Cephalosporin Hypersensitivity: Descriptive Analysis, Cross-reactivity, and Risk Factors

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Running title: Cephalosporin hypersensitivity in a large series

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Abstract

Background

Cephalosporins, which belong to the beta lactams therapeutic class, are increasingly used throughout the world. Few large studies on this issue have been conducted and most of them have been performed as part of penicillin hypersensitivity studies.

Objective

We described our 26-year experience exploring cephalosporin drug hypersensitivity, from which we identified epidemiological and cross-reactivity data.

Methods

We included 476 patients who reported Drug Hypersensitivity Reaction (DHR) to cephalosporin and underwent an allergy workup between January 1992 and July 2018 in the Allergy Unit of the University Hospital of Montpellier (France). According to their structural side chain R1 homology we worked with four classes of cephalosporins. Logistic regression analysis was used to search for risk factors for hypersensitivity to cephalosporin (positive skin test or provocation test results).

Results

Cephalosporin hypersensitivity was proven in 22.3% of the patients referred in our Unit, according to positive ST (51.9%) or DPT to the culprit drug (48.1%). One in five patients were children and cephalosporin hypersensitivity was confirmed in 15% (47.6% of them by means of ST). In the cephalosporin hypersensitive population, initial reactions were mostly immediate (68.9%) and anaphylactic (72.7%). Cross-reactivity with aminopenicillins was the most frequent pattern of cross-reactivity. In multivariate analysis, immediate reactions (OR=3 (95%CI [1.6-5.5]), p<0.001)), anaphylactic shock (OR=6.5 (95%CI [3.3-13.1], p<0.001)) and anaphylaxis (OR=3.1 (95%CI [1.6-6.1], p<0.001)) and multiple reactions to the same or several

cephalosporins (OR=2.0 (95% CI [1-3.5], p=0.04)) were statistically associated with confirmed DHR. DPT was generally safe, but elicited anaphylaxis in 20% of patients. Systemic reactions during skin testing occurred in 9.1% of positive patients, almost always related to anaphylactic index reactions. Non-immediate confirmed DHR to cephalosporins were rare and occurred in less than 10% of the positive patients.

Conclusion

Almost a quarter of the tested patients were confirmed as hypersensitive to cephalosporins; sensitivity of skin testing was 51.9%, thus, half of the positive patients needed a DPT in order to prove the diagnosis.

Highlight box:

1. What is already known about this topic?

Few large studies on cephalosporin hypersensitivity have been conducted compared to penicillins. There is no global consensus amongst professional societies regarding the necessary reagents, concentrations, or criteria for a positive result for cephalosporin skin tests.

2. What does this article add to our knowledge?

In our series, 22.3% of patients with a suspicion of cephalosporin hypersensitivity had their diagnosis confirmed; non-immediate hypersensitivity occurred in less than 10% of the positive patients. Half of the confirmed cases were identified by skin testing (sensitivity 51.9%), which lead to systemic reactions in 5 cases (1%, including 2 anaphylactic shocks). Drug provocation test confirmed the hypersensitivity in the remaining 47%, eliciting anaphylaxis in 2.3% of patients.

3. How does this study impact current management guidelines?

A complete drug allergy work-up allows to confirm or rule out cephalosporin hypersensitivity. It needs expertise and a controlled environment.

Key words: betalactam, cephalosporin, cross-reactivity, drug provocation test, penicillin, skin-test

List of abbrevations:

BL: Betalactam
DAHD: Drug Allergy and Hypersensitivity Database
DHR: Drug Hypersensitivity Reaction
DPT: Drug Provocation Test
ENDA: European Network on Drug Allergy
ICON: International Consensus On Drug Allergy
MDM: Minor Determinant Mixture
PPL: Penicilloyl-Polylysin
PPV: Positive Predictive Value
ST: Skin Test

Introduction

Cephalosporins belong to the beta-lactam therapeutic class and are largely used all over the world. Cephalosporins are usually known and classified by generations, corresponding to their chronological availability. There are currently five generations of cephalosporins.

The beta-lactam ring, common to all beta-lactam antibiotics is unstable and for penicillins, its dislocation results in the emergence of several haptens (*Penicilloyl-Polylysin*, PPL and *Minor Determinant Mixture*, MDM), that have been extensively studied (*in vitro* and *in vivo*) in the context of IgE-mediated reactions. Allergenic determinants have not been reliably defined for cephalosporins and knowledge on cephalosporin hypersensitivity relies mostly on data emerging from *in vivo* drug allergy work up, with skin tests (ST) and drug provocation tests (DPT)[1-7]. In cephalosporin allergy, the R1 side chain is more often involved than the R2 side chain. Cross-reactivity between penicillins and cephalosporins has been shown and appears to be mainly related to structural R1 side chains homology, but peculiar profiles have been identified, without clear dissociation between cross-reactivity of co-sensitization[7].

In a recent European survey[8], cephalosporins were responsible for 10-40% of all beta-lactam hypersensitivity reactions, the most commonly involved cephalosporins being ceftriaxone, cefaclor, and cefuroxime. Amongst cephalosporins used for antibioprophylaxis, cefazolin is a frequent cause of perioperative anaphylaxis in the U.S. and in Europe[9,10].

Compared to penicillins, fewer large cephalosporin-centered studies have been conducted[1,3-7]. Indeed, many studies involving cephalosporins were primarily

addressing penicillin drug hypersensitivity reactions (DHR) and were inquiring about cross reactivity and tolerance between these two BL subgroups[1-3,5-7]. Many publications about cephalosporin hypersensitivity come from Italy[1,3-7,11,12], the country with the highest consumption of 3rd and 4th generation cephalosporins[13]. The aim of the present study was to analyze two decades of experience with the drug allergy work-up to cephalosporins.

Material and methods

In this single centre study, we describe cephalosporin DHRs in patients explored between 1996 and 2018 based on our historico-prospective cohort, the *Drug Allergy and Hypersensitivity Database (DAHD)* in Montpellier, France. Skin tests (ST) were performed according to ENDA recommendations[14], for penicillin reagents (penicilloyl polylysine (PPL), minor determinants mixture (MDM), amoxicillin 20 mg/ml, ampicillin 20mg/ml, benzyl benzathine penicillin 10 000 UI/ml) and the culprit cephalosporin (when known) as well as for a panel of other commercially available cephalosporins (2 mg/ml), in order to study cross-reactivity and find a tolerated alternative drug, in case of confirmed DHR. Since 2005, the panel of cephalosporins tested systematically in every patient included: cefazolin, cefuroxime, cefoxitine, ceftriaxone, cefotaxime, ceftazidime. Penicillin reagents PPL and MDM were removed (and therefore unavailable further on) from the French market in 2007. Cefatrizine and cefamandole were systematically tested until respectively 2011 and 2016, when they were removed from the market. Other cephalosporins were tested according to the clinical history or therapeutic needs of the patient. Cephalosporins were classified by adjusting published[15], classifications based on side chain R1 structural homology, i.e., we applied structural homology criteria previously established, and further

merged groups with very homologous structure for analysis purposes (e.g., Group 1, 2 and 3 by Kahn et al), because certain cephalosporins were poorly represented in our population (**Figure 1**). Of note, in the text, cross-reactivity in confirmed DHR is expressed as percentage of positive patients amongst those tested for the cephalosporins considered as cross-reactive. If ST were negative for the culprit cephalosporin, a drug provocation test (DPT) was performed according to Messaad D et al[16] until 2016 and according to Chiriac AM et al[17] since 2016. In case of positive allergy work-up, alternative BL were tested by means of DPT (to a penicillin, often amoxicillin, and an alternative cephalosporin). Part of the data presented in this study overlap with other publications from our group, directly addressing betalactams or cephalosporins[18,19].

Data were analyzed with R (1.1.456-©2009-2018 Rstudio, Inc). Besides descriptive analysis (chi square, Student, Wilcoxon), univariate and multivariate logistic regression (using variables with $P < .0.05$ in univariate analysis) were performed to evaluate risk factors after checking validity conditions. A P value of 0.05 or less was chosen to indicate statistical significance.

Results

Four hundred and seventy-six patients describing immediate (<1h) or delayed (≥1h) reactions with cephalosporins were included. One hundred and six patients (22.3%) had a proven cephalosporin DHR according to positive ST (sensitivity of ST assuming no false positive, 51.9%) or DPT to the culprit drug (48.1%) (**Table 1 and Figure 2**).

ST elicited five (9.1%) generalized reactions in the 55 positive ST patients (two anaphylactic shocks, and three cutaneous reactions) (**Table 2**). The chronology of

these reactions matched that of the corresponding index reaction (four immediate, all anaphylaxis with or without shock; one delayed cutaneous reaction). Out of 421 patients whose ST were negative, 12% (N=51) were found positive after DPT (**Figure 2**). During DPT, ten reactions (2.3% of the total cohort and 19.6% of the positive DPT) were anaphylactic (four with and six w/o shock, all occurring in patients with severe index reaction, i.e., either anaphylaxis in nine or isolated bronchospasm in one patient) and the other were cutaneous.

Within the whole tested cohort, one in five patients were children in whom cephalosporin hypersensitivity was confirmed in 14.3% (47.6% of them by means of ST) (**Figure E1**). In the cephalosporin hypersensitive population, initial reactions were mostly immediate (68.9%) and anaphylactic (72.7%) (**Table 3**).

We found a good match between the chronology of the index reaction and that of the reaction elicited during the allergy work-up (**Table 4**). Nine patients (8.5% of the positive group) presented delayed non-severe cutaneous reactions (>2h) during our tests (ST, one or DPT, eight). Of those patients, one had immediate and eight delayed index reactions. In accordance with the ICON definition[20] of the possible overlap of immediate and non-immediate reactions in the interval 1-6h, < 2h is considered here as immediate reaction. Indeed, after reviewing the files of the patients reacting by DPT within 2h after the last dose, almost all of them (33/34 patients) were considered as immediate reactions, i.e., rapidly resolving urticaria.

Based on skin testing results, unsurprisingly, Class 2 (aminocephalosporins) was the one cross-reacting the most with penicillin reagents (54%) and with aminopenicillins in our positive cohort, followed by Class 1, compared to only 3.8% (one patient) for cefazolin (**Table 5**).

Within the group of patients with confirmed DHR, we observed that a history of anaphylaxis was associated ($p<0.001$) with positive ST. When adjusted on other variables, immediate reactions (OR=3 (95%CI [1.6-5.5]), $p<0.001$)), anaphylaxis with (OR=6.5 (95%CI [3.3-13.1], $p<0.001$)) or without shock (OR=3.1 (95%CI [1.6-6.1], $p<0.001$)) and multiple reactions to the same or several cephalosporins (OR=2.0 (95%CI [1-3.5], $p=0.04$)) were statistically associated with confirmed DHR. Cefazolin was more often associated to confirmed DHR, but this association did not persist, in multivariate analysis. Cutaneous ($p<0.001$) and non-immediate reactions ($p<0.001$) and those of unknown chronology of the index reaction ($p<0.001$) were statistically correlated with a negative diagnosis.

Discussion

Cephalosporin hypersensitivity was proven in 22.3% of the patients referred in our Unit in our 26-year experience, equally by ST and DPT. These numbers are similar to others on the same topic[1-3].

As data on primary cephalosporin allergy is more limited than that on penicillin allergy, with differences between current recommendations from professional societies[21] (e.g., there is no global consensus regarding the necessary reagents, concentrations, or criteria for a positive test result for betalactam ST), the question might be raised about the value of positive ST to confirm allergy. All our patients were tested at recommended concentrations for cephalosporins by the ENDA group (2 mg/ml), which have now been recommended for more than two decades. Moreover, in a recent narrative literature review by our group, the positive predictive value (PPV) of ST to betalactams was 100% for a clinical history of anaphylaxis and > 80% for immediate non-anaphylactic reactions and for delayed reactions. In this

review[21], all ten patients with positive ST for cephalosporins reacted when provoked for these cephalosporins, yielding a PPV of 100%. Considering these facts, would have little proof to argue that ST are false positive and thus the calculated sensitivity of ST in our series is 51.9%.

Not surprisingly, as for penicillins, immediate reactions, multiple reactions and anaphylaxis were risk factors for confirmed DHR. In half of the confirmed cases, DPT was necessary to confirm the diagnosis. We used recommended concentrations for ST, but recently, it has been suggested (and endorsed by the ENDA group in the upcoming update on BL DHR paper) that concentrations should be increased to 20 mg/ml instead of 2 mg/ml, to increase sensitivity of ST and avoid unnecessary DPT. Allergy work-up was globally safe, but anaphylaxis was elicited in 2.3% of DPT and 1% of all performed ST (9.1% of positive ST). With these considerations in mind (i.e., change to a higher recommended concentration for ST and risk of systemic reactions during ST), cautionary incremental concentrations should be used when testing patients with severe index reactions, from as early as ST exposure.

In our analysis, the study of cross-reactivity in confirmed DHR was mainly done by ST, since only one or two alternative BL (a penicillin and a cephalosporin) were systematically tested by DPT, unlike other studies[2-3,5-7] (**Table E1**). Therefore, we might have underestimated the rate of cross-reactivity. Also, throughout the years, the panel of tested cephalosporins slightly changed, according to removal of some cephalosporins from the French market and the increased utilization of others. Few studies mainly carried out by Romano A et al[3-7] and Antunez[2], have evaluated subjects with cephalosporin hypersensitivity and have assessed cross-reactivity with penicillins, on the basis on ST, serum specific IgE assays and DPT. They found a rate of cross-reactivity ranging from 13.3% to 40.1% in cephalosporin hypersensitive

patients (for the most majority of them involving ceftriaxone, ceftazidime, cefaclor and cefazolin) and penicillin reagents, including PPL, MDM, benzylpenicillin, amoxicillin and ampicillin. Moreover, they evaluated systematically the cross-reactivity with monobactams or carbapenems, which was not analyzed in our study. Our rate of cross-reactivity to penicillins might be higher for several reasons: (i) some of the previous publications[2] studied less patients; (ii) we considered patients positive on the basis of ST or DPT to cephalosporins, but also based on positive ST (prick test or intradermal test) to aminopenicillins w/o confirmatory DPT for the culprit aminocephalosporin when the skin prick test to this aminocephalosporin (some do not exist in sterile form to allow intradermal test performance) was negative; (iii) we studied cross-reactivity by class of cephalosporin, precisely due to more structural similarities with penicillins for some cephalosporins as compared to others.

We confirm the rarity of the delayed reactions to cephalosporins, as described by other groups[4].

Conclusion

In conclusion, our study adds-up solid data to the existing knowledge on cephalosporin DHR, proving the utility of the allergy work-up to delabel most patients with a suspicion of DHR to cephalosporins. Performed in a step-wise manner and tailored to the severity of the clinical reaction, the allergy work-up is generally safe and it needs expertise as well as a controlled environment.

This study was approved by the Institutional Review Board with the accreditation number: IRB-MTP-2020-01-202000333.

References

[1] ROMANO A, GUEANT-RODRIGUEZ RM, VIOLA M, AMOGHLY F, GAETA F, NICOLAS JP, et al. Diagnosing immediate reactions to cephalosporins. Clin Exp Allergy 2005;35(9):1234-42.

[2] ANTUNEZ C, BLANCA-LOPEZ N, TORRES MJ, MAYORGA C, PEREZ-INESTROSA E, MONTANEZ MI et al. Immediate Allergic Reactions to Cephalosporins: Evaluation of Cross-Reactivity With a Panel of Penicillins and Cephalosporins. J Allergy Clin Immunol. 2006;117(2):404-10.

[3] ROMANO A, GAETA F, VALLUZZI RL, CARUSO C, RUMI G, BOUSQUET PJ. IgE mediated
hypersensitivity to cephalosporins : Cross-reactivity and tolerability of penicillins, monobactams, and carbapenems. J Allergy Clin Immunol. 2010;126(5):994-9.

[4] ROMANO A, GAETA F, VALLUZZI RL, CARUSO C, ALONZI C, VIOLA M, et al. Diagnosing non immediate reactions to cephalosporins. J Allergy Clin Immunol 2012;129(4):1166-1169.

[5] ROMANO A, GAETA F, VALLUZZI RL, MAGGIOLETTI M, ZAFFIRO A et al. IgE-mediated hypersensitivity to cephalosporins: Cross-reactivity and tolerability of alternative cephalosporins. J Allergy Clin Immunol.2015;136(3):685-91.

[6] ROMANO A, GAETA F, VALLUZZI RL, MAGGIOLETTI M , CARUSO C, QUARATINO D. Cross-reactivity and tolerability of aztreonam and cephalosporins in subjects with a T-cell mediated hypersensitivity to penicillins. J Allergy Clin Immunol. 2016;138(1):179-186.

[7] ROMANO A, VALLUZZI RL, CARUSO C, MAGGIOLETTI M, QUARATINO D, GAETA F. Cross-reactivity and tolerability of cephalosporins in patients wih IgE-mediated hypersensitivity to penicillins. J Allergy Clin Immunol. 2018;6(5):1662-72.

[8] TORRES MJ, CELIK GE, WHITAKER P, ATANASKOVIC-MARKOVIC M, BARBAUD A, BIRCHER A et al. A EAACI Drug Allergy Interest Group Survey on how European Allergy Specialist Deal With Beta-lactam Allergy. Allergy. 2019;74(6): 1052-62.

[9] KUHLEN JL, Jr., CAMARGO CA, Jr., BALEKIAN DS, BLUMENTHAL KG, GUYER A, MORRIS T, et al. Antibiotics Are the Most Commonly Identified Cause of Perioperative Hypersensitivity Reactions. J Allergy Clin Immunol Pract. 2016;4(4):697-704.

[10] UYTTEBROEK AP, DECUYPER, II, BRIDTS CH, ROMANO A, HAGENDORENS MM, EBO DG, et al. Cefazolin Hypersensitivity: Toward Optimized Diagnosis. J Allergy Clin Immunol Pract. 2016;4(6):1232-36.

[11] ROMANO A, ATANASKOVIC-MARKOVIC M, BARBAUD A, BIRCHER AJ, BROCKOW K, CAUBET JC et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams – an EAACI position paper. Allergy. 2019. Nov 21. doi: 10.1111/all.14122.

[12] ROMANO A, GAETA F, VALLUZZI RL, ALONZI C, VIOLA M, BOUSQUET PJ. Diagnosing hypersensitivity reactions to cephalosporins in children. Pediatrics 2008;122(3):521-527.

[12] NOVEMBRE E, MORI F, PUCCI N, BERNARDINI R, ROMANO A. Cefaclor anaphylaxis in children. Allergy 2009;64(8):1233-35.

[13] VERSPORTEN A, COENEN S, ADRIAENSSENS N, MULLER A, MINALU G, FAES C, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient cephalosporin use in Europe (1997-2009). J Antimicrob Chemother 2011;66 Suppl 6:vi25-35.

[14] BLANCA M, ROMANO A, TORRES MJ, FERNANDEZ J, MAYORGA C, RODRIGUEZ J et al. Update on the evaluation of hypersensitivity reactions to betalactams. Allergy. 2009;64(2):183-93.

[15] KHAN DA, BANEERJI A, BERNSTEIN JA, BILGICER B, BLUMENTHAL K, CASTELLS M et al. Cephalosporin allergy: Current Understanding and Future Challenges. J Allergy Clin Immunol. 2019 ;7(7):2105-2114.

[16] MESSAAD D, SAHLA H, BENHAMED S, GODARD P, BOUSQUET J, DEMOLY P. Drug Provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. Ann Intern Med 2004;140:1001-1006.

[17] CHIRIAC AM, RERKPATTANAPIPAT T, BOUSQUET PJ, MOLINARI N, DEMOLY P. Optimal step doses for drug provocation tests to prove beta-lactam hypersensitivity. Allergy (72) 2017;552-561.

[18] GALERA C, KACIMI D, JOLIVET A, BOUSQUET PJ, DEMOLY P. Allergie aux céphalosporines. Intérêt des tests cutanés. Rev Fr Allergol 50 (2010) 398-405.

[19] PIPET A, VEYRAC G, WESSEL F, JOLLIET P, MAGNAN A, DEMOLY P et al. A statement on cefazolin immediate hypersensitivity: data from a large database, and focus on the cross-reactivities. Clin Exp Allergy. 2011;41(11):1602–1608.

[20] DEMOLY P, ADKINSON NF Jr., BROKOW K, CASTELLS M, CHIRIAC AM, GREENBERGER PA et al. International consensus on Drug Allergy. Allergy.2014;69(4):420-37.

[21] TORRES MJ, ADKINSON NF Jr., CAUBET JC, KHAN DA, KIDON MI, MENDELSON M et al. Controversies in Drug Allergy: Beta-Lactam Hypersensitivity Testing [published correction appears in J Allergy Clin Immunol Pract. 2019 Mar;7(3):1096. J Allergy Clin Immunol Pract. 2019;7(1):40-45.

Legend list :

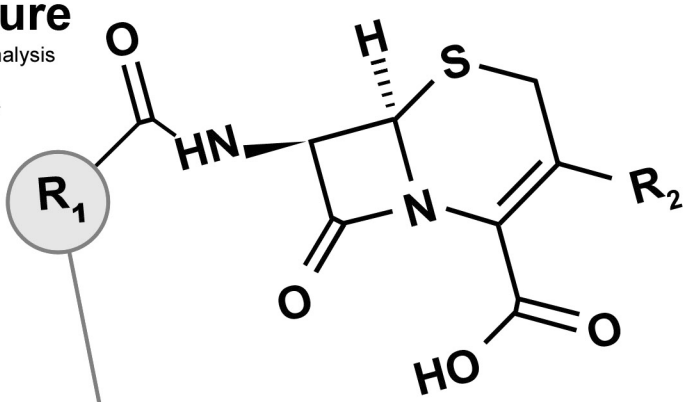
Figure 1: Classification of cephalosporins used in the article adapted from Khan et al[15]

Figure 2 : Flow chart of the study. The % are expressed as % of the total of the 476 tested patients (DHR, drug hypersensitivity reaction; DPT, drug provocation test).

Figure 1. Classification of cephalosporins used in the article adapted from Khan et al[15].

Cephalosporin core structure

Classes include grouping of cephalosporins according to the analysis performed for the purpose of this study.
They globally overlap with the groups (1,2,3,4A and B) from the classification of Khan et al[15].

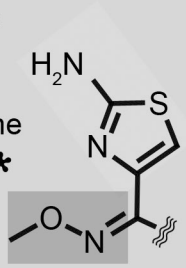


R_1 structure

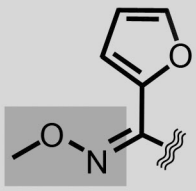
Class 1

Similar R1 side-chain between cephalosporins, involving 2nd, 3rd and 4th generation cephalosporins

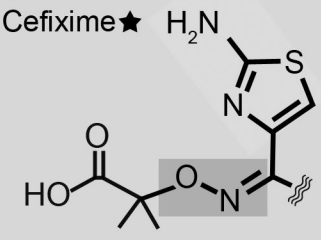
Group 1
Ceftriaxone
Cefotaxime
Cefepime
Cefpodoxime
Cefditoren *



Group 2
Cefuroxime



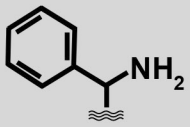
Group 3
Ceftazidime
Cefixime ★



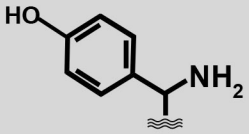
Class 2

Amino-cephalosporins, sharing a similar R1 side-chain with amino-penicillins

Group 4 A
Cefaclor
Cephalexin

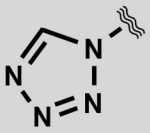


Group 4B
Cefatrizine ★
Cefadroxil
Cefprozil *



Class 3

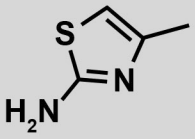
Cefazolin



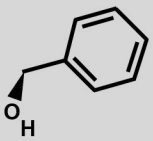
Class 4

Other cephalosporins

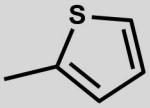
Cefotiam ★



Cefamandole ★



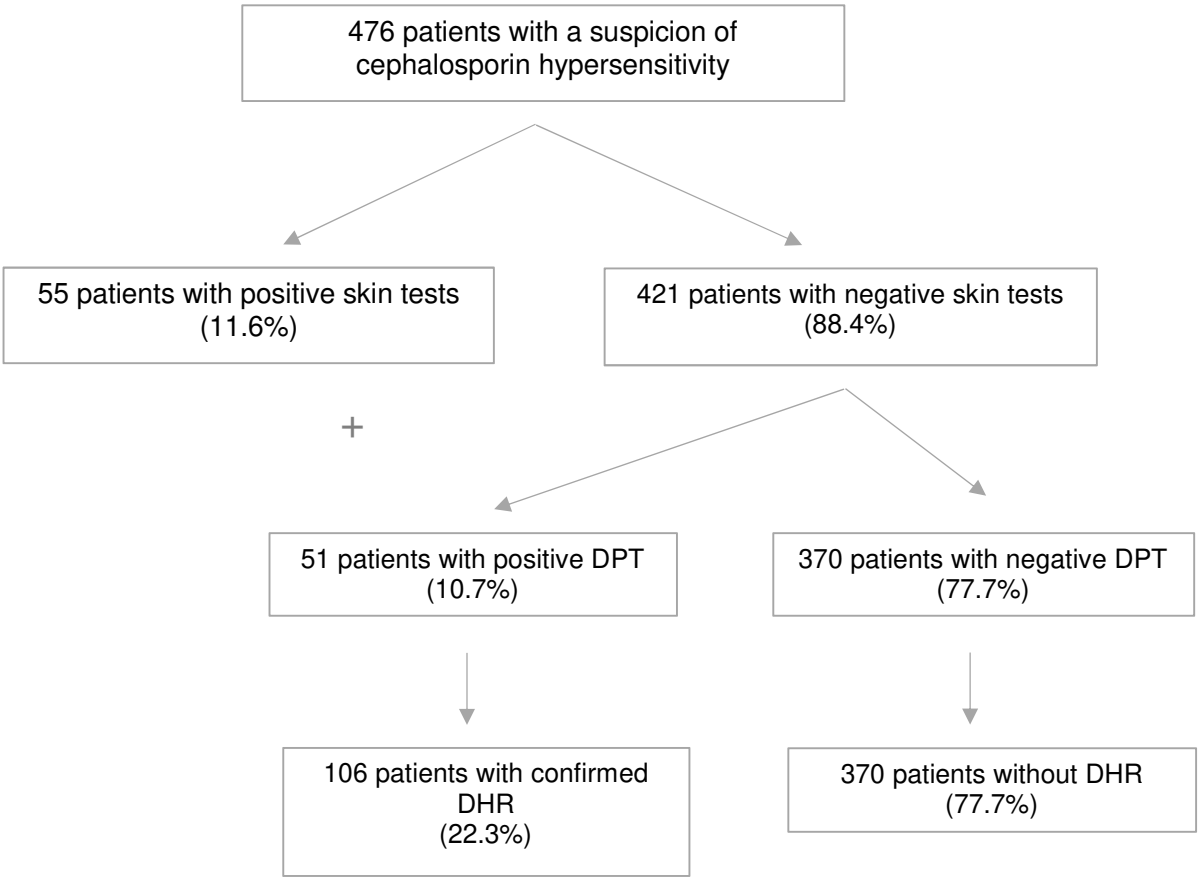
Cefalotine ★
Cefoxitine ★



★ tested in our study but not referenced in the paper of Khan et al[15]

* included in the paper of Khan et al[15] but not tested in our study

Figure 2: Flow chart of the study. The % are expressed as % from the total of 476 tested patients.



DHR, drug hypersensitivity reaction; DPT, drug provocation test

Table 1 : Tests' characteristics

	Overall (n)	Proportion(%)
Tests' characteristics		
RESULTS (n=476)		
Negative	370	77.7
Positive	106	22.3
ST with culprit cephalosporin	41	38,6
ST with penicillin with identical side chain*	14	13.2
DPT with culprit cephalosporin	51	48.1

* Amoxicillin, Ampicillin; ST : Skin test; DPT : Drug Provocation Test

Table 2. Detail of patients with systemic reactions during skin tests.

DAHD N° patient	Gender	Asthma	Atopy	Chronology of index reaction	Culprit cephalosporin	Symptoms of index reaction	Age (yrs)	Multiple reactions to cephalosporins	Name of ST eliciting the reaction	Chronology of positive ST	Delay reaction-tests (Mo)	Reaction during ST
779	F	No	No	< 1h	CEFOTAXIME	Anaphylactic shock	58	Yes	Cefradine	<1h	2.5	Angioedema, bronchospasm, hypotension
									Cefalotine Ceftriaxone Cefuroxime Cefotaxime			
									MDM			
									PPL			
									Ax Ap			
									Pg			
1506	F	No	Yes	< 1h	CEFATRIZINE	Anaphylaxis	32	Yes	Ax	<1h	25.5	Collapse, hypotension, loss of consciousness
									PPL			
									MDM			
4753	M	No	Yes	6h - 24h	CEFADROXIL	Urticaria	16	Yes	Ax Ap	6h-24h	186	Exanthema
23	F	No	No	< 1h	CEFTRIAXONE	Anaphylaxis	51	No	Ceftriaxone	<1h	4	Exanthema, pruritus, malaise
									Cefotaxime			
4652	F	No	No	< 1h	CEFTRIAXONE	Anaphylactic shock	57	No	Ceftriaxone	<1h	22.5	Pruritus

C%, concentration; ST, Skin Test; PT : Prick Test, IDR : IntraDermoReaction, F, female; M, male; Mo, months; Yrs, years
MDM, Minor Determinant Mixture; PPL, Penicilloyl-Polylysin; Ax, Amoxicillin; Ap, Ampicillin, Pg, Penicillin G

Table 3: Characteristics of the studied cohort with suspected cephalosporin hypersensitivity

	Whole patients (n) (n_{tot}=476)	Hypersensitive patients (n(%)) (n_{tot}= 106)
Socio demographic characteristics		
Sex		
Male	166	34(32)
Female	310	72(68)
Adult/child status at the index reaction		
Adult	330	85(80.2)
Child	146	21(19.8)
Patient's background		
Asthma		
Yes	74	18(17)
No	402	88(83)
Atopy		
Yes	272	45(43.3)
No	193	59(56.7)
Unknown	11	0(0)
Previous reactions with a cephalosporin		
Yes	120	32(30.2)
No	356	74(69.8)
Reaction's characteristics (with one or several cephalosporins)		
One reaction	350	72(67.9)
> 2 or more reactions with the same cephalosporin	40	25(23.6)
Several reactions with different cephalosporins	85	8(7.5)
Unknown	1	1(1)
Clinical history		
Anaphylactic shock	83	50(47.2)
Anaphylaxis[§]	85	27(25.5)
Other*	308	29(27.3)
Chronology of the index reaction		
Immediate (<1h)	160	73(68.9)
Non immediate (>1h)	267	31(29.2)
Unknown	49	2(1.9)
Culprit drug		
By generation		
C1G	194	61(57.5)
C2G	73	18(17)
C3G	206	27(25.5)
Others	3	0(0)
By group		
Class 1	256	40(37.3)
Class 2	124	35(33)
Class 3	66	26(24.5)
Class 4	30	5(4.7)

[§]Isolated low respiratory signs and symptoms (i.e., chest tightness, bronchospasm), described by 85 patients were grouped with anaphylaxis following descriptive analysis
*Other includes: urticaria, angioedema, maculo-papular exanthema, severe cutaneous adverse reactions (1 DRESS,1 Stevens-Johnson Syndrome), unknown index reaction. The choice to regroup these entities was decided following descriptive analysis.

Groups considering generation:

C1G : CEFAZOLINE, CEFATRIZINE, CEFACLOR,CEFADROXIL
C2G : CEFUROXIME, CEFAMANDOLE
C3G : CEFTRIAXONE, CEFOTAXIME, CEFTAZIDIME, CEFPODOXIME, CEFIXIME, CEFOTIAM,CEFEPIME

Groups considering structural homology:

Class 1 = CEFTRIAXONE, CEFOTAXIME, CEFEPIME, CEFPODOXIME, CEFTAZIDIME, CEFIXIME, CEFUROXIME
Class 2 = CEFACLOR, CEFALEXINE, CEFADROXIL, CEFATRIZINE
Class 3 = CEFAZOLINE
Class 4 = CEFALOTINE, CEFOXITINE, CEFOTIAM, CEFAMANDOLE

Table 4: Crossmatch table between the chronology of the index reaction and that of positive tests

		Chronology when positive tests (DPT/ST)¶		n
Chronology of the index reaction*		<2h (%)	>2h (%)	106
	<1h (%)	60(83)	13(17)	73
	>1h (%)	24(73)	9(27)	33

DPT, Drug Provocation Test; ST, Skin Test

* 2 patients with unknown chronology were included in chronology of the index reaction > 1h
¶ In accordance with the ICON definition of the possible overlap of immediate and non-immediate reactions in the interval 1-6h, and after careful review of patient charts and the precise semiology and chronology of the reaction elicited by the allergy work-up, < 2h is considered here as immediate reaction.

Table 5: Cross-reactivity with penicillins in cephalosporin hypersensitive patients

Groups	% of cross-reactivity (penicillin reagents)	% of cross-reactivity (ampicillin and/or amoxicillin only)
Class 1	20	10
Class 2	52	37.1
Class 3	0	0
Class 4	3.8	0

Groups considering structural homology:

Class 1 = CEFTRIAXONE, CEFOTAXIME, CEFEPIME, CEFPODOXIME, CEFTAZIDIME, CEFIXIME, CEFUROXIME
Class 2 = CEFACLOR, CEFALEXINE, CEFADROXIL, CEFATRIZINE
Class 3 = CEFAZOLINE
Class 4 = CEFALOTINE, CEFOXITINE, CEFOTIAM, CEFAMANDOLE