



# Macrolide Allergy in Children and the Negative Predictive Value of Drug Provocation Tests in Mild Index Reactions

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## ABSTRACT

**Objective:** Macrolide allergy is rarely reported, and there is limited knowledge of hypersensitivity reactions (HRs) in children. The negative predictive value (NPV) of drug provocation tests (DPTs) for macrolides is unresolved. We aim to evaluate the clinical features of macrolide allergy in children, and determine the NPV of macrolide DPTs.

**Materials and Methods:** Pediatric patients who were referred to our allergy department with a suspicion of macrolide allergy were evaluated by DPTs with or without prior skin tests between 2011 and 2020. Characteristics of the HRs and patients, the results of skin and DPTs were recorded. At least three months after evaluation of the patients with allergy work up, telephone interviews were performed. Patients were asked whether they had reused the suspected macrolide or not. Patients who reported HR during subsequent drug intake were invited for reevaluation.

**Results:** A total of 160 children (161 reactions) (55.6% male) with a suspicion of macrolide allergy were enrolled for the study, and all children had a mild index reaction. The median age was 48 (18-102) months, and the median time between the suspected allergic reaction and allergy work-up was 3 (2-8) months. The most frequently reported suspected agent was clarithromycin, in 151 patients (94.4%). Macrolide allergy was confirmed in 8 (5%) patients. Only one patient reported skin eruptions upon reuse despite a negative DPT and he was invited to be reevaluated. A second DPT was performed resulting in urticarial lesions. The NPV was found to be 97.4% for negative DPT with macrolides.

**Conclusion:** Confirmed macrolide allergy is rare in children, and DPTs are the gold standard to assess suspected macrolide allergy. The NPV of macrolide provocation tests seems to be high in children.

**Keywords:** Children, drug hypersensitivity, drug provocation test, macrolide, negative predictive value

## ABBREVIATIONS

**BL:** Beta lactam, **DHR:** Drug hypersensitivity reaction, **DPT:** Drug provocation test, **ENDA:** European Network for Drug Allergy, **HR:** Hypersensitivity reaction, **IDT:** Intradermal test, **Ig:** Immunoglobulin, **IR:** Immediate reaction, **MPE:** Maculopapular exanthem, **NBL:** Non beta lactam, **NIR:** Nonimmediate reaction, **NPV:** Negative predictive value, **SCAR:** Severe cutaneous adverse drug reaction, **SPT:** Skin prick testing

## INTRODUCTION

Antibiotics are the most common reason for the evaluation of adverse drug reactions and referral to allergy clinics. Beta lactams (BLs) are prominent culprit drugs for hypersensitivity reactions among antibiotics, whereas non beta lactams (NBLs) are less common (1).

Although antibiotics are the leading cause of suspected hypersensitivity reactions in children, confirmed drug allergy is less frequent than thought. Accompanying factors such as viral exanthemas may cause this confusion. Therefore, drug provocation tests (DPTs) are essential to confirm or exclude the suspected drug allergy as confirmed drug allergy is less frequent than expected (2).

Macrolides are classified in four subgroups according to their lactone rings (14-membered to 16-membered). The 15-membered azithromycin, and 14-membered clarithromycin are widely used in the treatment of gram-positive cocci, gram-negative bacilli, and also atypical pathogens in children. Furthermore, macrolides are good alternative drugs to BLs in the case of BL allergy (3,4).

There is scarcity of knowledge about macrolide allergies in children. Reported severe drug reactions are rare, and most of the reactions consist of mild cutaneous reactions. Macrolide allergy is relatively rare, and the estimated incidence is 0.4 to 3% of treatments (4). To the best of our knowledge, there is no study on the negative predictive value (NPV) of provocation tests in case of suspected macrolide allergy.

The aim of this study was to evaluate clinical features of confirmed macrolide allergy in children, the safety of subsequent use of suspected macrolides after negative DPTs, and to determine the NPV of macrolide antibiotics after negative provocation tests.

## MATERIALS and METHODS

### Study Population and Data Collection

Pediatric patients who were referred to our tertiary outpatient allergy department, and were evaluated by DPT with or without prior skin tests from January 1, 2011 to May 31, 2020, with a suspicion of hypersensitivity reaction to macrolides were recruited, and the patient files were retrospectively reviewed for the study. The patients who presented between January 1, 2011 to June 15, 2015 were previously reported as a part of another study (5).

The data of the patients were collected from the patient files and medical documents. The European Network for Drug Allergy (ENDA) questionnaire, including details of drug hypersensitivity reactions (DHRs) was completed (6). Demographic features (age, gender, timing of the hypersensitivity reaction, timing of allergy testing, history of atopic diseases, etc.) of the participants were recorded.

Drug provocation tests with or without prior skin tests were performed at least 4 weeks after the index DHR, unless there was a history of severe cutaneous adverse drug reactions (SCARs).

### Allergy Assessment and Skin Testing

Participants were classified according to the timing of the hypersensitivity reaction. Immediate reactions (IRs) were considered as the symptoms that occurred within the 1 hour after drug intake, and reactions that developed later than 1 hour were regarded as nonimmediate reactions (NIRs) (7).

Baseline laboratory tests of the participants, including complete blood count values, and total Immunoglobulin E (IgE) levels, were recorded from medical files. Drug-specific IgE test for the suspected macrolides could not be performed due to their unavailability.

Skin tests for azithromycin could not be performed due to the unavailability of the injectable form in our country. The commercial solution form of clarithromycin was used for skin prick testing (SPT) without dilution and applied on the volar forearm, and SPT and intradermal test (IDT) were considered positive when a wheal diameter was larger than 3 mm with surrounding erythema, compared to negative control 20 minutes after injection. If prick testing was negative, all of the IDTs were performed with a maximum non-irritating dose (0.05 mg/ml) as there was no case with a history of anaphylaxis due to macrolides (8). Readings were performed 20 minutes after applying the injection form of 0.02 ml of clarithromycin intradermally. Histamine 10 mg/mL was used as a positive control, and 0.9% NaCl was used as a negative control.

### Drug Provocation Tests

After the negative results of SPT and IDT, DPTs were performed following the ENDA guidelines (9). In recent years, patients who reported mild cutaneous lesions (maculopapular rash, delayed urticaria), and had a consistent history of NIR underwent drug provocation tests directly in concordance with the latest approaches and guidelines (10- 12).

The DPTs were performed under observation of a pediatric allergy fellow with full resuscitation equipment available. Since all the reactions were mild and limited to the skin, we initiated DPT with 1/100 of the total dose. Totally the approximate age/weight-adjusted daily dose of the suspected macrolide (clarithromycin 15 mg/kg, maximum 1000 mg/day, and azithromycin 10 mg/kg, maximum 500 mg/day) was given orally with incremental doses at 30-minute intervals, in maximum 4 to 5 doses to restrain the possibility of desensitization (9).

In the case of any objective clinical findings of HR (urticaria, rash, angioedema, hypotension, persistent vomiting, cough, wheezing, etc.), DPT was discontinued and considered positive. After administration of the last dose, patients remained at least 2 hours in the clinic. If, there was no reaction, patients continued to take the calculated daily doses of the drug for 4 more days, and the parents were warned to contact or come back to the clinic in case of any reaction at home.

### Outcomes of Subsequent Use of Macrolides

Patients were contacted by phone at least three months after a negative allergy workup to evaluate the safety of the subsequent use after DPTs. Parents were asked whether their child reused the tested macrolide with or without any reaction. If they did not reuse it, the reasons were questioned. Patients who reported any reaction suggestive of drug allergy were invited to our clinic for re-evaluation.

The study protocol was approved by the local ethics committee of Ankara City Hospital (approval number: E1-20-698) and written informed consent was obtained from the parents.

### Statistical Analysis

Statistical analysis was conducted by using SPSS® version 22.0 for Windows (IBM SPSS, Chicago, IL, USA). Descriptive statistics were performed, and quantitative parameters were reported as means and standard deviations (SDs) or as medians (interquartile range [IQR]) with values in case of skewed distribution. Categorical variables were described using absolute frequencies, and proportions with 95% confidence interval (95% CI), and comparisons were performed with chi square tests. A *P*-value of <0.05 was considered statistically significant.

## RESULTS

A total of 160 children (161 reactions) (55.6% male) with a suspicion of macrolide allergy were enrolled for the study. The median [interquartile range (IQR)] age was 48 (18-102) months, and the median (IQR) time between the reaction and allergy work-up was 3 (2-8) months. The characteristics of the study population are summarized in Table I.

The most frequently reported suspected agent was clarithromycin in 151 patients (94.4%); azithromycin, and both clarithromycin and azithromycin were reported in 8

(5%) patients and 1 (0.6%) patient, respectively (Table I). All reactions occurred with the oral forms of the drugs. There were 123 (76.4%) NIRs and 38 (23.6%) IRs. The characteristics of the reactions are shown in Figure 1. None of the patients had a history of anaphylaxis.

All patients except one described cutaneous manifestations ([urticaria, maculopapular exanthem (MPE), undefined rash, angioedema]). One patient reported persistent vomiting without any signs of skin findings (Table I).

Totally, 78 patients [61 of them belonging to the previous study (5)] underwent skin tests, whereas DPTs were performed in 159 patients.

Only one patient reported HR to two different macrolides (azithromycin and clarithromycin). Urticaria and angioedema was described 2 hours after taking the last dose, DPTs were performed, and both of them had negative results.

Macrolide allergy was confirmed in 8 (5%) patients. Among them, 1 patient had a positive reaction to clar-

**Table I: Patient characteristics.**

| <b>Characteristics</b>                             |                       |
|--|-----------------------|
| Age (months) *                                     | 48 (18-102)           |
| Gender, M/F, n (%)                                 | 89/71 (55.6/44.4)     |
| Time between HR and allergy work-up (months) *     | 3 (2-8)               |
| Immediate/nonimmediate HR, n (%)                   | 38/123<br>(23.6/76.4) |
| Concurrent atopic disease, n (%)                   | 27 (16.9)             |
| <b>History of reactions to macrolides (n=160)</b>  |                       |
|  | <b>n (%)</b>          |
| Clarithromycin                                     | 151 (94.4)            |
| Azithromycin                                       | 8 (5)                 |
| Both Clarithromycin and azithromycin               | 1 (0.6)               |
| <b>Type of HR reactions (n=161)</b>                |                       |
|  | <b>n (%)</b>          |
| Urticaria  | 48 (29.8)             |
| Angioedema   | 8 (4.9)               |
| Urticaria and angioedema                           | 11 (6.8)              |
| Maculopapular exanthem                             | 44 (27.4)             |
| Undefined rash                                     | 49 (30.5)             |
| Persistent vomiting                                | 1 (0.6)               |
| <b>Number/positive results of diagnostic tests</b> |                       |
| Skin test  | 78/1                  |
| DPT  | 160/7                 |

\* median (interquartile range), **M**: Male, **F**: Female, **DPT**: Drug provocation test, **HR**: Hypersensitivity reaction.

ithromycin IDT and 7 patients had positive reactions to clarithromycin during the DPTs. Characteristics of the patients with proven macrolide allergy are depicted in Table II.

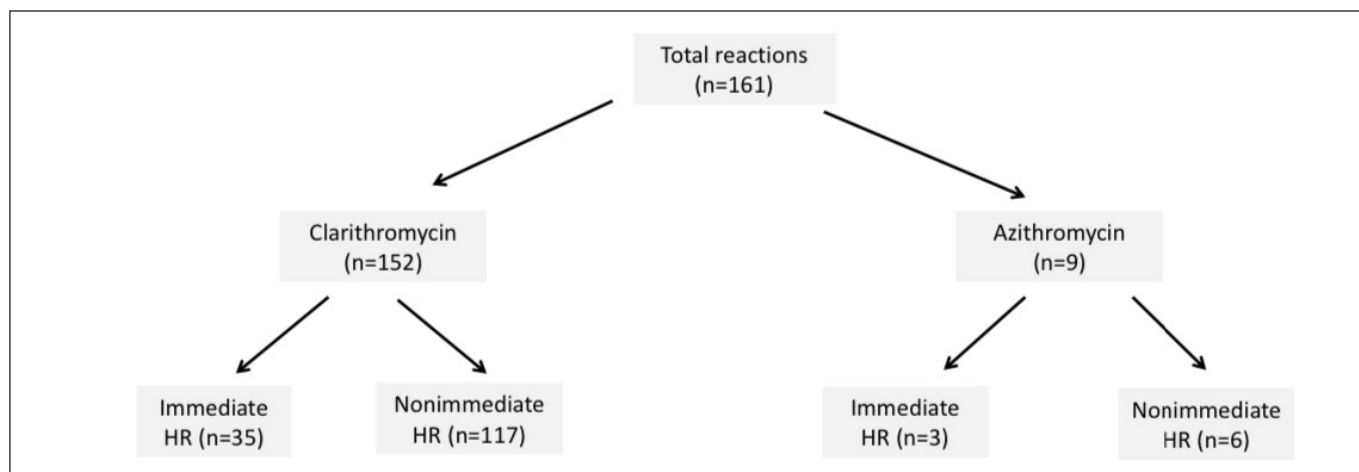
Of the participants with negative diagnostic tests, 100 out of 152 (65.8%) were contacted by phone. Of these patients, 61 did not reuse the tested macrolide. The reasons for not reusing were no need to use (n=46), family unwilling to reuse (n=13), and physician's reluctance to re-prescribe the same macrolide (n=2).

Thirty-nine of the patients reported subsequent use of the tested macrolide after negative DPT, and 38 of them tolerated it well without any signs of HR. Only one patient reported skin eruptions that were limited to his chest on the fourth day, 3 hours after taking the last dose for the treatment of his respiratory tract infection, and he was invited to be reevaluated. The patient was re-evaluated with a second DPT. Urticaria occurred 2 hours after receiving the last dose, and macrolide allergy was confirmed by the second DPT (Table III).

**Table II: Characteristics of the patients with proven macrolide allergy.**

| Patient No. | Age at reaction (months) | Gender | Concurrent atopic disease      | The day of HR occurred in the index reaction | Time interval between reaction and drug intake (hours) | SPT/IDT           | First reaction | Reaction of DPT |
|-------------|--------------------------|--------|--------------------------------|--|--|-------------------|----------------|-----------------|
| 1           | 30                       | F      | asthma                         | 1  | 3  | Negative/Positive | urticaria      | ND              |
| 2           | 167                      | M      | allergic rhinitis              | 1  | 1  | Negative/Negative | MPE            | MPE             |
| 3           | 100                      | M      | none                           | 2  | 1  | Negative/Negative | urticaria      | urticaria       |
| 4           | 63                       | F      | none                           | 3  | 2  | ND                | urticaria      | urticaria       |
| 5           | 118                      | M      | none                           | 3  | 4  | ND                | urticaria      | urticaria       |
| 6           | 95                       | M      | none                           | 1  | 2  | ND                | undefined rash | undefined rash  |
| 7           | 110                      | F      | asthma, recurrent urticaria-AE | 3  | 2  | ND                | MPE            | MPE             |
| 8           | 12                       | M      | none                           | 1  | 3  | ND                | urticaria      | urticaria       |

AE: Angioedema, DPT: Drug provocation test, F: Female, M: Male, HR: Hypersensitivity reaction, IDT: Intradermal test, MPE: Maculopapular exanthem, ND: Not done, SPT: Skin prick testing

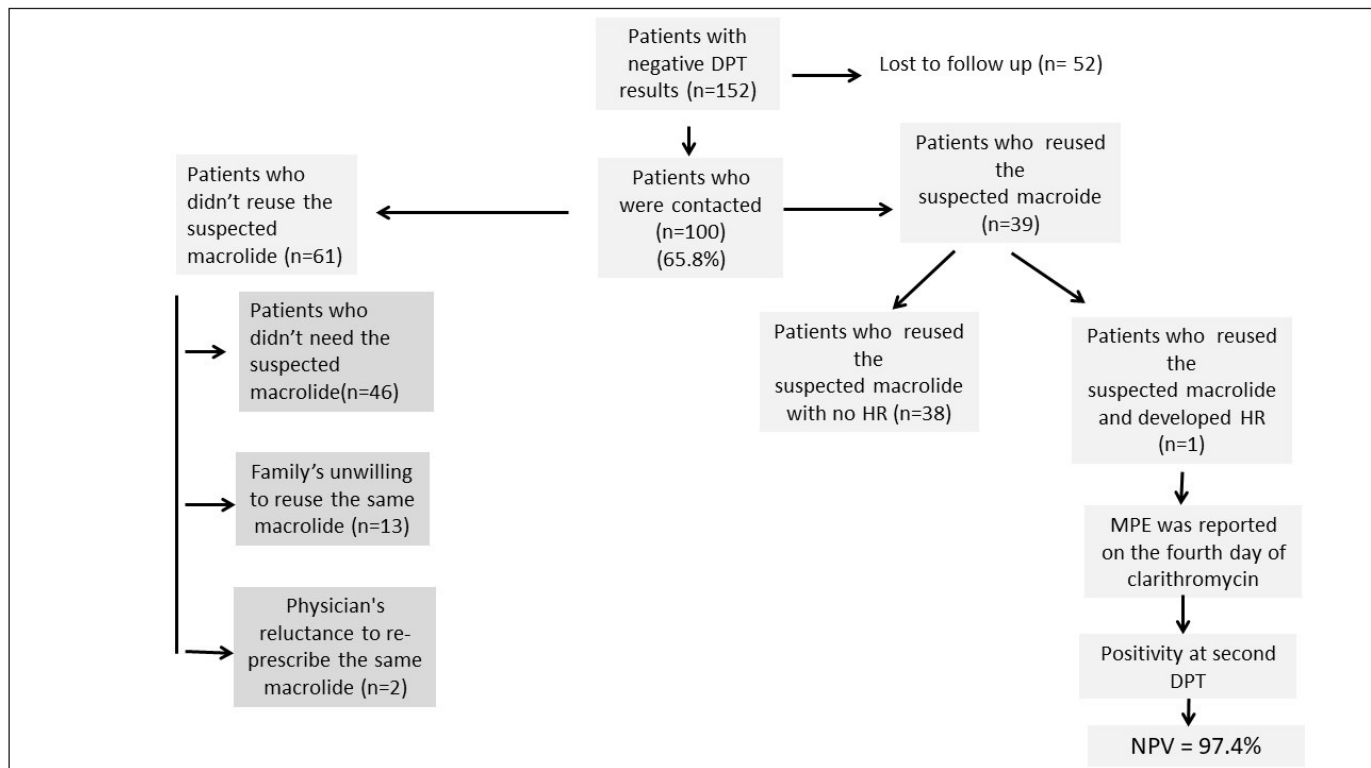


**Figure 1.** The characteristics of the reactions to macrolide antibiotics.  
HR: Hypersensitivity reaction

**Table III: Characteristics of the proven macrolide allergies after re-evaluation.**

| Age at reaction, months | Gender | Concurrent atopic disease | Time interval between reaction and drug intake, minutes | SPT/IDT | First DPT | Second DPT | First reaction       | Reaction of DPT |
|-------------------------|--------|---------------------------|---|---------|-----------|------------|----------------------|-----------------|
| 32                      | M      | none                      | 180   | ND      | negative  | positive   | urticaria-angioedema | urticaria       |

DPT: drug provocation test, IDT: Intradermal test, SPT: Skin prick testing



**Figure 2.** The flow chart of the study.

DPT: Drug provocation test, HR: Hypersensitivity reaction, NPV: Negative predictive value

The prevalence of proven macrolide allergy after provocation tests was found to be 5% in children with suspected allergy to macrolides. Negative predictive value for the provocation tests for macrolide allergy was calculated as 97.4%. The flow chart of the study is shown in Figure 2.

## DISCUSSION

In this study, the prevalence of proven macrolide allergy after provocation tests was found 5% in children. Most of the reactions were limited to skin with mild cutaneous lesions. In our study population, we determined the NPV of provocation tests with macrolides as 97.4%.

In accordance with our results, frequency of proven macrolide allergy was rare in previous studies. In two studies including pediatric patients with suspected clarithromycin allergy, confirmation after DPTs was reported as 6%, and 4.4%, respectively (11, 13). Barni et al. reported relatively high incidence of confirmed macrolide allergy in children with suspected HR to macrolides, as 15.5% clarithromycin, and 47.3% azithromycin (14). In this study, patients who had a history of HR to azithromycin 24.6% (n=19) were more than our patients 5.6% (n=9) which may be due to the differences in antibiotic use among countries. Azithromycin allergy was confirmed with early and late reading of IDTs in the aforementioned study, but we couldn't perform skin tests with azithromycin, all of DPTs with azithromycin were negative.



Mild cutaneous findings were major findings of our cohort. Similarly, in previous reports, urticaria, angioedema, undefined rash and MPE were the most commonly reported hypersensitivity reactions to macrolides (11,14). However, in earlier studies, anaphylaxis was also reported both in adults and in children (15, 16). Mori et al. have reported anaphylaxis in 3 of 48 children detected to have azithromycin allergy; one had received the drug by intravenous route, and the other two had atopy (16). None of our patients had a history of anaphylaxis, and this may be attributed to low number of patients that used azithromycin which is only available in oral form in Turkey.

In recent years, direct DPTs have been recommended in NIRs with mild cutaneous reactions (10-12). In the latest years of our study, DPTs were performed without initial prick and/or intradermal testing in patients with mild cutaneous reactions. We did not experience any serious side effects during direct DPTs, and only skin eruptions were detected that were compatible with the initial suspected HRs.

Furthermore, skin test concentrations of macrolides have low reliability due to the irritating effects especially in children, and there is a lack of knowledge of non-irritating concentrations (15,17). Cavkaytar et al. have reported false positive results of IDTs even in low concentrations. In their study, some of the patients underwent DPT regardless of the results of IDTs, and interestingly nine patients with positive IDTs had negative DPTs (11). In contrast, Barni et al. reported the NPV of skin testing to clarithromycin at rates of 100% for IRs and 94% for NIRs in children (14).

In our study, there was only one patient with positive IDT to clarithromycin, but we did not perform DPT due to this positivity and a compatible history of HR. In rest of the patients, macrolide allergy was confirmed with DPTs. Drug provocation tests are regarded as the gold standard to confirm or exclude drug allergy (9). Since there was no history of anaphylaxis, DPTs were performed in all of our patients except the IDT positive one. Seven of the patients were diagnosed with macrolide allergy in the first DPT.

Of the patients with negative diagnostic tests, 100 out of 152 were reached; 39 patients reported subsequent use of the tested macrolide, and only one reported a mild cutaneous skin reaction. DPT was repeated, and his macrolide allergy was proven during the second DPT after the occurrence of hives.

False negative DPT results may be due to the absence of accompanying factors such as infection and fever during the provocation test. However, this patient was re-evaluated with a second DPT, when there was no infection, and he still had hives with drug ingestion. Desensitization during DPTs may also accompany a false negative DPT, but we performed DPTs at a maximum of 5 steps to avoid desensitization (9). Inadequate time interval between HR and the test may also cause false negative results. However, we performed provocation tests at least 4 weeks after the suspected HR. In some of our patients, there was a long-time interval like this patient, as the first DPT was performed 36 months after the initial suspected HR. A reduction in the degree of sensitivity over time can be expected as time passes after sensitization with the drug. In such cases, a provocation test may be negative but it may have a “booster” effect, and this may be the case in our patient (18).

Another explanation for a HR after a negative provocation test is re-sensitization (2,19). Ponvert et al. have reported a rate of 7.5% for suspected reactions after de-labelling of BL allergy with negative diagnostic tests, and 2.1% of them were confirmed at the second allergy evaluation (20). In another study conducted on children, the rate of IgE-mediated reactions was reported to be 1.8% after subsequent use of the tested BL (21). In studies with re-testing BLs after negative allergy work-up, a rate of 1 to 2% positivity is reported in children (22, 23). To the best of our knowledge, there is no study that evaluates re-sensitization rates or the recurrence of HRs after negative diagnostic tests for NBL antibiotics.

The negative predictive value of DPTs in children was reported to be 95.6%, regardless of the type of drugs including antibiotics, nonsteroid anti-inflammatory drugs, etc. (24). The negative predictive value of negative provocation tests to suspected macrolide allergy is unknown in children. To our knowledge, our study is the first report of subsequent use of the tested macrolide, after negative provocation tests, and the reaction rates following use. In our study, the NPV of macrolide allergy after negative DPTs was as high as 97.4% in the children.

Indeed, we contacted fewer patients than we expected, which might have negatively affected the results of our study. If we had communicated with more patients, our results would become more reliable. Generally, there is an alternative antibiotic to macrolides in the treatment of bacterial infections. In addition, although the drug

tests resulted negative, families and sometimes their physicians hesitated to reuse the tested macrolide. All the aforementioned reasons may have impacted the outcomes of this study.

Three-months of follow-up data were available for 100 (65.8%) patients. Over half of them (61%) did not use the tested macrolide. The leading reason for not using the tested macrolide was “no need to use again”. The presence of effective alternative antibiotics such as BLs in childhood may explain the no need for re-use (25).

The second reason for not using the tested macrolide was the family’s reluctance to re-use. Previous studies have pointed out the family’s perception for keeping on not using the tested antibiotics for future infections (26,27). After negative DPTs, families should be adequately informed for de-labelling antibiotic allergy. The minority of the patients did not use the tested macrolide because of the physician’s reluctance to re-prescribe. Insufficient communication between health practitioners may cause unnecessary drug avoidance (28,29).

The most important limitation of this study was not being able to make contact with all patients with negative DPTs to assess subsequent use of the tested macrolide, which may affect the NPV and cause a selection bias. This study consists of almost ten years medical records. Unfortunately, it is not always possible to fully access the patients’ data. Furthermore, the contact numbers of the families may have changed or they may have ignored follow-up visits when there is no further allergic reaction. All of these reasons may have caused us to reach a small number of the patients.

The other limitations include the lack of available skin testing or drug-specific IgE testing for azithromycin allergy. There are also strengths of our study, as we evaluated a considerable number of patients with DPTs and/or SPTs.

In conclusion, proven macrolide allergy is rare; therefore, provocations tests should be performed to diagnose true drug allergy unless there are contraindications. Our findings suggest that DPT may be started without previous skin testing for children with nonimmediate mild cutaneous reactions after macrolide use. The NPV of macrolide provocation test seems relatively high in children, which may encourage the families and physicians for future use of the tested macrolide after negative DPTs.

### **Statement of Ethics**

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, and the use of data for this study was approved by the local Ethics Committee of Ankara City Hospital (approval number: E1-20-698).

### **Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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### **Author Contributions**

B.K collected the data, made the statistical analysis, and wrote the article, S.B.Y, I.K.C, O.Y.T, and E.C contributed to acquisition and interpretation of the data, M.T. contributed to the study design and the discussion, E.D.M planned the study and supervised the whole manuscript. All of the authors reviewed the article and gave final approval to the version to be published.

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