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

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1 **Title:** Cephalosporin hypersensitivity: descriptive analysis, cross-reactivity and risk
2 factors

3
4 **Running title:** Cephalosporin hypersensitivity in a large series

5
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44 **Abstract**

45 **Background**

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

49 **Objective**

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

52 **Methods**

53 We included 476 patients who reported Drug Hypersensitivity Reaction (DHR) to
54 cephalosporin and underwent an allergy workup between January 1992 and July
55 2018 in the Allergy Unit of the University Hospital of Montpellier (France). According
56 to their structural side chain R1 homology we worked with four classes of
57 cephalosporins. Logistic regression analysis was used to search for risk factors for
58 hypersensitivity to cephalosporin (positive skin test or provocation test results).

59 **Results**

60 Cephalosporin hypersensitivity was proven in 22.3% of the patients referred in our
61 Unit, according to positive ST (51.9%) or DPT to the culprit drug (48.1%). One in five
62 patients were children and cephalosporin hypersensitivity was confirmed in 15%
63 (47.6% of them by means of ST). In the cephalosporin hypersensitive population,
64 initial reactions were mostly immediate (68.9%) and anaphylactic (72.7%). Cross-
65 reactivity with aminopenicillins was the most frequent pattern of cross-reactivity. In
66 multivariate analysis, immediate reactions (OR=3 (95%CI [1.6-5.5]), $p<0.001$),
67 anaphylactic shock (OR=6.5 (95%CI [3.3-13.1], $p<0.001$)) and anaphylaxis (OR=3.1
68 (95%CI [1.6-6.1], $p<0.001$)) and multiple reactions to the same or several

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

74 **Conclusion**

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

78

79 **Highlight box:**

80 **1. What is already known about this topic?**

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

85

86 **2. What does this article add to our knowledge?**

87 In our series, 22.3% of patients with a suspicion of cephalosporin hypersensitivity
88 had their diagnosis confirmed; non-immediate hypersensitivity occurred in less than
89 10% of the positive patients. Half of the confirmed cases were identified by skin
90 testing (sensitivity 51.9%), which lead to systemic reactions in 5 cases (1%, including
91 2 anaphylactic shocks). Drug provocation test confirmed the hypersensitivity in the
92 remaining 47%, eliciting anaphylaxis in 2.3% of patients.

93 **3. How does this study impact current management guidelines?**

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

96

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

99

100 **List of abbreviations:**

101

102 BL: Betalactam

103 DAHD: Drug Allergy and Hypersensitivity Database

104 DHR: Drug Hypersensitivity Reaction

105 DPT: Drug Provocation Test

106 ENDA: European Network on Drug Allergy

107 ICON: International Consensus On Drug Allergy

108 MDM: Minor Determinant Mixture

109 PPL: Penicilloyl-Polylysin

110 PPV: Positive Predictive Value

111 ST: Skin Test

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133 **Introduction**

134

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

139 The beta-lactam ring, common to all beta-lactam antibiotics is unstable and for
140 penicillins, its dislocation results in the emergence of several haptens (*Penicilloyl-*
141 *Polylysin*, PPL and *Minor Determinant Mixture*, MDM), that have been extensively
142 studied (*in vitro* and *in vivo*) in the context of IgE-mediated reactions. Allergenic
143 determinants have not been reliably defined for cephalosporins and knowledge on
144 cephalosporin hypersensitivity relies mostly on data emerging from *in vivo* drug
145 allergy work up, with skin tests (ST) and drug provocation tests (DPT)¹⁻⁷. In
146 cephalosporin allergy, the R1 side chain is more often involved than the R2 side
147 chain. Cross-reactivity between penicillins and cephalosporins has been shown and
148 appears to be mainly related to structural R1 side chains homology, but peculiar
149 profiles have been identified, without clear dissociation between cross-reactivity of
150 co-sensitization⁷.

151 In a recent European survey⁸, cephalosporins were responsible for 10-40% of all
152 beta-lactam hypersensitivity reactions, the most commonly involved cephalosporins
153 being ceftriaxone, cefaclor, and cefuroxime. Amongst cephalosporins used for
154 antibioprophyllaxis, cefazolin is a frequent cause of perioperative anaphylaxis in the
155 U.S. and in Europe^{9,10}.

156 Compared to penicillins, fewer large cephalosporin-centered studies have been
157 conducted^{1,3-7}. Indeed, many studies involving cephalosporins were primarily

158 addressing penicillin drug hypersensitivity reactions (DHR) and were inquiring about
159 cross reactivity and tolerance between these two BL subgroups^{1-3,5-7}. Many
160 publications about cephalosporin hypersensitivity come from Italy^{1,3-7,11,12}, the country
161 with the highest consumption of 3rd and 4th generation cephalosporins¹³. The aim of
162 the present study was to analyze two decades of experience with the drug allergy
163 work-up to cephalosporins.

164

165 **Material and methods**

166 In this single centre study, we describe cephalosporin DHRs in patients explored
167 between 1996 and 2018 based on our historico-prospective cohort, the *Drug Allergy*
168 *and Hypersensitivity Database (DAHD)* in Montpellier, France. Skin tests (ST) were
169 performed according to ENDA recommendations¹⁴, for penicillin reagents (penicilloyl
170 polylysine (PPL), minor determinants mixture (MDM), amoxicillin 20 mg/ml, ampicillin
171 20mg/ml, benzyl benzathine penicillin 10 000 UI/ml) and the culprit cephalosporin
172 (when known) as well as for a panel of other commercially available cephalosporins
173 (2 mg/ml), in order to study cross-reactivity and find a tolerated alternative drug, in
174 case of confirmed DHR. Since 2005, the panel of cephalosporins tested
175 systematically in every patient included: cefazolin, cefuroxime, cefoxitine, ceftriaxone,
176 cefotaxime, ceftazidime. Penicillin reagents PPL and MDM were removed (and
177 therefore unavailable further on) from the French market in 2007. Cefatrizine and
178 cefamandole were systematically tested until respectively 2011 and 2016, when they
179 were removed from the market. Other cephalosporins were tested according to the
180 clinical history or therapeutic needs of the patient. Cephalosporins were classified by
181 adjusting published¹⁵, classifications based on side chain R1 structural homology,
182 i.e., we applied structural homology criteria previously established, and further

183 merged groups with very homologous structure for analysis purposes (e.g., Group 1,
184 2 and 3 by Kahn et al), because certain cephalosporins were poorly represented in
185 our population (**Figure 1**). Of note, in the text, cross-reactivity in confirmed DHR is
186 expressed as percentage of positive patients amongst those tested for the
187 cephalosporins considered as cross-reactive. If ST were negative for the culprit
188 cephalosporin, a drug provocation test (DPT) was performed according to Messaad
189 D et al¹⁶ until 2016 and according to Chiriac AM et al¹⁷ since 2016. In case of positive
190 allergy work-up, alternative BL were tested by means of DPT (to a penicillin, often
191 amoxicillin, and an alternative cephalosporin). Part of the data presented in this
192 study overlap with other publications from our group, directly addressing betalactams
193 or cephalosporins^{18,19}.

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

199

200 **Results**

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

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

208 these reactions matched that of the corresponding index reaction (four immediate, all
209 anaphylaxis with or without shock; one delayed cutaneous reaction). Out of 421
210 patients whose ST were negative, 12% (N=51) were found positive after DPT (**Figure**
211 **2**). During DPT, ten reactions (2.3% of the total cohort and 19.6% of the positive
212 DPT) were anaphylactic (four with and six w/o shock, all occurring in patients with
213 severe index reaction, i.e., either anaphylaxis in nine or isolated bronchospasm in
214 one patient) and the other were cutaneous.

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

219 We found a good match between the chronology of the index reaction and that of the
220 reaction elicited during the allergy work-up (**Table 4**). Nine patients (8.5% of the
221 positive group) presented delayed non-severe cutaneous reactions (>2h) during our
222 tests (ST, one or DPT, eight). Of those patients, one had immediate and eight
223 delayed index reactions. In accordance with the ICON definition²⁰ of the possible
224 overlap of immediate and non-immediate reactions in the interval 1-6h, < 2h is
225 considered here as immediate reaction. Indeed, after reviewing the files of the
226 patients reacting by DPT within 2h after the last dose, almost all of them (33/34
227 patients) were considered as immediate reactions, i.e., rapidly resolving urticaria.

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

232 Within the group of patients with confirmed DHR, we observed that a history of
233 anaphylaxis was associated ($p<0.001$) with positive ST. When adjusted on other
234 variables, immediate reactions (OR=3 (95%CI [1.6-5.5]), $p<0.001$), anaphylaxis with
235 (OR=6.5 (95%CI [3.3-13.1], $p<0.001$)) or without shock (OR=3.1 (95%CI [1.6-6.1],
236 $p<0.001$)) and multiple reactions to the same or several cephalosporins (OR=2.0
237 (95%CI [1-3.5], $p=0.04$)) were statistically associated with confirmed DHR. Cefazolin
238 was more often associated to confirmed DHR, but this association did not persist, in
239 multivariate analysis. Cutaneous ($p<0.001$) and non-immediate reactions ($p<0.001$)
240 and those of unknown chronology of the index reaction ($p<0.001$) were statistically
241 correlated with a negative diagnosis.

242

243 **Discussion**

244 Cephalosporin hypersensitivity was proven in 22.3% of the patients referred in our
245 Unit in our 26-year experience, equally by ST and DPT. These numbers are similar to
246 others on the same topic¹⁻³.

247 As data on primary cephalosporin allergy is more limited than that on penicillin
248 allergy, with differences between current recommendations from professional
249 societies²¹ (e.g., there is no global consensus regarding the necessary reagents,
250 concentrations, or criteria for a positive test result for betalactam ST), the question
251 might be raised about the value of positive ST to confirm allergy. All our patients
252 were tested at recommended concentrations for cephalosporins by the ENDA group
253 (2 mg/ml), which have now been recommended for more than two decades.
254 Moreover, in a recent narrative literature review by our group, the positive predictive
255 value (PPV) of ST to betalactams was 100% for a clinical history of anaphylaxis and
256 > 80% for immediate non-anaphylactic reactions and for delayed reactions. In this

257 review²¹, all ten patients with positive ST for cephalosporins reacted when provoked
258 for these cephalosporins, yielding a PPV of 100%. Considering these facts, would
259 have little proof to argue that ST are false positive and thus the calculated sensitivity
260 of ST in our series is 51.9%.

261 Not surprisingly, as for penicillins, immediate reactions, multiple reactions and
262 anaphylaxis were risk factors for confirmed DHR. In half of the confirmed cases, DPT
263 was necessary to confirm the diagnosis. We used recommended concentrations for
264 ST, but recently, it has been suggested (and endorsed by the ENDA group in the
265 upcoming update on BL DHR paper) that concentrations should be increased to 20
266 mg/ml instead of 2 mg/ml, to increase sensitivity of ST and avoid unnecessary DPT.
267 Allergy work-up was globally safe, but anaphylaxis was elicited in 2.3% of DPT and
268 1% of all performed ST (9.1% of positive ST). With these considerations in mind (i.e.,
269 change to a higher recommended concentration for ST and risk of systemic reactions
270 during ST), cautionary incremental concentrations should be used when testing
271 patients with severe index reactions, from as early as ST exposure.

272 In our analysis, the study of cross-reactivity in confirmed DHR was mainly done by
273 ST, since only one or two alternative BL (a penicillin and a cephalosporin) were
274 systematically tested by DPT, unlike other studies^{2-3,5-7} (**Table E1**). Therefore, we
275 might have underestimated the rate of cross-reactivity. Also, throughout the years,
276 the panel of tested cephalosporins slightly changed, according to removal of some
277 cephalosporins from the French market and the increased utilization of others. Few
278 studies mainly carried out by Romano A et al³⁻⁷ and Antunez², have evaluated
279 subjects with cephalosporin hypersensitivity and have assessed cross-reactivity with
280 penicillins, on the basis on ST, serum specific IgE assays and DPT. They found a
281 rate of cross-reactivity ranging from 13.3% to 40.1% in cephalosporin hypersensitive

282 patients (for the most majority of them involving ceftriaxone, ceftazidime, cefaclor and
283 cefazolin) and penicillin reagents, including PPL, MDM, benzylpenicillin, amoxicillin
284 and ampicillin. Moreover, they evaluated systematically the cross-reactivity with
285 monobactams or carbapenems, which was not analyzed in our study. Our rate of
286 cross-reactivity to penicillins might be higher for several reasons: (i) some of the
287 previous publications² studied less patients; (ii) we considered patients positive on
288 the basis of ST or DPT to cephalosporins, but also based on positive ST (prick test or
289 intradermal test) to aminopenicillins w/o confirmatory DPT for the culprit
290 aminocephalosporin when the skin prick test to this aminocephalosporin (some do
291 not exist in sterile form to allow intradermal test performance) was negative; (iii) we
292 studied cross-reactivity by class of cephalosporin, precisely due to more structural
293 similarities with penicillins for some cephalosporins as compared to others.
294 We confirm the rarity of the delayed reactions to cephalosporins, as described by
295 other groups⁴.

296

297 **Conclusion**

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

303

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

306

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391 **Legend list :**

392 Figure 1: Classification of cephalosporins used in the article adapted from Khan et al¹⁵

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

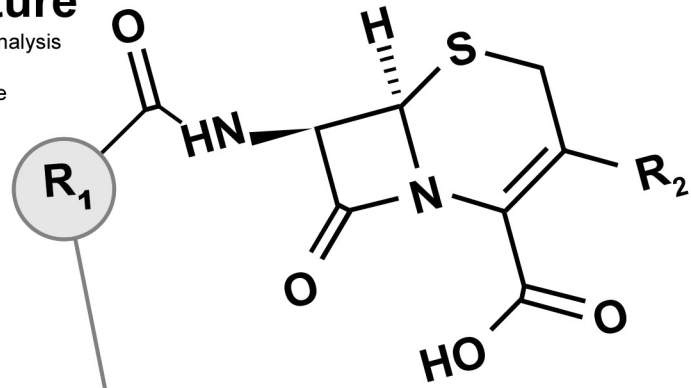
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Figure 1. Classification of cephalosporins used in the article adapted from Khan et al¹⁵.

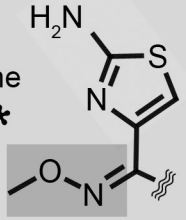
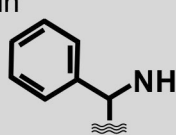
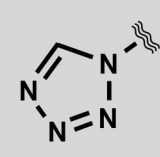
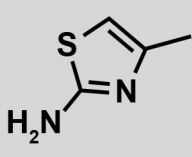
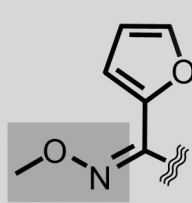
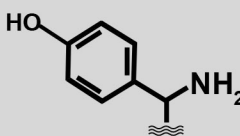
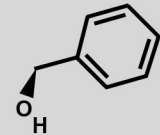
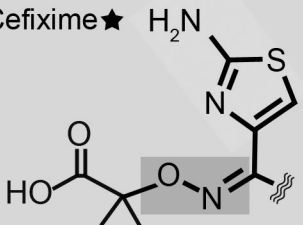
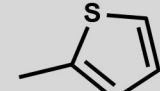
Cephalosporin core structure

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 al¹⁵.



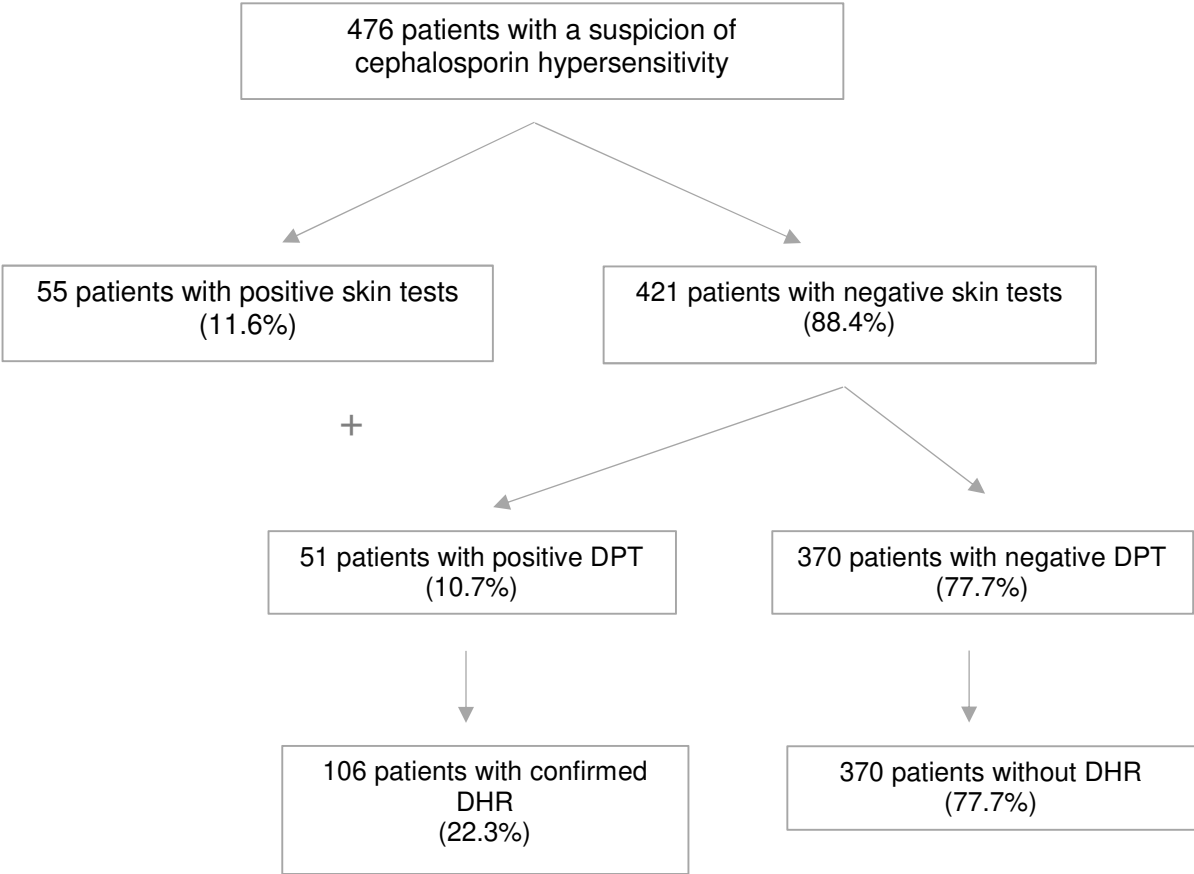
R₁ structure

Class 1	Class 2	Class 3	Class 4
Similar R1 side-chain between cephalosporins, involving 2nd, 3rd and 4th generation cephalosporins	Amino-cephalosporins, sharing a similar R1 side-chain with amino-penicillins		Other cephalosporins
Group 1 Ceftriaxone Cefotaxime Cefepime Cefpodoxime Cefditoren * 	Group 4 A Cefaclor Cephalexin 	Cefazolin 	Cefotiam ★ 
Group 2 Cefuroxime 	Group 4 B Cefatrizine ★ Cefadroxil Cefprozil * 		Cefamandole★ 
Group 3 Ceftazidime Cefixime★ 			Cefalotine★ Cefoxitine★ 

★ tested in our study but not referenced in the paper of Khan et al¹⁵

* included in the paper of Khan et al¹⁵ but not tested in our study

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



19
20 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												
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	CEFTRIAZONE	Anaphylaxis	51	No	Ceftriaxone	<1h	4	Exanthema, pruritus, malaise
									Cefotaxime			
4652	F	No	No	< 1h	CEFTRIAZONE	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, CEFOTAZIDIME,
 CEFPODOXIME, CEFIXIME, CEFOTIAM, CEFEPIME

Groups considering structural homology:

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

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

Chronology of the index reaction*	Chronology when positive tests (DPT/ST) [†]		n
	<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