}

The frequency of cross-reactivity is reported to be higher in children than in adults²; therefore, it is usually recommended to withdrawal all classes of BLAs in children with anaphylactic and immediate reactions.^{3,4} However, this approach may cause overuse of antibiotics that are less effective with more adverse effects and are more expensive. Defining patients who are selective responders may help to determine patients who should not avoid all BLAs. A workup based on skin tests with suspected and other BLAs and provocation tests should be performed to confirm hypersensitivity and to determine if the child is sensitized to one or several BLAs.^{3,4} The aim of this study was to evaluate the clinical characterization of patients who were diagnosed with immediate-type BLA hypersensitivity and to determine the frequency of selective responders.

METHODS

This study was conducted in the Department of Pediatric Allergy and Immunology, Ankara Children's Hematology/Oncology Training and Research Hospital, Ankara, Turkey. The study included patients who were diagnosed with immediate-type BLA hypersensitivity between January 2011 and May 2016 in the pediatric allergy outpatient clinic. Patients admitted

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with a history of a drug reaction within 1 hour of drug intake were diagnosed as BLA hypersensitivity if they had positive drug skin test or drug provocation test (DPT) results with the suspected BLAs. Patients with nonimmediate reactions and/or patients who had a reaction with drugs other than BLA were not included. Skin tests and/or DPTs could not be performed in cases in which the parents did not give consent. The local ethics committee approved the study design and protocol.

The drug allergy workup started with the standardized European Network for Drug Allergy (ENDA) questionnaire on drug allergy.⁵ Reactions that occurred within the first hour were labeled as immediate reactions, mostly manifested clinically by urticaria, angioedema, rhinitis, bronchospasm, and anaphylaxis. If the history of the reaction was compatible with drug hypersensitivity, then skin tests and oral DPTs with the suspected drug were performed. Antihistamine medications that could affect the skin tests or DPTs were stopped 1 week before testing.^{6–8} The diagnostic algorithm of the ENDA was used for diagnosing immediate BLA hypersensitivity.^{9,10}

Prick and Intradermal Skin Testing

The patients were subjected to prick and intradermal skin testing with the classic penicillin test and the suspected drug.^{6,7} Skin tests included the classic penicillin test (benzylpenicilloypoly-L-lysine, minor determinant mixture, and penicillin G [10,000 IU/mL]), amoxicillin-clavulanate (20 mg/mL), and the suspected drug. If the suspicious drug is cephalosporin, then skin tests were performed with the culprit drug by using the suggested concentration (2 mg/mL).⁷ Because there is no separate preparation in our country, patients could not be tested separately for amoxicillin and clavulanic acid.

All of the drugs were initially tested on the volar forearm skin by using the prick method, and reactions were considered positive when a wheal diameter of >3 mm that of 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 volar forearm skin. Readings were made 20 minutes after injections. Results were considered positive when an increase of >3 mm in the wheal diameter accompanied by erythema was present. Positive controls for prick tests were carried out with histamine at 10 mg/mL. A negative control sample, of 0.9% NaCl, for prick and intradermal tests was used. When a skin test result was positive, the patient was considered to be hypersensitive to the tested drug, and the procedure was ceased.

DPTs

The DPTs were performed if other investigations were inconclusive and the DPTs were not contraindicated according to the ENDA guideline.⁸ An open DPT was performed by a physician with full resuscitation backup (H.G., E.V., M.C.). An oral DPT involved administering the suspected drug at divided doses every 30 minutes until a cumulative dose close to the age- and weight-adjusted daily dose of the drug was achieved. The drug was given in a maximum of five doses.¹¹ The test was discontinued in the event of any adverse drug reaction. The DPT result was considered positive if any objective symptoms or signs were documented and negative if no sign of drug hypersensitivity occurred after the usual daily doses were administered. After the last dose, the patient was observed for at least 2 hours.

Classification of the Patients According to the Allergy Workup

For patients who had a reaction with penicillin and had negative skin test results, we performed a DPT with penicillin V. If the test result was negative, then we concluded that the patient did not have hypersensitivity. If the skin test or the DPT result was positive, then we concluded that the patient was hypersensitive to penicillin and was grouped as being “cross-reactive.” For the patient who had a reaction with aminopenicillins and had a negative skin test result with classic penicillin and aminopenicillin, we performed DPT with aminopenicillin. If this test result was negative, then we concluded that the patient did not have hypersensitivity. When the DPT result or the skin test result with aminopenicillin was positive, we performed a DPT with penicillin V and cefuroxime (a cephalosporin with a dissimilar side chain). If the patient had a positive DPT result with penicillin V, we concluded that the patient was in the cross-reactive group; if the patient had a negative DPT result with penicillin V and cefuroxime, we concluded that the patient was in the selective-responder group.

When the patient had a reaction with cephalosporins and had negative skin test results, we performed DPT with the suspected drug. If the test result was negative, then we concluded that the patient did not have hypersensitivity. If the test result was positive, then the patient underwent DPT with penicillin V and/or amoxicillin clavulanate and a cephalosporin with a dissimilar side chain. If DPT with penicillin V or a skin test with classic penicillin result was positive, then we concluded that the patient was in the cross-reactive group. If the patient had a negative DPT result with penicillin V and cephalosporin with a dissimilar side chain, then the patient was considered a selective re-

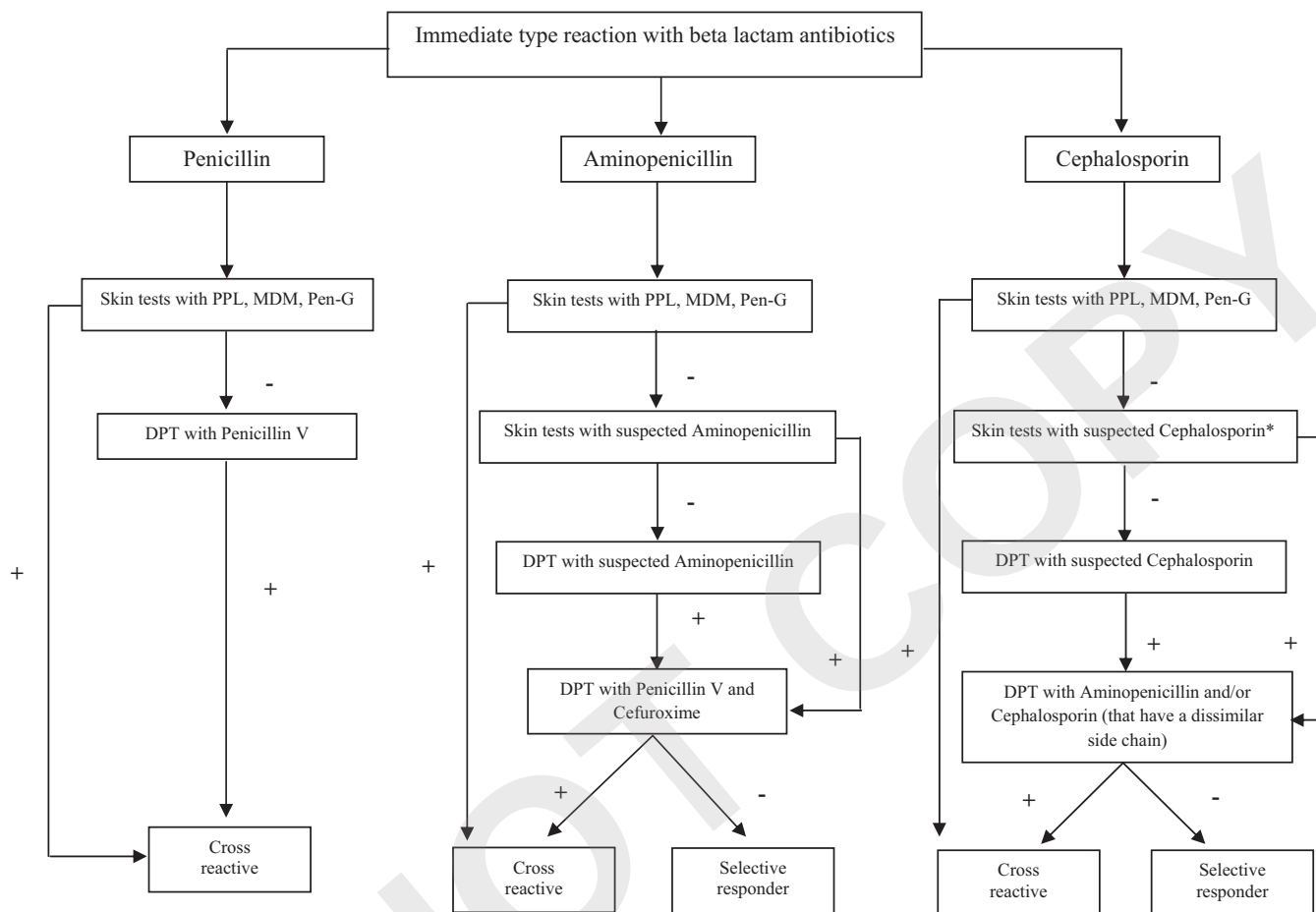


Figure 1. Algorithm for allergy workup. *If there is no parenteral form of the drug, direct provocation was applied with suspected cephalosporin. PPL = Penicillin major determinant; MDM = Penicillin minor determinant; Pen-G = Penicillin-G; DPT = Drug provocation test.

sponder (The flow chart of the study is summarized in the Fig. 1).

Statistical Analysis

Statistical analyses were completed using SPSS statistical software, version 22 (SPSS Inc, Chicago, IL). Descriptive data for categorical and numerical variables with non-normal and normal distributions were rendered as frequencies, median (interquartile range) and mean $\pm$ standard deviation, respectively.

RESULTS

During the study period, 357 patients (55.2% girls) were admitted to our clinic with suspected immediate-type BLA hypersensitivity. Parents of 11 patients did not give consent for an allergy workup with the suspected drug. Forty-five of the patients (45/346 [13%]) were diagnosed according to skin test or DPT results. Characteristics of these patients are shown in Table 1. Of these patients, the reaction was anaphylaxis in 19 (42.2%), urticaria in 19 (42.2%), and urticaria and angioedema in 7 (15.6%) at referral. The susceptible an-

tibiotics were penicillin in 29 patients (64.4%) and cephalosporin in 16 patients (35.6%). The classic penicillin test results were positive for 9 of the patients and negative for 36 (Fig. 2).

Of the 29 patients who reported a reaction to penicillin, the classic penicillin test result was found to be positive in 8 children (27.6%). Among the 21 patients with negative classic penicillin test results, skin test results with the offending drug were positive in 7 patients and DPT results were positive in 14 patients. In 26 patients who reported a reaction to amoxicillin-clavulanate, a classic penicillin test result was positive in 6 patients. Among the 20 patients with a negative classic penicillin test, 7 patients had a positive result to skin tests and 13 patients had a positive reaction to DPTs. In addition, two patients with a history of immediate reaction to ampicillin-sulbactam had positive reactions to the classic penicillin test.

Among the 16 patients who reported a reaction to cephalosporins, only 1 patient (6.3%) had a positive classic penicillin test result. In the 15 patients with a negative classic penicillin test result, the skin test re-

Table 1 Characteristics of patients with confirmed BLA hypersensitivity

	Classic Penicillin Test Result, Positive (<i>n</i> = 9)	Classic Penicillin Test Result, Negative (<i>n</i> = 36)	For All the Patients (<i>n</i> = 45)
Girls, no. (%)	6 (66.7)	19 (52.8)	25 (55.6)
Reaction age, y			
mean $\pm$ SD	7.42 $\pm$ 5.14	8.57 $\pm$ 4.97	8.34 $\pm$ 4.97
median (IQR)	6.35 (4.01–11.86)	7.78 (4.73–12.83)	7.13 (5.03–12.75)
Test age, y			
mean $\pm$ SD	7.91 $\pm$ 4.68	8.9 $\pm$ 4.89	8.70 $\pm$ 4.81
median (IQR)	6.71 (4.5–11.99)	8.1 (4.9–12.9)	7.84 (5.16–12.91)
Time between reaction and allergy workup, mo			
mean $\pm$ SD	6.0 $\pm$ 11.3	4.23 $\pm$ 6.33	4.58 $\pm$ 7.45
median (IQR)	2 (1.5–4)	2 (1.1–3)	2 (1.25–3.0)
History of reactions to BLAs, no. (%)			
Penicillins	8 (88.9)	21 (58.3)	29 (64.4)
Amoxicillin-clavulanate	6	20	26
Ampicillin-sulbactam	2	—	2
Penicillin G	—	1	1
Cephalosporins	1 (11.1)	15 (41.7)	16 (35.6)
Ceftriaxone	1	11	12
Cefixime	—	1	1
Cefotaxime	—	1	1
Cefprozil	—	1	1
Cefdinir	—	1	1
Reaction in history, no. (%)			
Anaphylaxis	5 (55.6)	14 (38.9)	19 (42.2)
Urticaria	3 (33.3)	16 (44.4)	19 (42.2)
Urticaria + angioedema	1 (11.1)	6 (16.7)	7 (15.6)
Family history for BLA allergy, no. (%)	—	2 (5.6)	2 (4.4)

BLA = β -Lactam antibiotic; SD = standard deviation; IQR = interquartile range.

sults with the offending drug were positive in 12 and the DPT results were positive in 3 patients. In all of these 15 patients who underwent DPT with penicillin V and cephalosporin with a dissimilar side chain, there were no reactions. Of these patients, 71.4% (20/28) who had a reaction to sulbactam-ampicillin and amoxicillin-clavulanate and 93.7% of the patients (15/16) who had a reaction to cephalosporins tolerated penicillin V and cephalosporin with a dissimilar side chain and were classified as selective responders (Fig. 2). None of the patients had a reaction during skin tests. Only one patient had mild anaphylaxis (urticaria, angioedema, and dyspnea) during a DPT with penicillin G and recovered completely after use of adrenaline.

DISCUSSION

In our study, we showed that the most common sign for immediate-type BLA allergy was anaphylaxis and that the most common susceptible drug was amoxicillin-clavulanate. Among the patients, 71.4% who had a

reaction to aminopenicillin and 93.7% of the patients who had a reaction to cephalosporins were classified as selective responders. Skin test and DPT results showed a wide range of frequency for real BLA hypersensitivity among the children (7–60%).¹² Proven immediate hypersensitivity reactions are more frequent than non-immediate reactions.¹³ In two recent reports conducted in large series of children with suspicion of immediate BLA reactions, proven hypersensitivity was reported as 13.6%¹⁴ and 30.9%.¹³ In our study 13% of the patients with immediate reactions (45/346) reported BLA hypersensitivity were proven with an allergy workup. This low frequency of real hypersensitivity showed that patients with suspected BLA reactions should be evaluated with skin tests and DPTs before ceasing drug use.

A diagnosis of BLA allergy was based on a detailed clinical history, skin tests, and DPTs.¹⁵ The recommended approach is to begin allergy workup with skin tests by using benzylpenicilloylpoly-L-lysine and mi-

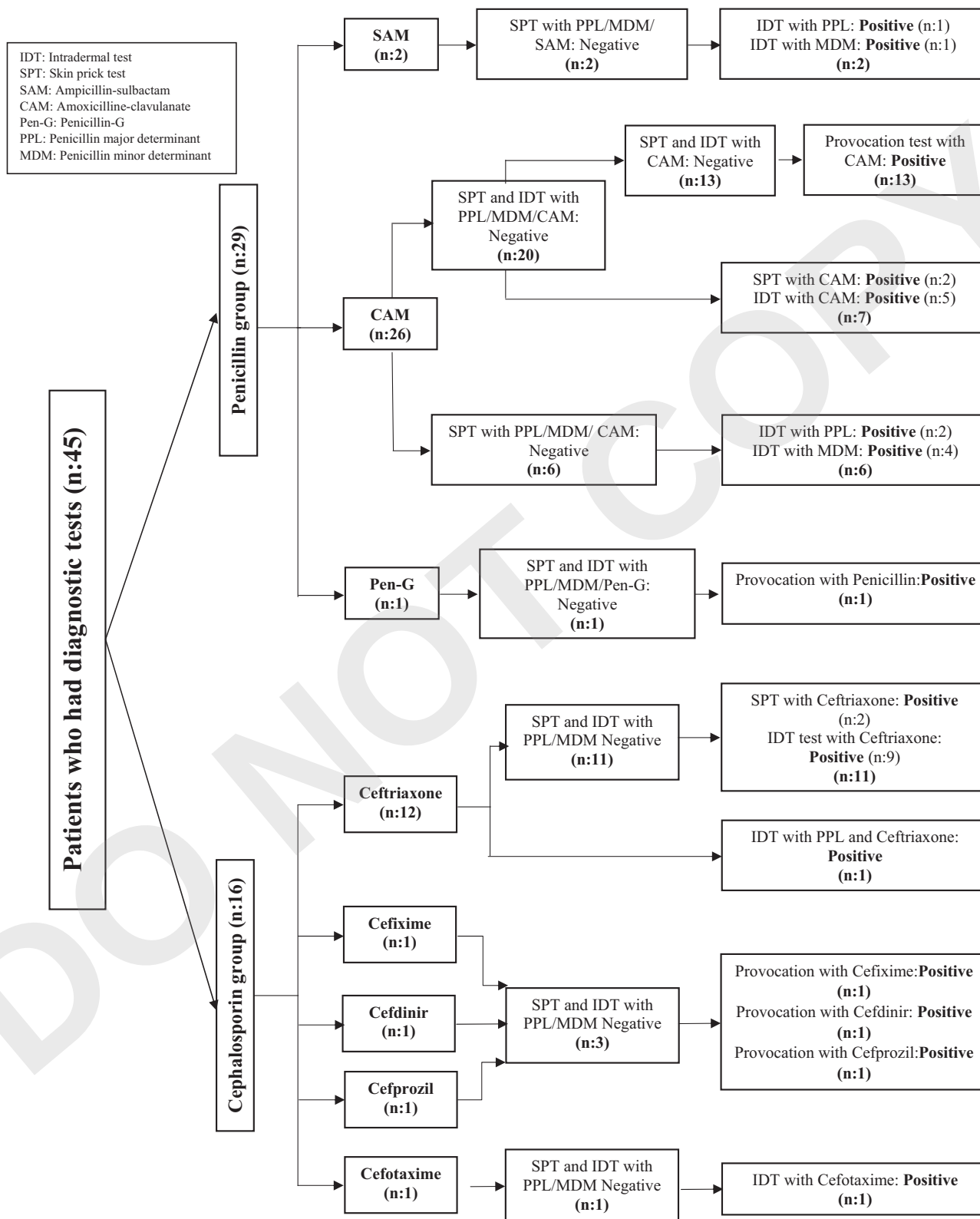


Figure 2. Patients diagnosed according to allergy workup.

nor determinant mixture. If the results are positive, then a diagnosis can be made. If the results are negative, then the use of the culprit drug provides addi-

tional information about hypersensitivity and cross-reactivity.^{8,9} Immediate reading of the skin tests have good diagnostic value in suspected BLA hypersensitivity.

ity but up to 30% patients with immediate allergic reaction to BLAs will fail to be diagnosed if a DPT is not performed.¹ In our study, 62.2% of the patients (28/45) were determined to have BLA hypersensitivity by using skin-prick test and 37.7% (17/45) were diagnosed by using DPT.

Drug tests, including skin tests and DPTs, were shown, in previous reports, to be safe.⁶ Systemic reactions are reported in 1.3% of patients during allergy workup, which is more frequent among patients with a history of anaphylaxis (8.8%).¹⁶ None of our patients had any adverse reaction during the skin tests, and only one patient had mild anaphylaxis during a DPT with penicillin G and totally recovered with the use of adrenaline. When available DPT should be performed because it is the criterion standard and the last step of an allergy workup for drug allergy.⁹

Aminopenicillins are reported to be the most frequently prescribed BLAs and the most common cause of sensitization.¹ Although patients who had a reaction with aminopenicillins were expected to have cross-reactivity with other BLAs, it has been shown that some patients with a positive response to aminopenicillins could tolerate other compounds, such as Penicillin G and/or penicillin V.¹⁶ In two recent studies conducted among adults, 42% and 78% of the patients with aminopenicillin hypersensitivity were shown to tolerate penicillin and were classified as selective responders.^{17,18} However, there are limited data on this subject among children. Ponvert *et al.*¹³ reported that 76% of patients with immediate reactions to BLAs showed cross-reactivity and/or cosensitization with other BLAs; however, whether the cross-reactive BLAs had similar or dissimilar side chains was not specified. In our study, 71.4% of patients with aminopenicillin hypersensitivity were shown to tolerate penicillin V. Our results resembled adult studies that highlighted the need for allergy workup for children who reported an aminopenicillin reaction before labeling the patients as allergic to all BLAs.

Besides penicillins V and G, the patients with aminopenicillin hypersensitivity are reported to tolerate cephalosporins with dissimilar side chain. In an adult study, including three children, none of the patients with aminopenicillin allergy were reported to react with cephalosporins with dissimilar side chains (cefuroxime and/or cefixime).¹⁹ Zambonino *et al.*¹⁴ performed DPTs with cefuroxime in nine patients with immediate amoxicillin hypersensitivity and reported that none of them had a positive reaction. Accordingly, during the DPT, none of our patients with amoxicillin hypersensitivity reacted to cephalosporin that had a dissimilar side chain (with cefuroxime).

Cross-reaction among patients with cephalosporin hypersensitivity is more complicated. The rate of cross-reactivity is reported at ~10%, especially in first-gen-

eration cephalosporins.¹⁰ Because cephalosporins and penicillins share a common β -lactam ring, one might expect that this structure is responsible for the cross-reactivity. However, most patients with immediate reactions to cephalosporin will tolerate penicillin, which indicates that side chains rather than the β -lactam ring play an important role in immunologic cross-reactivity.^{16,20} In a recent report, 24 patients (22 adults, 2 children) with an immediate reaction to cephalosporins were evaluated with skin tests and Radioallergen sorbent test, and reported that only two of them had positive skin test results with penicillin and another 22 tolerated penicillin V.²¹ Ponvert *et al.*¹³ claimed that 18.7% of the children with immediate reactions to second- and/or third-generation cephalosporins also reacted to penicillins.

Zambonino *et al.*¹⁴ reported three patients with cephalosporin allergy, one had specific IgE for penicillin and one had a positive skin test result with amoxicillin, but it was not specified whether the cephalosporin had a side chain similar to amoxicillin. Atanasković *et al.*²² reported that 31.5% of children allergic to penicillin were cross-reactive to some cephalosporins, but the side chain homology was not specified. They also reported that, if a child was allergic to a cephalosporin, the frequency of positive reactions to penicillin was 84.2%. Contrary to this high frequency, in our study, only one patient with cephalosporin hypersensitivity had a positive classic penicillin skin test result. All other patients could tolerate penicillin V and cephalosporins with dissimilar side chains.

There were some limitations to our study. Although selective responders were shown to tolerate BLAs with dissimilar side chain in this study, the main immunologic mechanism of cross-responding and selective responding was not investigated. Detailed studies on the pathogenesis of BLA hypersensitivity will help to reveal the exact mechanism. Furthermore, we could not test amoxicillin and clavulanic acid separately; some of our patients, who had negative classic penicillin test results but positive skin test results with amoxicillin-clavulanate may be hypersensitive to clavulanic acid instead of the amoxicillin side chain.

CONCLUSION

Among children with immediate BLA hypersensitivity, selective responders constitute an important group. Most of the patients with reactions to amoxicillin and cephalosporins safely tolerated penicillin V and BLAs with dissimilar side chains after a negative allergy workup. The use of alternative drugs when they are not really needed increases the economic burden, the risk of adverse effects, and the rate of clinical failure. For better management of children with BLA hypersensitivity, skin tests and DPTs, which included the

culprit drug, should be performed before withholding BLA use.

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