

DR AYSE SULEYMAN (Orcid ID : 0000-0002-9190-6849)

DR SEVGI SIPAHI (Orcid ID : 0000-0003-3026-0906)

PROFESSOR CEVDET OZDEMIR (Orcid ID : 0000-0002-9284-4520)

Article type : Original Article

CLARITHROMYCIN HYPERSENSITIVITY IN CHILDREN: IS THERE A LINK WITH β -LACTAM HYPERSENSITIVITY?

Ayşe Suleyman ¹, Esra Yücel ¹, Sevgi Sipahi Cimen ¹, Zeynep Hizli Demirkale ¹, Cevdet Ozdemir ^{1, 2}, Zeynep Ulker Tamay ¹, Nermin Guler ¹

¹ Istanbul University, Istanbul Faculty of Medicine, Department of Pediatrics, Division of Pediatric Allergy and Immunology, Istanbul, Turkey.

² Istanbul University, Institute of Child Health, Department of Pediatric Basic Sciences, Istanbul, Turkey.

Running Title: Clarithromycin Hypersensitivity in Children

Clinical Implications: In this study, children with a suspicion of clarithromycin hypersensitivity were evaluated. Oral provocation confirmed clarithromycin hypersensitivity was found in 5.6% of the patients. Our findings showed that β -lactam hypersensitivity, particularly sequential usage with amoxicillin-clavulanic acid, are found as risk factors for confirmed clarithromycin hypersensitivity.

Ayşe Suleyman, M.D., ORCID ID: 0000-0002-9190-6849

Esra Yücel, M.D., ORCID ID: 0000-0003-3712-2522

Sevgi Sipahi Cimen, M.D., ORCID ID: 0000-0003-3026-0906

Zeynep Hizli Demirkale, M.D., ORCID ID: 0000-0001-6159-9895

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/PAI.13588](#)

This article is protected by copyright. All rights reserved

Cevdet Ozdemir, M.D., ORCID ID: 0000-0002-9284-4520

Zeynep Ulker Tamay, M.D., ORCID ID: 0000-0002-3200-5493

Nermin Guler, M.D., ORCID ID: 0000-0002-9702-0491

Corresponding Author:

Cevdet Ozdemir, M.D. Professor of Pediatrics/Allergy

Istanbul University, Institute of Child Health, Department of Pediatric Basic Sciences & Istanbul University, Istanbul Faculty of Medicine, Department of Pediatrics, Division of Pediatric Allergy and Immunology, Capa, Istanbul, Turkey.

E-mail:cozdemir@superonline.com Phone: +90 532 285 3189

Word Count: 2528

Figure Count: 1

Table Count: 2

Supplementary Table Count: 1

Supplementary Figure: 1

CONFLICT OF INTEREST: The authors have no conflict of interest in relation to this manuscript.

FUNDING: There is no funding.

ABBREVIATIONS

AMC	Amoxicillin-clavulanic acid
Confidence interval	CI
CLR	Clarithromycin
CRO	Ceftriaxone
ENDA	European Network of Drug Allergy
HR	Hypersensitivity reaction
IDT	Intradermal test
IQR	Interquartile range
MDH	Multiple drug hypersensitivity
MPE	Maculopapular eruption
OPT	Oral provocation test

Abstract

Background: Clarithromycin hypersensitivity is reported as the most common cause of non- β -lactam antibiotic allergy in children. Clarithromycin is frequently prescribed in cases of suspected β -lactam hypersensitivity. Oral provocation tests stand as the gold standard to confirm drug hypersensitivity as diagnostic value of skin tests is variable. We analyzed the frequency of true clarithromycin hypersensitivity ratio and its relationship with β -lactam allergy among children with suspected clarithromycin hypersensitivity and evaluated the diagnostic value of skin tests.

Methods: The study included 160 children referred with suspected clarithromycin hypersensitivity. Clinical history and allergy workups including skin tests or/and oral provocation tests were retrieved from medical records.

Results: Oral provocation test confirmed clarithromycin hypersensitivity rate was 5.6% (n=9/160). Skin tests with clarithromycin showed positivity in 32.6% (n=29/89) of the tested patients. The sensitivity of clarithromycin skin tests was negligible, and specificity was 73.9% [95% confidence interval (CI), 64.7-81.8]. Eighty-eight of the patients (55%) reported that they had previously tolerated a β -lactam antibiotic. β -lactam hypersensitivity was suspected in 40% (n=64/160) of the patients [simultaneous (n=10), sequential (n=19), distant form (n=35)] in relation with clarithromycin usage. β -lactam hypersensitivity (95% CI, 2.1-70.6, p=0.005), and sequential usage of clarithromycin after the development of a rash with amoxicillin-clavulanic acid (95% CI, 2.0-96.4, p=0.007), were found as risk factors for confirmed clarithromycin hypersensitivity.

Conclusion: The frequency of confirmed clarithromycin hypersensitivity was found low among suspected patients. Oral provocation test is crucial for definite diagnosis. Confirmed β -lactam allergy may be attributed as a risk factor for clarithromycin hypersensitivity, particularly clarithromycin treatment after a developing rash with amoxicillin-clavulanic acid in sequential usage.

Keywords: β -lactam, clarithromycin, children, drug allergy, intradermal test, macrolides, oral provocation test, skin prick test

KEY MESSAGE: Oral provocation confirmed clarithromycin hypersensitivity was found in 5.6% of suspected clarithromycin hypersensitive children. β -lactam hypersensitivity, particularly sequential usage with amoxicillin-clavulanic acid are found as risk factors for confirmed clarithromycin hypersensitivity.

INTRODUCTION

Clarithromycin (CLR) is a commonly prescribed macrolide antibiotic especially in respiratory tract infections. CLR is among the drugs of choice in patients with a history of suspected or confirmed hypersensitivity reaction (HR) to β -lactam antibiotics¹. Although CLR is reported as the most common cause of non- β -lactam antibiotic induced HRs in children, confirmed cases are relatively rare^{2,3}.

It is well known that detailed history and physical examination are fundamental steps in evaluating drug HRs. History is generally unreliable as various conditions such as multiple drug usage or concomitant infections may affect the reported symptoms. Skin tests are the most widely used diagnostic tools to evaluate sensitization patterns in allergic disorders. However, the predictive values of these tests are variable especially in drug HRs, exceptionally higher for β -lactams than for macrolides. Besides, drug provocation tests stand as the gold standard for the diagnosis of drug allergies, including CLR-HRs⁴⁻⁹.

Hypersensitivity to more than one drug was reported in one-third of patients who were evaluated for drug HRs, however confirmed in only 2.5%⁷. In our daily practice, a patient presenting with a suspected CLR-HR may also describe a β -lactam HR, as CLR is often preferred in case of a suspicious β -lactam HR history. The potential role of β -lactam HR as a risk factor for another drug HR is well established, especially in T cell-mediated reactions such as maculopapular eruptions (MPE) and severe cutaneous drug reactions¹⁰⁻¹².

To the best of our knowledge, there is no large-scale study evaluating risk factors for CLR-HRs in children. The aim of this study is to evaluate the true frequency and possible risk factors for CLR hypersensitivity in children with suspected CLR allergy. In addition, we evaluated the temporal relationship between β -lactam allergy and CLR-HR.

METHODS

Patients and data collection

Patients who were admitted with suspicion of CLR-HR, in between June 2012-May 2018 at the outpatient clinic of Istanbul University, Istanbul Faculty of Medicine, Division of Pediatric Allergy-Immunology, were retrospectively evaluated. One hundred-sixty patients were included into the study, all of whom underwent allergy workups to evaluate CLR-HRs. The patients' demographic, clinical and laboratory data were retrieved according to the European Network of Drug Allergy (ENDA) questionnaire ¹³. Reactions were classified as immediate, mixed or delayed types depending on the onset of duration of the symptoms after CLR consumption ⁶. In order to define as a risk factor and find out the temporal relationship between suspected β -lactam-HRs and CLR-HRs, patients were grouped into sequential, simultaneous and distant forms in the order of the usage of the two drugs ¹⁰. The sequential form is defined as ongoing rash in a patient whose treatment was altered from a β -lactam antibiotic to CLR due to suspected β -lactam HR in the course of the infection. Simultaneous form is defined as HRs occurring during usage of both β -lactam and CLR at the same time. Distant form is defined as suspected HR to β -lactam and a suspected HR to CLR which occurred a long time apart.

Clarithromycin skin tests

Clarithromycin skin tests were performed at the earliest 4 weeks after the suspected reaction. Skin prick test was performed with CLR (50 mg/mL vial parenteral form) at full strength and read after 20 minutes. 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 intradermal test (IDT) was performed at a concentration of 1:1000 (0.05mg/mL), and if this dilution was negative, concentration was increased to 1:100 (0.5mg/mL) with 20 minutes interval. The response was recorded as positive if the mean diameter of the wheal was ≥ 5 mm. Histamine was used as the positive control, and 0.9% NaCl was used as negative control ¹⁴.

Clarithromycin oral provocation tests

Clarithromycin oral provocation tests (OPTs) were performed as open challenge procedures to all study patients. Considering the ENDA recommendations, only CLR-OPTs were performed without prior skin testing in patients with a convincing history ^{13,15}. Oral dose of CLR was calculated as 7.5

mg/kg/dose twice daily. Starting at a ratio of 1:10 of the dose that should be taken, a single full dose was reached after three applications in 30 minutes increments. (1st dose: 0.75mg/kg, 2nd dose as twice of the first dose, 3rd dose as the rest of the single full dose). OPT was accepted as positive and terminated in patients who developed abnormal signs and or symptoms ¹⁵. Patients were followed-up up to 2 hours after the procedure. The patients who were negative for the test continued to take the drug for 5 days at the therapeutic doses at their homes to be assessed for delayed type reactions.

β-lactam oral provocation tests

In the allergic evaluation of β-lactams, ENDA guidelines were strictly followed ¹⁵.

Ethics

Informed consents were obtained from the patients and their parents for further allergic evaluation. The Local Ethics Committee of the Istanbul Faculty of Medicine has approved the study protocol (No: 2018/1516-1539).

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) program (Version 23.0. NY.). Pearson Chi-Square test or Fisher's exact test was used to compare the categorized data. The normality of the distribution of continuous variables was evaluated with the skewness-kurtosis and the Kolmogorov Smirnov test or Shapiro Wilks test. Those with abnormal distribution among continuous variables were given as median and interquartile range (IQR). Logistic regression analysis was performed to find the risk factors for confirmed CLR-HRs. A value of $p < 0.05$ was accepted to be statistically significant.

RESULTS

The median age of the study group was 7 years (IQR: 4-11 years). Of the hypersensitivity reactions, 79.4% (n=127) occurred in between 1-24 hours, and 61.9% (n=99) presented with a maculopapular eruption. Clinical characteristics of the patients with suspected CLR-HRs are presented in Table-1. The median onset time of suspected reaction to CLR reported by the parents was the 1st day (1-3 days)

of the therapy. While 60% of patients (n=96) had a suspected reaction to CLR alone, 40% of patients (n=64) had a history of suspected HR to both CLR and β -lactam antibiotics. (Supplementary Figure-1).

Suspected hypersensitivity reaction only to clarithromycin

Hypersensitivity reactions to CLR alone was suspected in 96 patients. Eighty-eight of the patients (55%) had previously reported that they tolerated a β -lactam antibiotic. CLR hypersensitivity was confirmed in 3 of these patients with OPT. Two of them developed MPE, one developed urticaria during OPT.

Suspected hypersensitivity reaction to clarithromycin in addition to confirmed or suspected hypersensitivity reaction to β -lactam antibiotics

There were 64 patients with a suspected CLR-HR with a previous suspected or confirmed β -lactam antibiotic HR. Of these patients, 54.7% (n=35) were classified in the distant form, 29.7% (n=19) in the sequential form and 15.6% (n=10) in the simultaneous form. The distant form also included 5 patients with previously confirmed β -lactam HRs [(3 patients with ceftriaxone (CRO), 1 patient with cefuroxime, 1 patient with amoxicillin-clavulanic acid (AMC)]. In the distant form, the median time interval between parent-reported suspected CLR and β -lactam HRs was 12 months (IQR: 8-24 months). In the sequential form, patients were switched to CLR treatment due to an emerging rash while receiving AMC/amoxicillin. In the simultaneous form, CLR and CRO used together were both discontinued on suspicion of HR (Table 1).

Of the 4 patients with both confirmed CLR and beta-lactam antibiotic HRs, 2 were in the distant form (1 patient with CRO+CLR, 1 patient with AMC+CLR), and 2 were in sequential form (AMC+CLR). Allergy test results of these patients are as follow: The first patient (patient no: 4) developed anaphylaxis to CRO during the skin prick test and urticaria-angioedema to CLR during OPT. The second patient (patient no:5) developed urticaria-angioedema while using AMC and also during OPT with CLR. The third patient (patient no:7) developed MPE with AMC and during OPT with CLR. The last patient (patient no:9) had a history of MPE after AMC and CLR with sequential use, in the past. This patient developed anaphylaxis after the first dose of CLR during OPT. Clinical features of

patients with confirmed CLR-HRs, skin test results, and temporal relationship with β -lactam antibiotic usage are shown in Table 2.

Comparison of the clinical characteristics of the patients based on CLR OPT results is presented in Supplementary Table-1. In patients with OPT confirmed CLR-HR, the rates of verified β -lactam ($p<0.001$) and AMC hypersensitivities ($p<0.001$), and the percentage of the patients treated in sequential form ($p=0.012$) were significantly higher.

Patients presenting initially with urticaria-angioedema showed a positive correlation with simultaneous usage of a β -lactam and CLR ($r=0.372$, $p=0.002$). Similarly, a positive correlation was observed between the presentation with MPE and sequential usage of a β -lactam and CLR ($r=0.486$, $p<0.001$). Regression analyses showed that a confirmed HR to a β -lactam antibiotic is a risk factor for true CLR-HR [95% confidence interval, 2.1-70.6, $p=0.005$]. Together with this, sequential usage of AMC and CLR was also found as a significant risk factor [95% confidence interval, 2.0-96.4, $p=0.007$].

Skin test results

Skin tests with CLR were performed in 89 patients. Skin prick tests of all of these patients were negative, whereas IDTs were found to be positive in 32.6% ($n=29$). Among these patients, 10 of them were positive at 1:1000 (0.05 mg/mL) dilution and, 19 of them were positive at 1:100 (0.5 mg/mL) dilution (Figure-1).

The sensitivity of CLR skin tests was found negligible, the specificity was 73.9% (95% CI, 64.7-81.8), the positive predictive value was negligible, the negative predictive value was 92.1% (95% CI, 92.3-93.0), and the accuracy was found 69.5% (95% CI, 60.3- 77.6).

DISCUSSION

In this study, we confirmed true CLR-HRs in only 5.6% of patients with a suspected history of CLR allergy. We found the specificity of skin tests with CLR as 73.9% and the sensitivity as negligible. In our analyses, β -lactam allergy was found as a significant risk factor for CLR-HRs. Furthermore,

sequential treatment with CLR after developing a rash with AMC was found as another risk factor for CLR-HRs.

Hypersensitivity reactions to macrolides are reported in 0.4% to 3% of all treatments ¹. In parallel with increases in macrolide usages, awareness of allergic reactions to this group of antibiotics are more marked¹⁶. It is essential to perform OPT for diagnosing true CLR allergy, as a wide range of clinical presentations may ensue varying from generally mild HRs to life threatening severe cutaneous reactions ¹⁷.

It is known that drug allergy may be generally overestimated in children and a suspected history of drug allergy needs to be confirmed by detailed allergy work-up ¹⁸. Our results showed that 94.4% of study patients with a suspected history of CLR-HRs could in fact tolerate this antibiotic. This may be explained by; firstly, cutaneous reactions seen in the course of a viral or bacterial infection may be labelled as drug allergy incorrectly; secondly, the interaction of non-specific infection with a drug or its metabolites may lead to an enhanced immune reactivity, and non-persistent sensitization; thirdly, the reaction may develop via non-immunologic mechanisms, and lastly HRs may disappear over time.

It was previously reported that positivity based on the skin tests was 15-45%, and OPT positivity as 2-15% in patients with suspected CLR-HR. Varying concentrations of CLR in between 1:100.000 to 1:10 dilutions were used for CLR skin testing in previous studies ^{2,16,19,20}. On the other hand, due to the content of lactobionic acid and sodium hydroxide in the intravenous preparations of CLR, false positivity relevant to irritation may occur during skin tests ¹⁶. As skin tests with CLR are not validated yet; OPT with CLR is crucial to confirm the definite diagnosis. Mori et al. have previously reported 6.2% OPT confirmed CLR-HRs and 15.6% IDT positivity in 64 patients with suspected CLR-HRs ¹⁹. The non-irritating dose of CLR was determined as 1:100 dilution (0.5mg/ml) in healthy children in whom the sensitivity and specificity rates of IDT were found as 75% and 90%, respectively ¹⁹. Although we performed CLR skin tests with the same concentration, our skin test positivity rate was about twice that in the report of Mori et al. ¹⁹. On the other hand, in another pediatric series of 45 sequential patients referred with suspected CLR-HRs, sensitivity and specificity rates of skin tests were found as negligible and 50%, respectively. All of these patients with OPT-confirmed CLR-HRs had negative skin test results. Although they performed drug tests with much lower concentrations

(1:1000 to 1:100.000), their results were compatible with ours ¹⁶. In our evaluation, the skin test results were also not compatible with CLR OPT results. OPT results were negative in all 29 patients whose CLR skin tests were found to be positive. Furthermore, none of our patients with OPT confirmed CLR-HRs had a positive skin test reaction. These results may query the role of skin testing in predicting CLR-HRs, especially in children.

Multiple drug hypersensitivity (MDH) is defined as hypersensitivity to two or more drugs that differ chemically by means of skin tests or *in vitro* tests ^{21,22}. MDH is generally T cell-mediated and dose-dependent ¹⁰. Daubner et al. showed that drug reactive T cells in patients with MDH display an enhanced state of reactivity ¹¹. Therefore, patients may give an exaggerated, non-specific response to various drugs even at lower thresholds. Although frequency of MDH is reported as 10% to 40% based on parental questionnaires, true MDH rates confirmed by *in vivo* or *in vitro* tests are much lower ^{2,7}. In a pediatric study, the diagnosis of MDH was confirmed only in 2.7% of the patients, and AMC and CLR were the most commonly reported culprit drugs. In a recent study, it was shown that β -lactams can be inducers of HRs in patients with MDH, while macrolides were regarded as safe drugs ¹⁰.

In the case of a suspected history of a β -lactam HR, the general tendency is to avoid all β -lactams and preference of macrolides ^{23,24}. It was not a surprising scenario to detect high rates of CLR-HR due to the frequent use of this drug as an alternative in β -lactam HRs. However, we observed highest rates of CLR-HRs in the sequential form among the three forms of β -lactam HRs. This finding supports the hypothesis that if the first reaction is a real HR while on β -lactam therapy, the emerging rash appearing with the use of alternative antibiotics may be the outcome of a new HR or exacerbation of the former reaction in this hyperreactive state ¹⁰. It may be hypothesized that CLR may enhance the reactivity of T cells in the event of a previously triggered drug induced HR, as macrolides are known to be too small molecules to induce immunoglobulin E production directly, or are generally unable to haptenize other serum proteins ²⁵.

As this study is performed in a tertiary allergy outpatient clinic, our sample may not exactly represent the general population. This may be attributed to over presentation of cases suspected with MDHs. The strength of our study is the high number of patients and performance of OPTs to all study subjects.

Accepted Article

In conclusion, although true clarithromycin HR is low among suspected patients, oral provocation tests are essential for definite diagnosis. Confirmed β -lactam allergy, particularly clarithromycin treatment after a developing rash with amoxicillin-clavulanic acid in sequential usage may be a risk factor for clarithromycin HR.

ACKNOWLEDGMENTS: There is no acknowledgment.

REFERENCES:

1. Araujo L, Demoly P. Macrolides allergy. *Curr Pharm Des.* 2008;14(27):2840-2862.
2. Guvenir H, Dibek Misirlioglu E, Capanoglu M, Vezir E, Toyran M, Kocabas CN. Proven Non-beta-Lactam Antibiotic Allergy in Children. *Int Arch Allergy Immunol.* 2016;169(1):45-50.
3. 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.
4. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy.* 2013;68(6):702-712.
5. Solensky R, Khan DA. Evaluation of antibiotic allergy: the role of skin tests and drug challenges. *Curr Allergy Asthma Rep.* 2014;14(9):459.
6. Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. *Allergy.* 2014;69(4):420-437.
7. Atanaskovic-Markovic M, Gaeta F, Gavrovic-Jankulovic M, Cirkovic Velickovic T, Valluzzi RL, Romano A. Diagnosing multiple drug hypersensitivity in children. *Pediatr Allergy Immunol.* 2012;23(8):785-791.
8. Kidon M, Blanca-Lopez N, Gomes E, et al. EAACI/ENDA Position Paper: Diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents. *Pediatr Allergy Immunol.* 2018;29(5):469-480.
9. Diaferio L, Chiriac AM, Leoni MC, et al. Skin tests are important in children with beta-lactam hypersensitivity, but may be reduced in number. *Pediatr Allergy Immunol.* 2019;30(4):462-468.
10. Jorg L, Yerly D, Helbling A, Pichler W. The role of drug, dose, and the tolerance/intolerance of new drugs in multiple drug hypersensitivity syndrome. *Allergy.* 2020;75(5):1178-1187.
11. Daubner B, Groux-Keller M, Hausmann OV, et al. Multiple drug hypersensitivity: normal Treg cell function but enhanced in vivo activation of drug-specific T cells. *Allergy.* 2012;67(1):58-66.

12. Ariza A, Fernandez-Santamaria R, Meng X, et al. Characterization of amoxicillin and clavulanic acid specific T-cell clones from patients with immediate drug hypersensitivity. *Allergy*. 2020.
13. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity: questionnaire. EAACI interest group on drug hypersensitivity. *Allergy*. 1999;54(9):999-1003.
14. Brockow K, Romano A. Skin tests in the diagnosis of drug hypersensitivity reactions. *Curr Pharm Des*. 2008;14(27):2778-2791.
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.
16. 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):330-332 e331.
17. Shaeer KM, Chahine EB, Varghese Gupta S, Cho JC. Macrolide Allergic Reactions. *Pharmacy (Basel)*. 2019;7(3).
18. Sipahi Cimen S, Yucel E, Ozceker D, et al. Behind the scene: Paracetamol hypersensitivity in children. *Pediatr Allergy Immunol*. 2020.
19. 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.
20. Unal 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.
21. Pichler WJ, Srinoulprasert Y, Yun J, Hausmann O. Multiple Drug Hypersensitivity. *Int Arch Allergy Immunol*. 2017;172(3):129-138.
22. Gex-Collet C, Helbling A, Pichler WJ. Multiple drug hypersensitivity--proof of multiple drug hypersensitivity by patch and lymphocyte transformation tests. *J Investig Allergol Clin Immunol*. 2005;15(4):293-296.
23. Caubet JC. Management of children with a suspicion of immediate drug hypersensitivity. *Allergy*. 2020.
24. Mayorga C, Fernandez TD, Montanez MI, Moreno E, Torres MJ. Recent developments and highlights in drug hypersensitivity. *Allergy*. 2019;74(12):2368-2381.

25. 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.

TABLES:

Table 1. Clinical characteristics and features of the patients with suspected CLR-HRs

	n (%)
Gender	
Female	69 (43.1)
Male	91 (56.9)
Age [median (IQR)], years [†]	7 (4-11) [†]
Reaction type according to the history (CLR related)	
MPE	99 (61.9)
Urticaria-angioedema	54 (33.8)
Subjective or unclear symptoms [‡]	7 (4.4)
Reaction time according to the last dose of the drug	
≤ 1 hour	14 (8.8)
1-24 hours	127 (79.4)
> 24 hours	19 (11.9)
Patients with suspected only CLR-HRs	96 (60)
Previous usage of a β-lactam uneventfully	88 (55)
Patients with suspected CLR and β-lactam HRs	64 (40)
Temporal relationship with suspected CLR+β-lactam HRs	
Simultaneous usage	10 (15.6)
<i>CLR + CRO</i>	10
Sequential usage	19 (29.7)
<i>CLR+AMX and or AMC</i>	19
Distant usage	35 (54.7)
<i>CLR and AMX/AMC</i>	14
<i>CLR and CRO</i>	8
<i>CLR and CXM</i>	10
<i>CLR and SAM</i>	3
Previous CLR usage before the suspected reaction	
Yes	109 (68.1)
No	51 (31.9)
Family history of drug allergy	51 (31.9)

Concomitant allergic disease	55 (34.4)
Atopic dermatitis	5
Asthma and/or allergic rhinitis	50

[†]The median and interquartile range [IQR]; [‡]Non-specific findings refer to feeling unwell, or discomfort.

AMC: Amoxicillin-clavulanic acid; AMX: Amoxicillin; CLR: Clarithromycin; CRO: Ceftriaxone; CXM: Cefuroxime; MPE: Maculopapular eruption; SAM: Ampicillin-sulbactam.

Table-2. Clinical features, skin test results and temporal relationship with usage of β -lactam antibiotics of the patients with confirmed CLR-HRs

Patient id number	Age at the first HR (years) & gender	Culprit drug	Clinical type of the reaction	Onset of the reaction	Time interval between the 1 st & 2 nd HRs (months)	Previous safe usage of culprit drugs before the reaction	Skin tests with drugs	Time interval between the drug reaction & diagnostic tests (months)	Confirmatory procedure of HR	Observed reaction during OPT
Only CLR-HR										
1	2, F	CLR	MPE	1-24 h	-	+	Negative	1,5	OPT	MPE
2	2, M	CLR	MPE	24 h	-	+	NP	2	OPT	MPE
3	8, M	CLR	U-AE	1-24 h	-	+	Negative	4	OPT	Urticaria
CLR and β-lactam- distant form										
4	7, F	CRO	A	<1 h	24	+	Positive	6	Prick test	NP
		CLR	AE	4 h		+	Negative	4	OPT	U-AE
5	2, M	CLR	U-AE	0.5 h	8	+	Negative	1,5	OPT	Urticaria
		AMC	U-AE	4 h		+	NP	6	OPT	U-AE
CLR and β-lactam- sequential form										
6	2.5, M	AMC	MPE	1-24 h	-	+	NP	1,5	OPT	No reaction
		CLR	MPE	1-24 h	-	-	Negative	2	OPT	MPE
7	8.5, M	AMC	MPE	1-24 h	-	+	NP	1,5	OPT	MPE

		CLR	NS	1-24 h	-	+	Negative	5	OPT	MPE
8	7, M	AMC	MPE	1-24 h		+	NP	24	OPT	No reaction
		CLR	MPE	1-24 h	-	+	Negative	4	OPT	MPE
9	15, F	AMC	MPE	1-24 h	-	+	NP	6	OPT	MPE
		CLR	MPE	1 h		+	Negative	2	OPT	A
CLR and β -lactam-simultaneous form										
No patients with CLR-HRs confirmed										

A: Anaphylaxis; AE: Angioedema; AMC: Amoxicillin-clavulanic acid; MPE: Maculopapular eruption; NP: Not performed; OPT: Oral provocation test; U-AE: Urticaria-angioedema;

FIGURE LEGENDS:

FIGURE-1 Confirmatory evaluation of patients with suspected clarithromycin hypersensitivity reactions

Diagnosis was confirmed by oral provocation test in 3 of 96 patients with a reaction history to clarithromycin (upper side of the figure). Of these 96 patients, 88 had previously used β -lactam uneventfully. Clarithromycin hypersensitivity was confirmed in 6 of 64 patients with a reaction history to β -lactam in addition clarithromycin (lower side of the figure). Patients with a non-immediate reaction to clarithromycin were evaluated directly by oral provocation test without skin test. Patients with immediate or mixed reaction to clarithromycin were evaluated by skin tests and oral provocation tests. Oral provocation test was performed to determine false positive or false negative skin test results in patients regardless of clarithromycin skin test results.

Abbreviations: IDT: Intradermal test, SPT: Skin prick test, OPT: Oral provocation test.

SUPPLEMENTARY FIGURE-1

In our study population we confirmed CLR-HR in 9 of 160 patients by oral provocation tests.

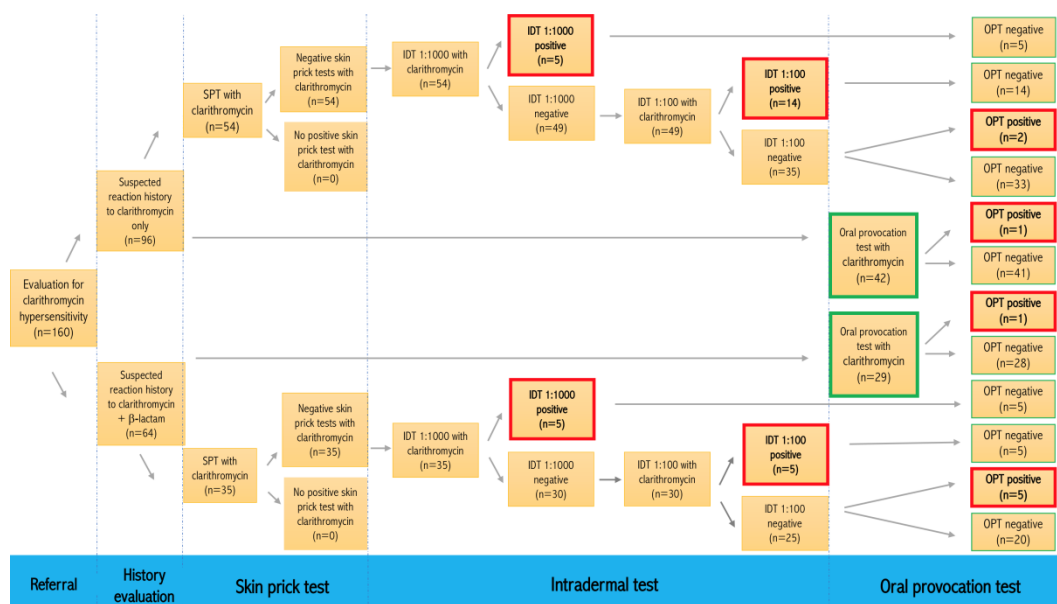
Among the patients with a suspected CLR-HR with a previous suspected or confirmed β -lactam antibiotic HR (n=64), we confirmed CLR-HR in 6 of these patients (2 in the distant form and 4 in the sequential form). Also, β -lactam antibiotic HR was confirmed in 10 patients (6 in the distant form, 1 in the simultaneous form and 3 in the sequential form). Among these 10 patients CLR-HR together with β -lactam antibiotic HR was detected in 4 patients.

On the other hand, in patients with only suspected CLR-HR (n=96), diagnosis was confirmed in 3 of them by oral provocation tests. *CLR: clarithromycin, HR: hypersensitivity reaction*

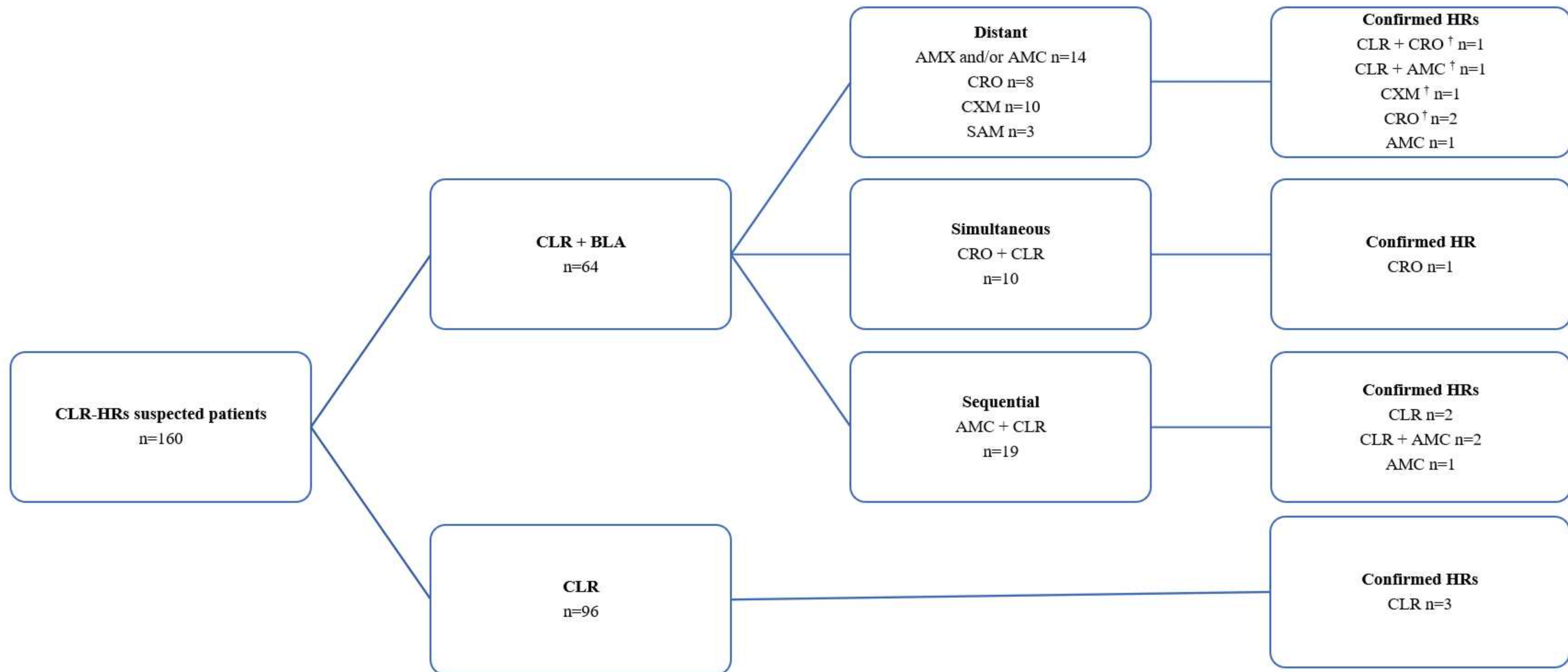
†Previously known drug allergy (3 CRO, 1 CXM, 1 AMC).

BLA: β -lactam antibiotic, CLR; Clarithromycin,

AMX; Amoxicillin, AMC: Amoxicillin-clavulanate, SAM: Ampicillin-sulbactam, CRO: Ceftriaxone, CXM: Cefuroxime



pai_13588_f1.png



SUPPLEMENTARY FILE:

Supplementary Table-1. Comparison of the clinical characteristics of the patients with positive and negative OPT results with CLR.

	OPT positive n=9 n(%)	OPT negative n=151 n(%)	p value
Gender; male	6 (66.7)	85 (56.3)	0.541
Age (IQR), year [†]	7 (2-8)	7 (4.5-11)	0.195
Latent period between index reaction and allergic work up (months)	2 (2-18)	12 (2-24)	0.117
Latent period ≤ 1 year	6 (66.7)	84 (55.6)	0.517
Reaction time			
≤1 hour	1 (11.1)	13 (8.6)	0.109
1-24 hour	5 (55.5)	122 (80.8)	
>24 hour	3 (33.3)	16 (10)	
History of clarithromycin usage with no reaction			
Yes	8 (88.9)	101 (66.9)	0.169
No	1 (11.1)	50 (33.1)	
MPE	5 (55.6)	98 (64.9)	0.570
Urticaria-angioedema	4 (44.4)	46 (30.7)	0.387
Culprit drugs			
Only CLR	3 (33.3)	93 (61.6)	0.093
CLR+ β-lactam	6 (66.7)	58 (38.4)	
<i>Confirmed drug allergy</i>			
CLR+ β-lactam (more than one drug)	4 (44.4)	0	<0.001
Only CLR	5 (55.6)	151(100)	
Temporal relationship of suspected CLR and β-lactam HRs			
Distant form	2 (22.2)	33 (21.9)	1 *
Simultaneous form	0 (0)	10(6.6)	0.475
Sequential form	4 (44.4)	15 (9.9)	0.012 *
Atopic disease	3 (33.3)	52 (34.4)	1*
Family history	1 (11.1)	50 (33.1)	0.169

[†]: The median and interquartile range (IQR); * Fisher's exact test was used.

AMC: Amoxicillin-clavulanic acid, CLR: Clarithromycin, MPE: Maculopapular eruption, SAM: Ampicillin-sulbactam

