

The Diagnosis of Ceftriaxone Hypersensitivity in a Paediatric Population

Francesca Mori^a Giulia Liccioli^a Alessandra Piccorossi^b Lucrezia Sarti^a
Simona Barni^a Mattia Giovannini^a Chiara Azzari^c Mariangela Manfredi^d
Elio Novembre^a

^aDepartment of Paediatrics, Allergy Unit, Anna Meyer Children's University Hospital, Florence, Italy; ^bDepartment of Paediatrics, San Salvatore Hospital, University of L'Aquila, L'Aquila, Italy; ^cSection of Paediatrics, Division of Immunology, Department of Health Sciences, Anna Meyer Children's Hospital, University of Florence, Florence, Italy; ^dLaboratory of Immunology and Allergology, S. Giovanni di Dio Hospital, Florence, Italy

Keywords

Ceftriaxone · Hypersensitivity · Drug allergy · Children · Paediatric population

Abstract

Introduction: Penicillins and cephalosporins are the most frequent causes of hypersensitivity reactions (HRs) to drugs in children. Among cephalosporins for intravenous use, ceftriaxone (CT) is the most frequently prescribed in Italy. The aims of this study were to evaluate the diagnostic methods for CT hypersensitivity in a population of children with suspected HRs to this drug and their tolerance toward amoxicillin/clavulanic acid (AMX/CLV). **Materials and Methods:** From 2012 to 2018, 90 children were investigated for suspected HRs to CT according to the European Academy of Allergy Asthma and Clinical Immunology (EAACI) guidelines. **Results:** Ninety children had a history of reaction to CT. The majority (79/90; 77.8%) had a history of immediate reactions (IRs). CT hypersensitivity was confirmed in 26/90 patients (28.9%). In case of IRs, skin tests can be useful (24% of posi-

tive CT intradermal tests – IDTs) particularly in cases of anaphylaxis (81.8% of positive CT IDTs). Only 5 out of 28 drug provocation tests were positive. Serum-specific IgE (slgE) determination for CT correlated with positivity upon skin/drug provocation tests (high specificity 95.6%) but had a low sensitivity; slgE for AMX had a very low positive predictive value (14.3%), advocating against its use. In case of non-IRs, only 7/11 patients reached a confident diagnosis, but the low number of children does not enable proper conclusions. Only 2 children showed cross- and/or co-allergy (2.2%) between CT and AMX/CLV. **Conclusion:** IDTs seem to be useful for diagnosing CT IRs. Hypersensitivity to CT is confirmed in 28.9% of children, although a large fraction of parents refused an intravenous rechallenge (45.6%). It remains unknown whether this is due to the fact this was intravenous rather than a rechallenge with the culprit, but it reflects a clinical reality. Otherwise, cross- and/or co-allergy between CT and AMX/CLV is a rare event.

© 2019 S. Karger AG, Basel

Edited by: H.-U. Simon, Bern.

Introduction

Today, β -lactams (BLs) are among the most frequent causes of hypersensitivity reactions (HRs) to drugs, with penicillins and cephalosporins the two main classes of BL antibiotics in terms of culprit drugs and prescription rates, especially in children [1]. BLs may provoke both IgE-mediated and T-cell-mediated HRs. The former usually occur within 1 h after the last drug administration (i.e., immediate reactions [IRs] from urticaria to anaphylaxis), while the latter appear more than 1 h later (i.e., non-IRs from maculopapular exanthemas [MPEs] to severe cutaneous adverse reactions). Both penicillins and cephalosporins share a common BL ring attached to a 5-membered thiazolidine ring with a side chain (R) or a 6-membered sulphur-containing dihydrothiazine (cephem) ring with 2 side chains (R1 and R2), respectively [1]. The BL ring, thiazolidine/dihydrothiazine rings and side groups are all potentially immunogenic. In particular, side chains are important sites of immunological recognition and may therefore cause allergic cross-reactivity that is probably less than 1–2% between penicillin and cephalosporin [2, 3]. While several studies have been published on cephalosporin HRs in children, the majority focus on HRs to oral cephalosporins [4]. Ceftriaxone (CT) is the most frequently prescribed cephalosporin for intravenous or intramuscular use in Italy [5], and it causes the highest number of severe adverse reactions in Italian children [6]. This is the first study investigating such a high number of children with suspected HRs to intravenous CT, the aim being to evaluate the diagnostic methods for CT hypersensitivity in a paediatric population with suspected HRs to this drug. Moreover, tolerance towards amoxicillin (AMX) was investigated, in order to provide a valid alternative to treat the most common paediatric infections, AMX being among the first-choice antibiotic treatments in children.

Materials and Methods

From January 2012 to September 2018, 90 children with a history of CT reactions were consecutively enrolled and subjected to drug allergy work-up according to the European Network on Drug Allergy (ENDA) guidelines. In case of IRs to CT skin testing (skin prick tests [SPT] and intradermal tests [IDT]) with CT and other BLs and assays for total serum and serum-specific IgE (sIgE) to BLs were performed by using ImmunoCap. CT sIgEs were also determined using a radio-immunoenzymatic assay (Table 1) [7]. In particular sIgEs were measured before skin testing in those with severe reactions according to the guidelines of Brockow et al. [8]. In case of a clear history of non-IRs, only in vivo tests were performed. In case of negativity to the in vivo tests and in the majority of patients with

negative in vitro tests with CT, a drug provocation test (DPT) with the culprit was performed. If there was no history of severe reactions (anaphylaxis or history of severe cutaneous adverse reactions), the DPT was performed with CT, otherwise it was performed with AMX. In about half of the cases, it was not possible to perform the DPT with CT, because the parents refused a challenge or did not attend follow-up visits. Beforehand, all subjects or their families were informed about the possible risks involved, and they signed an informed consent form. An intravenous DPT was performed by administering gradually increasing doses of CT (Table 1). In case of diagnosis of hypersensitivity to CT and negativity of in vivo tests with AMX, tolerance towards AMX was tested with a 3-step oral DPT (Table 1), according to ENDA guidelines [8]. Patients were instructed to withhold systemic antihistamines for at least 5 days prior to the SPT/IDT and systemic corticosteroids for at least 5 weeks prior to the DPT. The DPT was performed in a ward by a trained physician with continuous monitoring of vital signs and full access to resuscitation support. Upon discharge, all patients had full hospital access for reporting any non-IRs, considered to be related to the drug when occurring within 96 h after the end of treatment.

Results

During the enrolment period, 1,264 children were referred to the Allergy Unit of the Anna Meyer Children's Hospital with a history of reactions to BL antibiotics. Ninety children (7.1%) had a history of CT reactions. Table 1 contains the demographic characteristics of the population studied, the clinical symptoms of IRs and non-IRs, and the allergy work-up. Seventy-nine out of 90 (87.8%) children had an IR and 11 out of 90 (12.2%) a non-IR. Eleven out of 79 children (13.9%) with IRs had experienced anaphylaxis; in the other cases they mainly developed cutaneous symptoms. Among the non-IRs, the most frequent symptoms were MPEs and urticaria; however, there were 2 cases of drug reaction with eosinophilia and systemic symptoms (DRESS). The results of the allergy work-up are summarised in Figure 1. Nineteen out of 79 (24%) children with a history of IR had a positive SPT/IDT with CT, therefore the reactions to CT were considered true HRs. Among those children only 1 child with a history of urticaria was also positive to minor determinant mixture and benzylpenicilloyl polylysine but he passed the DPT with AMX. In particular, 9 out of 19 had a history of anaphylaxis. Moreover, 15/19 had also positive CT sIgE measured by radio-immunoenzymatic assay (9/15 of children with a history of anaphylaxis); 6 out of 19 had also a mild positivity to the BL sIgE measured by ELISA (3/6 children with a history of anaphylaxis). Five out of 19 children with a positive skin test (ST) to CT were also positive to both sIgE to CT and sIgE to BLs. Sixty out of 79 (76%) patients had a negative SPT/

Table 1. Demographic characteristics of children enrolled and allergy work-up**a** Demographic characteristics

	Total	Allergic	Non-allergic	Uncertain
Patients, <i>n</i>	90	26 (28.9%)	23 (25.5%)	41 (45.6%)
Mean age at reaction, years	6.5 (3 months to 17 years)	8.1 (2–17 years)	6.9 (3 months to 17 years)	5.3 (1–16 years)
Sex	54 M/36 F	17 M/9 F	13 M/10 F	24 M/17 F
Atopy, <i>n</i>	30/90	14/26	7/23	9/41
Latency from reaction and diagnostic work-up, months	12.9 (1 month to 12 years)	6 (1 month to 2 years)	17.6 (1 month to 12 years)	11.9 (1 month to 12 years)
Type of reaction, <i>n</i>				
A	11	9	0	2
U/AE/ER/MPE/UV	69	12	20	7
RS	6	2	2	2
GI	1	1	0	0
DRESS	2	2	0	0
Hypotonia	1	0	1	0

b Allergy work-up

Hapten	SPT	IDT	Immunoassays, kU/L	DPT
PPL (Diater, Madrid, Spain)	Undiluted	Undiluted	/	/
MDM (Diater, Madrid, Spain)	Undiluted	Undiluted	/	/
BP (Pharmacia, Milan, Italy)	10,000 IU	10,000 IU	/	/
AMX (Hymox Forte, Biochemie Spimaco, Saudi Arabia)	20 mg/mL	20 mg/mL	ImmunoCAP™ ELISAs to penicilloyl G, penicilloyl V, ampicillin, AMX and cefaclor were performed (ThermoFischer Scientific, Uppsala, Sweden)	Oral administration of gradually increasing doses of AMX (1/10–2/10–7/10) of the therapeutic dose calculated at 50 mg/kg/day every 20 min
CT (Mylan Generics, Milan, Italy)	2 mg/mL	2 mg/mL	RIA: the solid phase was obtained by coupling the drug to sepharose epoxy activated 6B	Endovenous administration of gradually increasing doses of CT (1/10–2/10–7/10 of the full therapeutic dose calculated at 50 mg/kg/day) every 20 min
Histamine phosphate (positive control)	10 mg/mL	1 mg/mL	/	/
Saline solution (negative control)	Undiluted	Undiluted	/	/
Positivity	Immediate reading (20 min): wheal accompanied by erythema 3 mm larger than a negative control (>5 mm)	Immediate reading (20 min) + late reading (24–48 h): wheal accompanied by erythema 3 mm larger than the injected papule in the IDT	ImmunoCAP: value ≥0.10 kU/L RIA: results are expressed as the percentage of radioactivity bound to the solid phase in relation to the total radioactivity introduced; values of at least 3 times the normal serum level were considered positive	Signs of a hypersensitivity reaction, defined by the occurrence of objective symptoms or throat tightness after 2 h of observation

A, anaphylaxis (urticaria and/or angio-oedema, dyspnoea with desaturation, bronchospasm); U, urticaria; AE, angio-oedema; ER, erythema; MPE, maculopapular exanthema; UV, urticaria and vasculitis; RS, respiratory symptoms; GI, gastrointestinal symptoms; DRESS, drug reaction with eosinophilia and systemic symptoms. CT, ceftriaxone; SPT, skin prick test; IDT, intradermal test; PPL, benzylpenicilloyl polylysine; MDM, minor determinant mixture; BP, benzylpenicillin; AMX, amoxicillin; ImmunoCap, ELISA for detecting BL-specific IgE; DPT, drug provocation test; RIA, radio-immunoenzymatic assay.

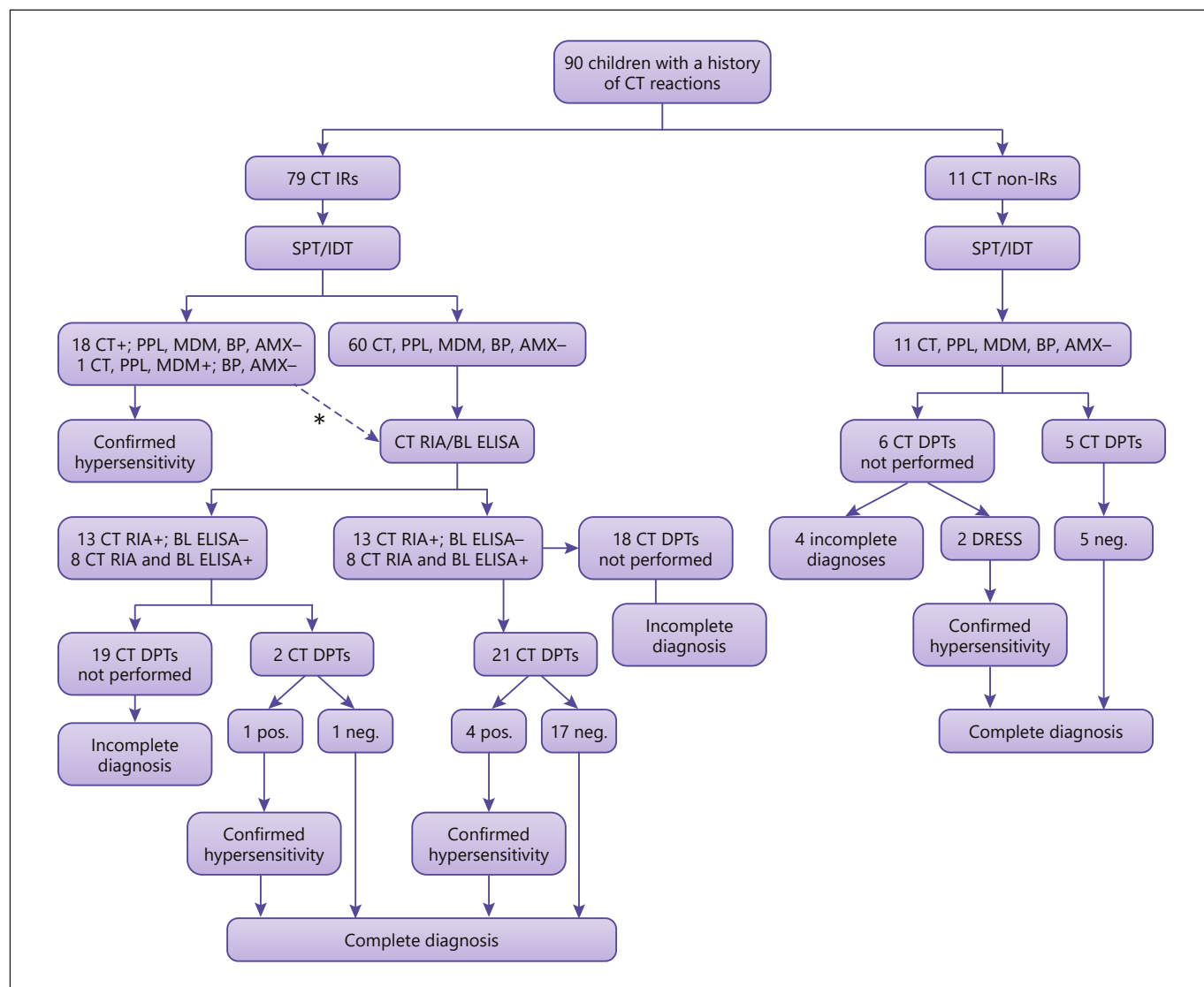


Fig. 1. Allergy work-up in 90 children with suspected ceftriaxone (CT) hypersensitivity reactions (HRs). IRs, immediate reactions; non-IRs, non-immediate reactions; SPT, skin prick test; IDT, intradermal test; PPL, benzylpenicilloyl polylysine; MDM, minor determinant mixture; BP, benzylpenicillin; AMX, amoxicillin; RIA,

radio-immunoenzymatic assay for detecting CT-specific IgE; BL, β -lactam; ELISA, enzyme-linked immunosorbent assay; DPT, drug provocation test; DRESS, drug reaction with eosinophilia and systemic symptoms; pos. or +, positive; neg. or -, negative. The asterisk marks results described in the text.

IDT to CT, and in that group sIgE to CT was positive in 21/60 patients. Only 2/21 children were provoked with CT but only 1 passed the DPT. Thirty-nine out of 60 (65%) patients with a negative ST had also a negative sIgE to CT, and only 1 had positive sIgE to BLs; 21/39 (53.8%) DPTs were performed with CT, with true hypersensitivity confirmed in 4 patients. Eighteen out of 39 families refused the DPT so the allergy work-up was not completed and no confident diagnosis was possible. All 11 children in the group with a history of non-IRs had a negative

in vivo test. Five out of 11 underwent a DPT with CT with negative results; 2/11 had a diagnosis of DRESS syndrome hence the DPT was not recommended with the culprit; 4/11 refused the DPT. Tolerance toward AMX was detected in all children of whom 88 passed the DPT. Two out of 90 (2.2%) children, instead, reacted to AMX: one was the patient with a history of DRESS with a negative ST to CT and penicillins, who developed an MPE 12 h after oral administration of AMX; the other had a history of anaphylaxis to CT with IDT and sIgE to CT and posi-

tive sIgE to BLs (AMX 0.13 kU/L) and a negative penicillin ST, who developed some wheals on his back within 1 h after the last dose (7/10) of AMX. Overall, we performed 28/90 (31.1%) DPTs with CT. Anyway, we considered 26/90 patients (28.9%) as allergic to CT (three groups): those with a positive DPT; those with positive IDTs; the 2 cases of DRESS syndrome. We considered 23/90 children (25.5%) with negative DPTs as non-allergic. In conclusion, the diagnostic certainty, as a result of a combination of DPT, STs and clinical features (DRESS cases), was obtained in 49/90 patients (54.4%). Conversely, the diagnosis remained doubtful in 41/90 patients (45.6%) not subjected to DPTs. On investigating the diagnostic accuracy of STs, the IDTs with CT were positive at the immediate reading in 19/26 (73%) of allergic patients. In our study only 11/79 (13.9%) patients had a history of anaphylaxis with the IDTs positive in 9/11 (81.8%) of them. Nevertheless, the 5 patients with a positive DPT with CT had negative IDT results. Anyway, all 5 patients reacted to the first dose (1/10) with mild cutaneous reactions, except one who showed MPE 3 h after the infusion. Consequently, IDTs are confirmed as a useful tool in diagnosing severe IRs (2 cases). In contrast, we cannot conclude on the value of STs in case of non-IRs given the low number of patients with a history of non-IR and the lack of patch tests in both cases of DRESS. As regards sIgE to CT, the sensitivity of this test is 20% with a specificity of 95.6% calculated on patients provoked, with positive and negative predictive values of 50 and 84.6%, respectively, which is in line with data in the literature [9]. When focusing on the specificity of sIgE to BLs, we found that the majority of CT allergic patients (6/7 with a positive sIgE to BLs) tolerated AMX through DPT (very low positive predictive value 14.3%), confirming that sIgE to BLs often led to an overestimation of the number of subjects with cephalosporin allergy, who were also sensitive to penicillins.

References

- Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol*. 2011 Mar; 127(3 Suppl):S67–73.
- Romano A. Cross-reactivity and tolerability of cephalosporins in patients with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol Pract*. 2018 Sep-Oct; 6(5): 1662–72.
- Zagursky RJ, Pichichero ME. Cross-reactivity in β -Lactam Allergy. *J Allergy Clin Immunol Pract*. 2018 Jan - Feb; 6(1): 72–81.e1.
- Ponvert C, Perrin Y, Bados-Albiero A, Le Bourgeois M, Karila C, Delacourt C, et al. Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. *Pediatr Allergy Immunol*. 2011 Jun; 22(4): 411–8.
- Piovani D, Clavenna A, Cartabia M, Bonati M; Antibiotic Collaborative Group. The regional profile of antibiotic prescriptions in Italian outpatient children. *Eur J Clin Pharmacol*. 2012 Jun; 68(6): 997–1005.
- Italian Medicine Agency. Ceftriaxone e reazioni avverse nei bambini. *Boll Inf Farm*. 2008;XV(4): 176–81.
- Manfredi M, Severino M, Testi S, Macchia D, Ermini G, Pichler WJ, et al. Detection of specific IgE to quinolones. *J Allergy Clin Immunol*. 2004 Jan; 113(1): 155–60.
- Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al; ENDA/EAACI Drug Allergy Interest Group. Skin test concentrations for systemically administered drugs— an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy*. 2013 Jun; 68(6): 702–12.
- Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Zaffiro A, Caruso C, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of alternative cephalosporins. *J Allergy Clin Immunol*. 2015 Sep; 136(3): 685–691.e3.
- Warrington R, Silviu-Dan F. Drug allergy. *Allergy Asthma Clin Immunol*. 2011 Nov; 7 Suppl 1:S10.

Conclusion

In conclusion, this is the first study to enrol such a high number of children investigated for suspected reactions to intravenous CT. Intravenous routes remain the more likely to cause severe reactions (79/90 IRs and 11/79 anaphylaxis) [10]. Moreover, this study showed the importance of DPT with CT in order to reach a confident diagnosis, but at the same time it reflected the poor acceptability of an intravenous DPT (41/90 children not provoked) or the severity of the index reaction leading to a bias of the results. Anyway, the advantage of an intravenous DPT is the possibility to stop it with the occurrence of any objective sign (5/5 reacted at the first dose). This study does not enable to conclude on the value of skin testing in non-immediate reactors given the low number of patients. At last, in this study we showed that patients with CT allergy could frequently tolerate AMX, suggesting that in patients with mild reactions to CT, paediatricians should be more confident when prescribing oral AMX.

Statement of Ethics

The authors have no ethical conflicts to disclose. All subjects or their families were informed about the possible risks involved, and they signed an informed consent form.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

F. Mori conceived and designed the research and made substantial contributions in writing the manuscript. S. Barni and E. Novembre critically revised the paper and gave the final approval of the version to be published. G. Liccioli, A. Piccorossi, L. Sarti and M. Giovannini made substantial contributions to data acquisition. C. Azzari and M. Manfredi performed in vitro tests.