Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2022.21223

# Evaluation of Suspected Macrolide Allergies in Children

Ayşe Süleyman, Esra Yücel, Zeynep Ülker Tamay, Nermin Güler

Division of Pediatric Allergy and Immunology, Department of Pediatrics, İstanbul University, İstanbul Faculty of Medicine, İstanbul, Turkey

## What is already known on this topic?

- *Macrolide allergy is rare, but cross-reactions can occur between different macrolide groups.*

## What this study adds on this topic?

- *Drug provocation testing is the only valid method to diagnose macrolide allergy and evaluate cross-reactivity between different macrolide groups. Drug provocation tests with different macrolide should be performed in patients with macrolide allergy before being used in treatment.*

## ABSTRACT

**Objective:** Macrolides are often accepted as safe antibiotics due to their low allergenicity. However, studies on macrolides, particularly studies evaluating cross-reactivity in macrolides, are highly rare in children. This study aimed to evaluate the clinical manifestations, confirmation rate, and frequency of cross-reactivity in children admitted with suspicious clarithromycin or azithromycin allergy.

**Materials and Methods:** A total of 61 children suspected of macrolide antibiotic allergy (clarithromycin, n = 39 and azithromycin, n = 22) were evaluated. Allergy work-up including drug provocation tests were performed in all patients to confirm drug allergy.

**Results:** Macrolide allergy was confirmed in 9.8% (n = 6) of patients (azithromycin, 18.2% [n = 4] and clarithromycin, 5.1% [n = 2]). There was no significant difference between the confirmation rate of clarithromycin and azithromycin ($P$ = .117). Cross-reaction with clarithromycin was confirmed in 2 (33.3%) patients with azithromycin allergy.

**Conclusion:** Drug skin tests are not capable of confirming or ruling out macrolide allergy, and oral provocation tests are essential for a definitive diagnosis. Cross-reactivity, albeit rare, can occur between clarithromycin and azithromycin, which are the most frequently used macrolides in children.

**Keywords:** Azithromycin, clarithromycin, cross-reaction, drug hypersensitivity, macrolides

## INTRODUCTION

Azithromycin and clarithromycin, 2 macrolide antibiotics belonging to different groups, are among the most common causes of non-β-lactam antibiotic allergy in children.[1-3] These drugs have been reported to cause various reactions including urticaria-angioedema, anaphylaxis, maculopapular rash, and severe skin reactions.[4]

Macrolides are a group of compounds with a lactone ring (14-16 atoms) attached to one or more deoxy sugar molecules. Erythromycin, dirithromycin, and clarithromycin have 14 carbon atoms in the lactone ring; therefore, they are classified in the same group. Azithromycin has 15 and spiramycin has 16 carbon atoms in the lactone ring; therefore, they are classified into different groups.[1,4]

Skin tests are not a standard and reliable test method for the diagnosis of macrolide allergy. Most macrolides do not have an appropriate parenteral form for skin tests. Oral provocation tests (OPT) remain the gold standard for the diagnosis of macrolide allergy.[5,6]

Although the antigenic determinant of macrolides is not well known,[7,8] cross-reactivities have been reported between different macrolide groups and the same group of

**Corresponding author:**
Ayşe Süleyman
✉draysesuleyman@yahoo.com
**Received:** July 13, 2021
**Accepted**: September 17, 2021



**Cite this article as:** Süleyman A, Yücel E, Tamay ZÜ, Güler N. Evaluation of suspected macrolide allergies in children. *Turk Arch Pediatr.* 2022;57(1):81-86.

macrolides.[3,9,10] Moreover, even with non-antibiotic macrolides such as tacrolimus, cross-reactivity has been reported in a case report.[11]

In this study, we aimed to investigate the diagnostic value of OPT in children with suspected macrolide allergy and to assess the cross-reactions between clarithromycin and azithromycin, the most frequently used macrolides in children.

## MATERIALS AND METHODS

### Patient Population

The prospective cross-sectional study evaluated children with suspected macrolide allergy who were admitted to Istanbul University, Faculty of Medicine, Department of Pediatric Immunology and Allergy between December 2019 and January 2021.

Patient data were collected using a questionnaire form based on the European Network of Drug Allergy (ENDA) questionnaire.[12] Comorbidities and family history of drug allergy were recorded for each patient. Suspected drugs were determined based on patients' records that were retrieved from the Electronic National Health System, and data on drug histories were obtained from their parents. An informed consent was obtained from each patient and/or parent. The study protocol was approved by the local ethics committee (No. 2020/1558).

Patients who had suspicious macrolide allergy but could not be tested with OPT due to various reasons such as uncontrolled asthma, severe skin reaction, and parental disapproval were excluded from the study.

### Drug Skin Tests

Skin tests were performed after the first 4 weeks following the first reaction.[5] Drugs that could affect the test result were discontinued at the recommended time for each drug.[13] Skin prick tests were performed with clarithromycin at a concentration of 50 mg/mL. A positive response was recorded if the mean diameter of the wheal was ≥3 mm and the negative control was non-reactive. If a patient had a negative skin prick test, then an intradermal test (IDT) was performed at a concentration of 1:1000 (0.05 mg/mL). If this dilution was negative, the concentration was increased to 1:10 (5 mg/mL) for 20 minutes. The response was recorded as positive if the mean diameter of the wheal was ≥5 mm. Histamine (10 mg/mL) was used as the positive control, and 0.9% NaCl was used as the negative control.[10,13,14]

We could not perform allergy skin tests with azithromycin because its parenteral form was not commercially available in our country.

### Oral Provocation Tests

Oral provocation tests were performed in the hospital setting.[15] The dose of clarithromycin was adjusted to 15 mg/kg/day, and the dose of azithromycin was adjusted to 5 mg/kg/day. Oral provocation tests were initiated with the optimal dose of 1:10 and were gradually increased to 3:10 and finally to 7:10 at 30-minute intervals until the reaction developed or the full dose was reached. Oral provocation tests were accepted as positive in those who developed skin, respiratory, cardiovascular, or gastrointestinal findings or changes in vital signs during or after the test. Patients with negative tests were treated at home for another 5 days.

Immediate reactions typically occur within 1 hour but may occur within 6 hours after the last administered dose. Reactions occurring between 1 and 6 hours were classified as immediate or non-immediate according to their clinical features. Therefore, we took into account both the chronology and the morphology of the reactions. Early readings of the skin prick test and intradermal test were performed in patients with immediate reactions. Late readings of the IDT were performed on the first and third days in those with delayed reactions.[16] Anaphylaxis was diagnosed according to the presence of clinical criteria.[17] Allergic assessments for other drugs were performed according to the ENDA guideline.[14,16]

### Statistical Analyses

Data were analyzed using The Statistical Package for Social Sciences version 23.0 software (IBM Corp.; Armonk, NY, USA). Pearson's chi-square test or Fisher's exact test was used for comparing the categorized data. Normal distribution of continuous variables was assessed using the skewness–kurtosis and Kolmogorov–Smirnov or Shapiro–Wilk test. Continuous variables with non-normal distribution were presented as the median and interquartile range (IQR). A non-parametric test (Mann–Whitney *U*-test) was used for comparing variables with non-normal distribution. A value of $P < .05$ was accepted to be statistically significant.

## RESULTS

The study included a total of 61 children with suspected macrolide allergy. Table 1 presents the demographic and clinical characteristics of the patients. Median age was 6 years (IQR: 3-8), 34 patients (55.7%) were male, the atopic disease was diagnosed in 22 (36.1%) patients, chronic autoimmune urticaria was detected in 3 (4.9%) patients, and non-macrolide drug allergy was confirmed in 18 (28.5%) patients. The culprit macrolide was reported as clarithromycin in 39 (63.9%) patients and azithromycin in 22 (36.1%) patients. Immediate hypersensitivity reactions were reported in the majority of the patients and urticaria was the most common reaction type (48.7% of clarithromycin and 55.4% of azithromycin) (Table 1).

Median duration between the suspected reaction and allergic assessment was 3 months (IQR: 2-7 months). The results of all patients who underwent skin prick tests with clarithromycin were considered negative (n = 25). IDTs were positive in 32% of the patients (n = 8/25). The sensitivity of CLR skin tests was 50% (95% CI, 1.3-98.7), the specificity was 69.6% (95% CI, 47.1-86.8), the positive predictive value was 12.5% (95% CI, 3.0-39.5), the negative predictive value was 92.1% (95% CI, 79.6-98.5), and the accuracy was found 68% (95% CI, 46.5-85.1).

Figure 1 presents the diagnostic approach we used for suspected macrolide allergy. Macrolide allergy was confirmed in a total of 6 (9.8%) patients, comprising 2 (5.1%) patients with clarithromycin hypersensitivity and 4 (18.2%) patients with

**Table 1.** Comparison of the Clinical Features and Diagnostic Results of the Patients According to the Suspected Macrolide

| | Clarithromycin, n = 39 | Azithromycin, n = 22 | *P* |
|---|---|---|---|
| Age, median (IQR) years | 6 (3.5-8) | 6 (3-11) | .656 |
| Latent period between the suspected reaction and allergic work up, median (IQR) months | 3 (2-8) | 3 (2-5) | .994 |
| Chronology of the reaction | | | |
| Within first hour | 6 (15.4) | 2 (9.1) | .338 |
| 1-6 hour | 25 (64.1) | 18 (81.8) | |
| >6 hour | 8 (20.5) | 2 (9.1) | |
| Clinical presentation | | | |
| Urticaria | 19 (48.7) | 12 (54.5) | .141 |
| Maculopapular eruptions | 15 (38.5) | 6 (27.3) | |
| Urticaria-angioedema | 5 (12.8) | 1 (4.5) | |
| Anaphylaxis | 0 | 1 (4.5) | |
| Aggravated atopic dermatitis lesions | 0 | 2 (9.1) | |
| Personal confirmed non-macrolide drug allergy* | 8 (20.5) | 10 (45.5) | **.040** |
| β -lactam | 7 | 6 | |
| Non-steroid | 3 | 2 | |
| Family history of a drug allergy | 11 (28.2) | 4 (18.2) | .383 |
| Atopic disease | 15 (38.5) | 7 (31.8) | .604 |
| Diagnostic results | | | |
| Confirmed | 2 (5.1) | 4 (18.2) | .117 |
| Excluded | 37 (94.9) | 18 (81.8) | |

IQR, interquartile range.
*Confirmed by allergic assessment (skin and drug provocation tests). Bold values are statistically significant.

azithromycin hypersensitivity (*P* = .117). Table 2 presents a comparison of patients' clinical characteristics and diagnostic results according to OPT results. Two patients who were confirmed as having azithromycin reaction were also reactive to clarithromycin, and the reaction of these patients was classified as cross-reactivity. On the other hand, the rates of non-macrolide drug allergy and immediate reactions were higher, and the latent period was shorter in children with confirmed macrolide allergy (*P* = .007, *P* = .038, and *P* = .040, respectively). Table 3 shows the clinical features of patients with OPT-proven macrolide allergy.

## DISCUSSION

This study, as shown in the literature, confirmed that OPT are the only valid method to assess macrolide allergy.[6,10,18,19] Moreover, the study also showed that cross-reactivity could occur between clarithromycin and azithromycin and that the

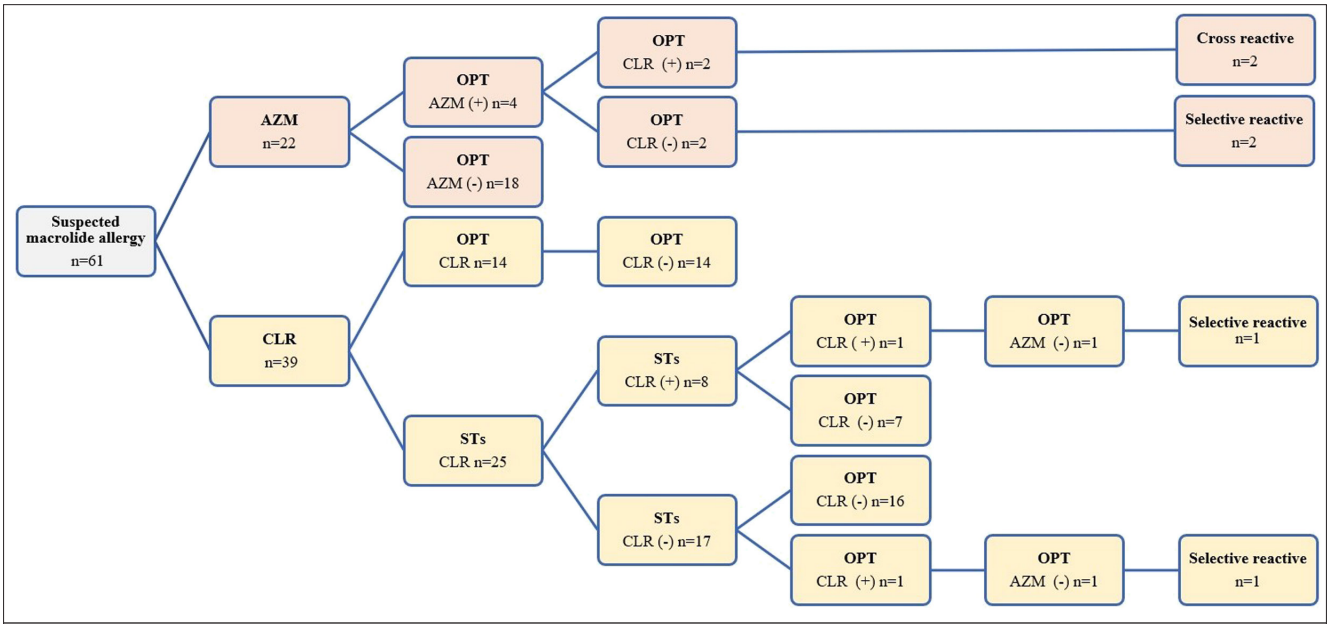


**Figure 1.** Diagnostic approach according to the culprit macrolide. AZM, azithromycin; CLR, clarithromycin; OPT, oral provocation test; ST, skin tests.

**Table 2.** Demographic and Clinical Characteristics of the Patients According to the Oral Provocation Tests Results

| | OPT Positive, n = 6 (9.8%) | OPT Negative, n = 55 (90.2%) | *P* |
|---|---|---|---|
| Median age, years (IQR)[*] | 7.5 (2-14) | 6 (3-8) | .543 |
| Culprit macrolide | | | |
| Clarithromycin | 2 (33.3) | 37 (67.3) | .176[†] |
| Azithromycin | 4 (66.7) | 18 (32.7) | |
| Latent period between suspected reaction and allergic work-up, median months (IQR)[*] | 2 (2-3) | 3 (2-7.5) | **.040** |
| Chronology of the reaction | | | |
| Within 1 hour | 1(16.7) | 7 (12.7) | .519 |
| 1-6 hour | 5 (83.3) | 38 (69.1) | |
| >6 hour | 0 | 10 (18.2) | |
| Clinical type of reaction | | | |
| Immediate | 6 (100) | 31 (56.4) | **.042**[†] |
| Delayed | 0 | 24 (43.6) | |
| Having a non-macrolide drug allergy | 5 (83.3) | 13 (23.3) | **.007**[†] |
| β -lactam | 3 | 10 | |
| Non-steroid | 2 | 3 | |
| Family history of drug allergy | 2 (33.3) | 13 (23.6) | .400[†] |
| Atopic disease | 2 (33.4) | 20 (36.4) | .833[†] |

OPT, oral provocation test.
[†]Fisher test was performed.
*It was expressed as the median and interquartile range. Bold values are statistically significant.

cross-reactivity was greater in children with confirmed non-macrolide drug allergy.

The immunogenicity of the drug and its prescribing habits are among the factors that determine whether the drug will cause an allergic reaction.[18] In a study conducted in Turkey, clarithromycin was found to be the most frequent agent responsible for macrolide allergy in children.[2] In another study investigating pediatric patients, azithromycin was reported to be more allergenic than clarithromycin.[3] In our study, clarithromycin was the most commonly suspected macrolide, while azithromycin was the most commonly confirmed macrolide. This finding could be associated with the fact that azithromycin may cause more allergic reactions and its long half-life may facilitate sensitization since it is more immunogenic than clarithromycin.[3]

Reactions due to macrolides are rare, but the clinical spectrum is highly diverse, including vasculitis, anaphylaxis, and severe skin reactions.[4,19] In a retrospective study from Spain, penicillin and macrolides were reported as the most common cause of antibiotics causing Steven–Johnson syndrome and toxic epidermal necrolysis.[20] Our results showed that immediate reactions were the most frequent reactions in both drugs (Table 1). Moreover, all confirmed macrolide allergies were immediate reactions, while only 1 patient with anaphylaxis was identified during OPT with azithromycin.

The positivity rate of clarithromycin skin tests is reported between 15% and 45%.[20,21] The results of all patients who underwent skin prick tests with clarithromycin were considered negative (25/25), while clarithromycin IDTs were positive in 32% of the patients (8/25). In a previous study we conducted in our center, we determined the sensitivity and specificity of the clarithromycin skin test as 0% and 73.9%, respectively, by using the maximum non-irritant concentration (1:100) in dilution.[22] In the current study, since we used the higher maximum non-irritant concentration (1:10), we determined the favorable effect of this concentration on sensitivity and specificity as 12.5% and 92.1%, respectively. Moreover, although we performed skin tests using clarithromycin at higher concentrations when compared to the studies mentioned above, the skin and provocation tests were compatible with only 1 patient. These findings could be attributed to the controversial reliability of skin tests in macrolides, although they are standardized for β-lactam antibiotics, local anesthetics, neuromuscular blockers, and chemotherapeutics.[6,8]

Latent time is crucial in the diagnosis of drug allergy, and thus allergic assessment is recommended in the period between the first month and the first year after the allergic reaction.[5] In our study, although there was no significant difference between the 2 macrolides with regard to latent time, it was significantly shorter in patients with a confirmed macrolide allergy.

In the event of a confirmed drug allergy, the responsible drug and cross-reacting drugs should be avoided.[23] Cross-reactivity is generally explained by the presence of common antigenic determinants among the drugs causing the reaction.[9] Due to the significant structural differences between different macrolides, the possibility of cross-reactivity is low. Nevertheless, cross-reactivity between macrolides has been reported only in case reports and small series.[3,10,24] Cross-reactivities are often reported in macrolides that have the same carbon number.[9] Cross-reactivity has also been reported between azithromycin (15C) and clarithromycin (14C), though they have a different number of carbon atoms and are classified in different groups.[10,24] Cross-reactivity between clarithromycin and a non-antibiotic macrolide, tacrolimus, has been reported only in a case report.[11] Therefore, cross-reactivity may not be based solely on the number of carbon atoms. Despite our low

**Table 3.** Clinical Characteristics of Patients with OPT-Proven Macrolide Allergy (n = 6)

| Patient Id | Age (Years) | Gender | Underlying Allergic Disease | Culprit Macrolide | Presenting Complaints | Skin Tests with CLR | OPT with Azithromycin | OPT with CLR | Confirmed Non-macrolid Drug Allergy* | Type of Hypersensitivity Reaction |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 16 | F | None | AZM | Anapylaxis | Not applied | Anaphylaxis | No reaction | NSAIDs | Selective |
| 2 | 2 | M | Asthma, chronic autoimmune urticaria | AZM | Urticaria | Not applied | Urticaria | Urticaria | β-lactam | Cross-reactive |
| 3 | 14 | F | Asthma | AZM | Urticaria | Not applied | Urticaria | No reaction | No | Selective |
| 4 | 5 | F | Chronic autoimmune urticaria | AZM | Urticaria-angioedema | Not applied | Urticaria-angioedema | Urticaria-angioedema | β-lactam | Cross-reactive |
| 5 | 2 | M | None | CLR | Urticaria | Negative | No reaction | Urticaria | β-lactam | Selective |
| 6 | 11 | F | None | CLR | Urticaria | Positive | No reaction | Urticaria | NSAIDs | Selective |

AZM, azithromycin; CLR, clarithromycin; F, female; M, male; NSAID, non-steroidal anti-inflammatory drugs; OPT, oral provocation test.
*Confirmed by allergic assessment (skin tests and /or drug provocation tests).

number of patients with confirmed allergy, we found that half of the patients reactive to azithromycin were also reactive to clarithromycin. Accordingly, our results are consistent with the literature.[10,24]

In studies conducted in adults with macrolide allergy, atopy and female gender have been identified as risk factors.[10,25] Our results showed that more than half of the patients with confirmed macrolide allergy had a concomitant β-lactam allergy and chronic autoimmune urticaria in both of the patients who were found to be cross-reactive. In case of suspected or confirmed β-lactam allergy, it is often expected that patients should avoid these drugs and use macrolide antibiotics. The frequency of allergic reactions may increase due to the increased use of these antibiotics. Recent data have shown that drug allergy can resolve over time with β-lactam and non-β-lactam antibiotics, and patients may develop tolerance to the drugs.[26,27] For this reason, we think that the need for provocation tests will rise in the diagnosis of macrolide allergy and in evaluating whether the allergy has passed or not.

A history of chronic urticaria is part of drug allergy questionnaires but causes significant confusion because of the overlap of drug allergy and urticaria symptoms.[28] To overcome this problem, we performed drug provocation tests in the period when chronic urticaria was not activated and interpreted clinically compatible findings in favor of drug allergy. Although in vitro tests such as basophil activation, lymphocyte transformation, and macrolide-specific immunoglobulin E detection were used in the case report, they are not standardized and practically not available.[29]

The most important limitation of our study was the limited number of patients. Nevertheless, the strength of our study was that we performed the allergic assessment at the recommended time for each suspected macrolide and we confirmed the diagnoses with OPT, which are the golden standard in the diagnosis of drug allergy.

In conclusion, drug skin tests are not capable of confirming or ruling out macrolide allergy and that OPT are essential for a definitive diagnosis. Cross-reactivity, albeit rare, can occur between clarithromycin and azithromycin, which are the most frequently used macrolides in children.

**Ethics Committee Approval:** This study was approved by Ethics committee of the Istanbul University Faculty of Medicine, (Approval No: 2020/1558).

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in the study.

**Peer Review:** Externally peer-reviewed.

**Author Contributions:** Concept – A.S., E.Y., Z.T., N.G.; Design – A.S., E.Y., Z.T., N.G.; Supervision – N.G.; Analysis and/or Interpretation – A.S.; Literature Search – A.S., E.Y., Z.T., N.G.; Writing Manuscript – A.S., E.Y., N.G.; Critical Review – A.S., E.Y., N.G.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

## REFERENCES


1. Araújo L, Demoly P. Macrolides allergy. *Curr Pharm Des*. 2008;14(27):2840-2862. [CrossRef]
2. Guvenir H, Dibek Misirlioglu E, Capanoglu M, Vezir E, Toyran M, Kocabas CN. Proven non-β-lactam antibiotic allergy in children. *Int Arch Allergy Immunol*. 2016;169(1):45-50. [CrossRef]
3. Barni S, Butti D, Mori F, et al. Azithromycin is more allergenic than clarithromycin in children with suspected hypersensitivity reaction to macrolides. *J Investig Allergol Clin Immunol*. 2015;25(2):128-132.
4. Shaeer KM, Chahine EB, Varghese Gupta S, Cho JC. Macrolide allergic reactions. *Pharmacy*. 2019;7(3):135. [CrossRef]
5. Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy*. 2014;69(4):420-437. [CrossRef]
6. Chia FL, Thong BY. Macrolide allergy: which tests are really useful? *Allergol Immunopathol (Madr)*. 2011;39(4):191-192. [CrossRef]
7. Solensky R, Khan DA. Evaluation of antibiotic allergy: the role of skin tests and drug challenges. *Curr Allergy Asthma Rep*. 2014;14(9):459. [CrossRef]
8. Kuyucu S, Mori F, Atanaskovic-Markovic M, et al. Hypersensitivity reactions to non-betalactam antibiotics in children: an extensive review. *Pediatr Allergy Immunol*. 2014;25(6):534-543. [CrossRef]
9. Kruppa A, Scharffetter-Kochanek K, Krieg T, Hunzelmann N. Immediate reaction to Roxithromycin and prick test cross-sensitization to erythromycin and clarithromycin. *Dermatology*. 1998;196(3):335-336. [CrossRef]
10. Ünal D, Demir S, Gelincik A, et al. Diagnostic value of oral challenge testing in the diagnosis of macrolide hypersensitivity. *J Allergy Clin Immunol Pract*. 2018;6(2):521-527. [CrossRef]
11. Riley L, Mudd L, Baize T, Herzig R. Cross-sensitivity reaction between tacrolimus and macrolide antibiotics. *Bone Marrow Transplant*. 2000;25(8):907-908. [CrossRef]
12. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity: questionnaire. EAACI interest group on drug hypersensitivity. *Allergy*. 1999;54(9):999-1003. [CrossRef]
13. Brockow K, Romano A. Skin tests in the diagnosis of drug hypersensitivity reactions. *Curr Pharm Des*. 2008;14(27):2778-2791. [CrossRef]
14. 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(2):149-161. [CrossRef]
15. Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy*. 2003;58(9):854-863. [CrossRef]
16. Romano A, Atanaskovic-Markovic M, Barbaud A, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams: an EAACI position paper. *Allergy*. 2020;75(6):1300-1315. [CrossRef]
17. Atanaskovic-Markovic M, Gomes E, Cernadas JR, et al. Diagnosis and management of drug-induced anaphylaxis in children: an EAACI position paper. *Pediatr Allergy Immunol*. 2019;30(3):269-276. [CrossRef]
18. Macy E. Practical management of patients with a history of immediate hypersensitivity to common non-beta-lactam drugs. *Curr Allergy Asthma Rep*. 2016;16(1):4. [CrossRef]
19. Cavkaytar O, Karaatmaca B, Yilmaz EA, Sekerel BE, Soyer O. Testing for clarithromycin hypersensitivity: a diagnostic challenge in childhood. *J Allergy Clin Immunol Pract*. 2016;4(2):330-2.e1. [CrossRef]
20. Ferrándiz-Pulido C, García-Fernández D, Domínguez-Sampedro P, García-Patos V. Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of the experience with paediatric patients in a university hospital. *J Eur Acad Dermatol Venereol*. 2011;25(10):1153-1159. [CrossRef]
21. Mori F, Barni S, Pucci N, et al. Sensitivity and specificity of skin tests in the diagnosis of clarithromycin allergy. *Ann Allergy Asthma Immunol*. 2010;104(5):417-419. [CrossRef]
22. Suleyman A, Yucel E, Sipahi Cimen S, et al. Clarithromycin hypersensitivity in children: is there a link with β-lactam hypersensitivity? *Pediatr Allergy Immunol*. 2021;32(8):1781-1787. [CrossRef]
23. Krasowski MD, Siam MG, Iyer M, Ekins S. Molecular similarity methods for predicting cross-reactivity with therapeutic drug monitoring immunoassays. *Ther Drug Monit*. 2009;31(3):337-344. [CrossRef]
24. Mori F, Pecorari L, Pantano S, et al. Azithromycin anaphylaxis in children. *Int J Immunopathol Pharmacol*. 2014;27(1):121-126. [CrossRef]
25. Benahmed S, Scaramuzza C, Messaad D, Sahla H, Demoly P. The accuracy of the diagnosis of suspected macrolide antibiotic hypersensitivity: results of a single-blinded trial. *Allergy*. 2004;59(10):1130-1133. [CrossRef]
26. Tonson la Tour A, Michelet M, Eigenmann PA, Caubet JC. 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(4):1321-1326. [CrossRef]
27. Grinlington L, Choo S, Cranswick N, Gwee A. Non-β-lactam antibiotic hypersensitivity reactions. *Pediatrics*. 2020;145(1):e20192256. [CrossRef]
28. Brockow K, Ardern-Jones MR, Mockenhaupt M, et al. EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. *Allergy*. 2019;74(1):14-27. [CrossRef]
29. Broyles AD, Banerji A, Barmettler S, et al. Practical guidance for the evaluation and management of drug hypersensitivity: specific drugs. *J Allergy Clin Immunol Pract*. 2020;8(suppl 9):S16-S116. [CrossRef]