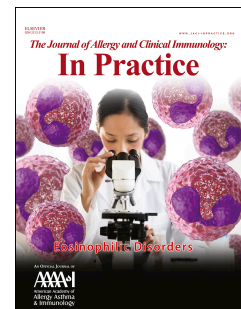


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Evaluating immediate reactions to cephalosporins: time is of the essence

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2 Abbreviations

3 AX: Amoxicillin

4 AX/CLV: Amoxicillin + Clavulanic acid

5 BP-OL: Benzylpenicilloyl-octa-L-lysine

6 CLV: Clavulanic acid

7 DDD: Defined Daily Dose

8 MD: Minor Determinant

9 MDM: Minor Determinant Mixture

ABSTRACT

10 *Background:* Few studies have assessed the diagnostic value of cephalosporin skin tests in
11 patients with immediate reactions to these β -lactams.

12 *Objective:* To evaluate the usefulness of skin tests and challenges in assessing such subjects.

13 *Methods:* We conducted a prospective study of 236 consecutive subjects who had suffered 249
14 immediate reactions (mostly anaphylaxis) to cephalosporins. Skin tests were performed with
15 penicillin reagents and suspected cephalosporins. Serum specific IgE assays (ImmunoCAP)
16 were also carried out for penicillins and cefaclor. Subjects with negative results underwent
17 challenges with the suspected cephalosporins; negative patients who had been assessed more
18 than 6 months after their reactions were re-evaluated.

19 *Results:* In the first allergy workup, an IgE-mediated hypersensitivity to cephalosporins was
20 diagnosed in 164 (69.5%) of the 236 patients on the basis of skin-test (162 patients) or cefaclor
21 ImmunoCAP positivity (2 patients). Of the 72 negative patients, 55 underwent cephalosporin
22 challenges; 3 reacted. Twenty subjects were re-evaluated after cephalosporin negative
23 challenges, with a conversion to cephalosporin skin-test positivity occurring in 5 of the 6
24 subjects who had had anaphylactic reactions and in none of the remaining 14 subjects with
25 other reactions. Overall, an immediate hypersensitivity to cephalosporins was diagnosed in 172
26 patients (of whom 5 after retesting).

27 *Conclusions:* Most immediate reactions to cephalosporins are IgE-mediated. Cephalosporin
28 skin testing is a useful tool for evaluating these reactions. IgE-mediated cephalosporin
29 hypersensitivity may be a transient condition; therefore, allergy exams should be repeated in
30 negative patients who experienced anaphylaxis more than 6 months before the allergy workup,
31 including challenges.

33 **Highlights box**

34 *What is already known about this topic?* Parent drugs are used as skin-test reagents for
35 evaluating subjects with hypersensitivity reactions to cephalosporins. However, few studies
36 have assessed the diagnostic value of cephalosporin skin tests in patients with immediate
37 reactions.

38 *What does this article add to our knowledge?* Skin testing with parent cephalosporins is a
39 useful tool in evaluating immediate reactions to these β -lactams, with a rate of positive results
40 that can reach 70%.

41 *How does this study impact current management guidelines?* IgE-mediated cephalosporin
42 hypersensitivity may disappear over time. Therefore, it is advisable to retest subjects who
43 experienced anaphylactic reactions and present negative allergy tests, including challenges,
44 when evaluated more than 6 months after their reactions.

45

46

47

48 Introduction

49 Cephalosporins can cause a variety of hypersensitivity reactions,¹⁻³ especially immediate ones,
50 which occur within 1-6 hours after the last administered dose,⁴ classically within 1 hour.² They
51 are generally IgE-mediated and characterized by urticaria, angioedema, rhinitis, bronchospasm,
52 and anaphylaxis.²⁻⁴

53 The allergenic determinants of cephalosporins have not been well-defined, unlike those of
54 penicillins.^{3,5} In any case, the literature data indicate that allergic reactions to cephalosporins
55 may occur because of sensitization to antigenic determinants that are unique to cephalosporins
56 or, less frequently, to determinants that are shared with other β -lactams, particularly
57 penicillins.^{2,3,5-15} For this reason, the European guidelines recommend parent drugs as skin-test
58 reagents, in addition to the classic benzylpenicillin reagents and semisynthetic penicillins.¹⁶⁻¹⁹
59 In 4 European studies involving adults,⁹ both children and adults,¹⁰ and children^{11,20} with
60 immediate reactions to cephalosporins, the rate of positive responses to cephalosporin skin tests
61 ranged from 24.1% (19 of 79)²⁰ to 72.1% (31 of 43).¹¹ In these studies,^{9-11,20} a cephalosporin
62 concentration of 2 mg/mL was used. Nevertheless, in 2013 a European position paper²¹ taking
63 into account the literature data^{22,23} endorsed the concentration of 20 mg/mL, except for
64 cefepime, which should be tested at 2 mg/mL.

65 Regarding *in vitro* tests for cephalosporins, the only commercially available serum specific IgE
66 assay is for cefaclor (ImmunoCAP, Thermo-Fisher, Uppsala, Sweden);²⁴ however, this test
67 appears to be less sensitive than skin tests.²

68 IgE-mediated hypersensitivity to cephalosporins may disappear over time, as is documented
69 with penicillin allergy.²⁵ One study followed 72 patients with such hypersensitivity
70 prospectively over 5 years and found that 37% and 67% of those sensitized only to
71 cephalosporins became skin-test negative within 1 year and 5 years, respectively.²⁶ Patients

72 who were also sensitized to penicillins were less likely to convert to negative skin tests (44%
73 after 5 years). Interestingly, a resensitization (i.e., a conversion to skin-test positivity) has been
74 described in patients retested about one month after negative cephalosporin challenges, whether
75 followed or not by full therapeutic courses.^{9,27,28}

76 In the present study, a specific diagnostic protocol employing standard techniques – skin tests,
77 serum specific IgE assays, and challenges – was applied to patients with immediate reactions to
78 cephalosporins to assess the techniques' usefulness in the diagnosis of such reactions. Subjects
79 who were evaluated more than 6 months after their last cephalosporin reaction underwent re-
80 evaluations within 2 to 4 weeks.

81 METHODS

82 Patients

83 We studied all participants older than 16 years of age who came to the allergy units of the
84 Columbus Hospital, Rome, Italy, IRCCS Oasi Maria S.S., Troina, Italy, and Istituto
85 Dermatologico dell'Immacolata, Rome between January 2007 and June 2019 because of histories
86 of immediate reactions to cephalosporins. We questioned patients to identify the suspected
87 antibiotic, as well as to obtain information about any adverse reactions to other drugs,
88 particularly penicillins. Symptoms were classified on the basis of medical records or, failing
89 that, according to patients' descriptions. Anaphylactic reactions were diagnosed according to
90 the clinical criteria proposed by Sampson et al²⁹ and classified as mild, moderate, or severe, as
91 previously described.³⁰ Prior to the study, all subjects received information about the possible
92 risks of skin and challenge tests, and written informed consent was obtained from each patient
93 or the parents of those under 18 years of age. The protocol was approved by the respective
94 institutional review boards.

95 Skin tests

96 We performed skin testing on 3 different days, as previously described.⁹

97 On the first day, prick and intradermal tests were carried out using penicilloyl-polylysine (PPL,
98 DAP, Diater Leganés, Spain), minor determinant mixture (MDM, DAP: benzylpenicillin,
99 sodium benzylpenicilloate, and benzylpenicilloic acid), and benzylpenicillin. The final
100 concentrations were, respectively, 1.07×10^{-2} mol/L (i.e., undiluted), 1.5 mol/L (i.e., undiluted),
101 and 10,000 IU/mL. From May 2011, the composition of the DAP changed: benzylpenicilloyl-
102 octa-L-lysine (BP-OL) replaced PPL and sodium benzylpenicilloate (minor determinant, MD)
103 replaced the MDM. The final concentrations of BP-OL and MD were 8.64×10^{-5} mol/L (i.e.,
104 undiluted) and 1.5×10^{-3} mol/L (i.e., undiluted), respectively.

105 On the second day, we used ampicillin and amoxicillin (AX) at concentrations of 1 and 20
106 mg/mL after dilution in 0.9% NaCl. Piperacillin and mezlocillin, at concentrations of 1 mg/mL
107 and 20 mg/mL, as well as aztreonam at 2 mg/mL, were also used in subjects who had
108 experienced adverse reactions to them, as previously described.³¹ From January 2018,
109 clavulanic acid (CLV, Diater), at concentrations of 1 mg/mL and 20 mg/mL, was also used in
110 subjects who had reacted to the combination AX + CLV (AX/CLV).

111 Suspected cephalosporins – both injectable (cefazolin, cefuroxime, cefodizime, cefonicid,
112 cefotaxime, cefoxitin, ceftazidime, ceftriaxone, or cefepime) and noninjectable (cephalexin,
113 cefatrizine, cefaclor, cephadrine, cefprozil, cefixime, cefpodoxime, or ceftibuten) – at a
114 concentration of 2 mg/mL in 0.9% NaCl were used on the third day. From June 2013, all
115 cephalosporins except cefepime were also tested at 20 mg/mL.

116 From January 2015, we performed skin tests on 2 different days. On the first day, we used
117 penicillin reagents and on the second day cephalosporins.

118 Cephalosporins were diluted with 0.9% NaCl no more than 2 hours before administration. For
119 injectable cephalosporins, we used the intravenous form under sterile conditions, while for
120 noninjectable ones we prepared sterile solutions with the powder contained in capsules or
121 obtained by removing with a scalpel the external layer of tablets, as previously described.⁹

122 All of the above reagents were initially tested on volar forearm skin by the prick method and
123 reactions were considered positive when a wheal larger than 3 mm in diameter with
124 surrounding erythema was present 20 minutes later. When prick tests were negative, 0.02 mL
125 of the reagent solution was injected intradermally on volar forearm skin. Readings were made
126 20 minutes after injections. Results were considered positive when there was an increase larger
127 than 3 mm in the initial wheal diameter accompanied by erythema.³² Positive controls for prick
128 and intradermal tests were done with histamine (at 10 and 1 mg/mL, respectively). As a

negative control for prick and intradermal tests, 0.9% NaCl was used. The concentrations used for cephalosporins had proved to be nonirritating in previous studies.^{13,22,23,33,34}

Detection of serum specific IgE

We performed assays for serum total and specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor with ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) in all subjects. We considered a positive result to be a value of 0.35 kUA/L or greater.

β -Lactam challenges and allergy re-evaluations

Challenges with suspected cephalosporins – cephalexin, cefaclor, cefprozil, cefuroxime axetil, cefixime, cefpodoxime, and ceftibuten, orally, and cefazolin, ceftazidime, ceftriaxone, and cefotaxime, intramuscularly – and suspected penicillins – AX, AX/CLV, orally, and mezlocillin and piperacillin, intramuscularly – were also performed in consenting subjects who displayed negative results in allergy tests.

We administered an initial dose of one-hundredth of the therapeutic one. In cases with negative results, one hour later we administered a dose of one-tenth and, if the result was again negative, after another hour a full therapeutic dose. The amount of the latter was 100 mg for cefpodoxime, 400 mg for cefixime and ceftibuten, 500 mg for cephalexin, cefprozil, cefaclor, and cefuroxime axetil, 1 g for AX, 875 mg of AX + 125 mg of CLV for this combination, and 1 g for the remaining cephalosporins, mezlocillin, and piperacillin. Subjects reporting hypersensitivity reactions to AX/CLV underwent challenges with AX and, in case of negative results, a further challenge with AX/CLV. For intramuscular challenges, doses of one-hundredth and one-tenth were injected in deltoid muscles and full therapeutic doses in the gluteus.

Each patient was carefully monitored during test dosing, and complete equipment for cardiopulmonary resuscitation was immediately available.

153 Patients who had had their last reaction more than 6 months before the allergy workup and
154 displayed negative allergy tests, including challenges, underwent re-evaluations 2-4 weeks
155 later. From January 2015, only negative patients who had had anaphylactic reactions more than
156 6 months before the allergy workup were re-evaluated.

157 **Statistical analysis**

158 We collected the data prospectively and analyzed them using Stata software (StataCorp,
159 College Station, Texas). We have presented the frequency of positive results as a percentage
160 and exact 95% CI. Age has been reported as the mean $\pm$ SD, and the time interval between the
161 last cephalosporin adverse reaction and testing as the median and range. The differences
162 between means were evaluated by Student's *t*-test for unpaired data. For all results, a two-tailed
163 P value less than 0.05 was considered significant.

164 RESULTS

165 We examined a total of 236 subjects, ranging in age from 17 to 87 years; 84 of them were
166 reported in a previous study.¹³

167 The clinical data and allergy-test results of the 236 patients are shown in Table I and Figure 1,
168 respectively. Two hundred and sixteen subjects had histories of immediate reactions only to
169 cephalosporins; each of 4 subjects had experienced 2 reactions to ceftriaxone, and 7 subjects
170 had reacted to 2 different cephalosporins (Table II). Twenty subjects had had hypersensitivity
171 reactions to both cephalosporins and other β -lactams, mostly penicillins (Table II). Our 236
172 patients had experienced a total of 249 hypersensitivity reactions to cephalosporins.
173 Specifically, 151 subjects (64%) had had 156 episodes of anaphylaxis, 2 subjects both
174 anaphylaxis and other reactions, and the remaining 83 patients had experienced 89 reactions
175 other than anaphylaxis, mostly cutaneous ones. The most frequent responsible compounds were
176 ceftriaxone, cefazolin, cefaclor, and ceftazidime (Table I).

177 In the first allergy workup (Figure 2), 170 (72%) of the 236 subjects displayed positive results
178 to cephalosporins and/or penicillins. Of these 170 patients, 6 were positive to penicillins and
179 negative to the suspected cephalosporins (Table II, subjects 67, 137, and 219; Table III,
180 subjects 162, 212, and 229) and 28 were positive to both skin tests with the culprit
181 cephalosporins and allergy tests (i.e., skin tests and/or ImmunoCAP) with penicillins (Tables II
182 and III). Of the remaining 136 positive patients, 2 were positive to skin tests with both the
183 responsible cephalosporins and other culprit β -lactams (1 to aztreonam, and 1 to CLV,
184 respectively; Table II, subjects 102 and 206) and 132 displayed positive skin tests to the culprit
185 cephalosporins (Figures 1 and 2); among them, 3 were positive to both the responsible
186 cephalosporins (cefaclor and cefprozil, cefotaxime and cefazolin, ceftazidime and ceftriaxone,
187 respectively) and 5 were positive also to cefaclor ImmunoCAP. Lastly, 2 patients who had

188 reacted to cefaclor were negative to skin tests with the culprit cephalosporin and positive to
189 cefaclor ImmunoCAP.

190 With regard to the ImmunoCAP, 32 (13.6% [95% CI, 9.8% to 18.5%]) of the 236 patients
191 displayed positive results: 14 were positive only to penicillin reagents, 9 to both penicillin
192 reagents and cefaclor (Tables II and III), and 9 only to cefaclor.

193 Of the 19 subjects who had reacted to cefaclor, 7 presented positive results to it in both skin
194 tests and ImmunoCAP, 5 only in skin tests, and 2 only in ImmunoCAP; the remaining 5
195 subjects were negative to both skin tests and ImmunoCAP.

196 Overall, in 164 (69.5%) of the 236 patients, an IgE-mediated hypersensitivity to the responsible
197 cephalosporins was diagnosed on the basis of positive responses to skin tests (162 subjects) or
198 cefaclor ImmunoCAP (2 subjects).

199 Seventy-two subjects displayed negative results in cephalosporin allergy tests. Fifty-five of
200 these 72 subjects underwent a total of 56 challenges with the suspected cephalosporins (Figure
201 2). Three subjects reacted: 2 to 1 g of ceftriaxone, experiencing urticaria and urticaria-
202 angioedema, respectively, within one hour, and one to 100 mg of cephalexin, developing
203 urticaria after 30 minutes. Fifty-two subjects tolerated 53 challenges (26 subjects tolerated
204 ceftriaxone, 7 cefazolin, 4 cefotaxime, 3 cefixime, 3 ceftazidime, 2 cefuroxime, 2 cefaclor, 1
205 cefpodoxime, 1 cefprozil, 1 ceftibuten, 1 cephalexin, and 1 both ceftriaxone and cefazolin). The
206 remaining 17 subjects did not undergo challenges, because 14 refused (Table E1) and there
207 were contraindications for 3, two of whom had reacted to cephalexin and cefaclor, respectively,
208 and were skin-test positive to aminopenicillins (Table III, subjects 162 and 229), and one had
209 experienced a severe anaphylactic reaction to ceftriaxone, with cardiac arrest.

210 The data on challenges with penicillins and AX/CLV are shown on Table II. Seven subjects
211 underwent these challenges and tolerated them; 3 subjects refused them.

212 The mean time interval between the most recent cephalosporin reaction and allergy
213 examination was significantly longer ($P < 0.0001$) in the 74 subjects negative to cephalosporin
214 skin tests (mean: 50.8 ± 77 months) than in the 162 subjects positive to them (mean: $12.7 \pm$
215 38.4 months). Indeed, the rate of positive patients decreased as such time interval increased
216 (Figure 3).

217 Twenty subjects underwent re-evaluations after negative cephalosporin challenges (Figure 2): a
218 conversion to cephalosporin skin-test positivity occurred in 5 of the 6 subjects who had had
219 anaphylactic reactions and in none of the remaining 14 subjects with other reactions (Table IV).
220 Of the 5 subjects found positive to cephalosporins in the re-evaluation, 1 was positive only to
221 penicillins in the first exam (Tables II and IV, subject 67).

222 Taking into account both the first and the second skin-test evaluation results, the rate of
223 cephalosporin positivity increased from 68.6% (162 of 236 patients) to 70.8% (167 of 236). A
224 total of 170 positive responses to skin tests with the responsible cephalosporins were observed
225 in the 167 patients (5 in re-evaluations); 46 were determined by prick testing and 124 by
226 intradermal tests, 11 of the latter at the concentration of 20 mg/mL (Figure 1).

227 On the basis of positive responses to skin tests, ImmunoCAP, and challenges, we classified our
228 177 positive patients into 3 groups: Group I, with 5 (2.8%) positive only to penicillin reagents
229 (Table II, subjects 137 and 219; Table III, subjects 162, 212, and 229); Group II, with 31
230 (17.5%) positive to at least one cephalosporin and another β -lactam: 29 to penicillins, 1 to
231 aztreonam, and 1 to CLV (Tables II and III), and Group III, with 141 (79.7%) positive only to
232 cephalosporins.

233 Overall, a hypersensitivity to the suspected cephalosporins was diagnosed in 172 (72.9%) of
234 236 subjects; 167 were positive to skin tests, 2 to cefaclor ImmunoCAP, and 3 to challenges
235 (Figure 2). The rate of cephalosporin allergy test positivity was significantly higher ($P < 0.001$)

236 among subjects who had experienced anaphylactic reactions (88.2%, 135 of 153 patients) than
237 among those who had had reactions other than anaphylaxis (44.6%, 37 of 83 patients). In
238 particular, a cephalosporin hypersensitivity was diagnosed in 54 (93.1%) of the 58 subjects
239 with severe anaphylaxis, 39 (92.9%) of the 42 with moderate anaphylaxis, 42 (79.2%) of the 53
240 with mild anaphylaxis, 29 (41.4%) of the 70 with urticaria and/or angioedema, and 8 (61.5%)
241 of the 13 with generalized erythema, bronchospasm, or syncope. A cephalosporin
242 hypersensitivity was excluded in 47 subjects (19.9%) who tolerated cephalosporin challenges,
243 15 of whom remained negative in the re-evaluation. Definitive diagnoses could not be provided
244 for 17 subjects (7.2%) who were negative to cephalosporin skin tests and cefaclor ImmunoCAP
245 and did not undergo challenges, 5 of whom formed group I.

246 An IgE-mediated allergy to the culprit β -lactams other than cephalosporins was diagnosed in 9
247 of the 20 subjects who had also reacted to them: 6 subjects were positive to AX, 1 to ampicillin,
248 1 to CLV, and 1 to aztreonam. Another subject had reacted to ampicillin and was skin-test
249 positive to benzylpenicillin (Table II). Of these 10 subjects, 2 belonged to group I (Table II,
250 subjects 137 and 219) and 8 to group II (Table II, subjects 67, 140, 93, 102, 147, 158, 166, and
251 206).

252 DISCUSSION

253 The present study indicates that skin testing with cephalosporins is a useful tool in evaluating
254 immediate reactions to these β -lactams. In effect, 167 (70.8%) of the 236 subjects with such
255 reactions displayed 170 positive skin-test responses to the responsible cephalosporins, 5 of
256 them in the re-evaluation. The high rate of positive skin tests is likely related to the
257 characteristics of our population of adults, 64.8% of whom (153 of 236) had experienced
258 anaphylactic reactions. As expected, a cephalosporin hypersensitivity was diagnosed more
259 frequently ($P < 0.001$) in patients who had experienced such reactions than in those who had
260 had reactions other than anaphylaxis. This high number of subjects with anaphylactic reactions
261 can be explained by the fact that from 2001 to 2017 in the Columbus Hospital allergy unit a
262 telephone number was active exclusively for booking allergy visits, with priority for subjects
263 with severe reactions to drugs, especially anaphylactic ones. The high rate of hypersensitivity
264 reactions to ceftriaxone (61.4%, 153 of 249 reactions to cephalosporins) observed in our study
265 probably should be attributed to the fact that in Italy ceftriaxone is the most consumed
266 antibiotic (0.3 Defined Daily Dose [DDD]/1,000 inhabitants per day) after AX/CLV (5.8
267 DDD/1,000 inhabitants per day).³⁵

268 Interestingly, a Korean study,³⁶ which performed cephalosporin skin tests at 2 mg/mL and
269 challenges in 1,421 healthy controls, found a false-positivity rate of 5.2%. For ethical reasons,
270 we did not challenge patients with positive skin tests, and therefore we could not assess the
271 sensitivity of such tests. In any case, authors who challenged immediate reactors with the
272 responsible cephalosporins to which they were positive elicited immediate urticarial or
273 anaphylactic reactions.^{37,38} Specifically, Christiansen et al³⁸ evaluated patients with histories
274 suggestive of cefuroxime perioperative anaphylaxis, and 7 of 7 with positive skin-test results

275 reacted to challenges. This suggests that for patients with anaphylaxis, skin testing has a very
276 high positive predictive value.³

277 In our study, the negative predictive value of cephalosporin skin tests was 94.6%: there were 3
278 positive challenges out of the 56 performed with the suspected cephalosporins found negative
279 in skin testing. In other studies carried out on at least 20 subjects, cephalosporin skin testing
280 proved to be reliable and effective for selecting alternative cephalosporins in subjects with a
281 well-demonstrated IgE-mediated hypersensitivity either to penicillins (11 positive controlled
282 administrations out of 1,564)³⁹⁻⁴⁵ or cephalosporins (no positive controlled administrations out
283 of 344).^{13,46} In a large Korean study,⁴⁷ however, routine screening intradermal tests with
284 cephalosporins before administration of the cephalosporin concerned was not clinically useful
285 for the prevention of anaphylaxis and related mortality.

286 The fact that the mean time interval between the most recent cephalosporin reaction and allergy
287 examination was significantly longer ($P < 0.0001$) in subjects negative to cephalosporin skin
288 tests than in those positive to them indicates that such time interval may influence the
289 sensitivity of the allergy evaluation. Consequently, in order to avoid false negative results, it is
290 crucial to assess patients with immediate reactions to cephalosporins within a few months. The
291 present study also indicates that cephalosporin IgE-mediated hypersensitivity may be a
292 transient condition. Therefore, according to the literature data^{9,27,28} and the results of this study,
293 in order to exclude a possible resensitization after loss of sensitivity, it is advisable to retest
294 subjects who experienced anaphylactic reactions to cephalosporins and present negative allergy
295 tests, including challenges, when evaluated more than 6 months after their reactions.^{16,19} On the
296 other hand, this approach has not proven to be useful in subjects with other reactions, such as
297 urticaria and/or angioedema (Table IV). It should be noted that the immunological reactivity to
298 cephalosporins (i.e., positive responses to skin tests) might be transient but not the risk of

299 clinical reactivity. Therefore, responsible cephalosporins found positive in the allergy workup
300 must be avoided for life, together with other potentially cross-reactive β -lactams.

301 Among our patients, 34 (14.4%) displayed skin-test and/or ImmunoCAP positivity to
302 penicillins (groups I and II). In some of them, such as those who had reacted to cefaclor or
303 cefatrizine, this positivity may be due to cross-reactivity with penicillins. In fact, these
304 aminocephalosporins have side-chain structures similar or identical to those of
305 aminopenicillins.^{5,15,48} Specifically, cefaclor shares the same R1 side-chain with ampicillin, and
306 cefatrizine with AX. In other patients who had reacted to cephalosporins, such as ceftriaxone,
307 ceftazidime, and cefuroxime, which have side chains dissimilar from those of penicillins,
308 coexisting sensitivities to both penicillins and cephalosporins can be hypothesized, as
309 previously observed in penicillin-allergic subjects.^{41,43} In effect, some patients could have been
310 sensitized earlier to a particular penicillin, which would not automatically imply cross-
311 reactivity with the culprit cephalosporin. In this connection, Antúnez et al⁴⁹ described subjects
312 who had experienced anaphylactic reactions to AX, ampicillin, or cefixime and displayed IgE
313 responses not directed only to the culprit β -lactams, but also to benzylpenicillin. The
314 phenomenon of an IgE response not directed only to the culprit β -lactam, but also to other
315 compounds to which the patient had likely been exposed, can be explained by the theory of
316 original antigenic sin:⁵⁰ in an antibody response, memory B cells are more easily triggered than
317 naïve B cells. In the present study, this phenomenon was observed especially in subjects
318 evaluated a few months after an anaphylactic reaction to ceftriaxone (Table III). However, an *in*
319 *vitro* positivity does not always predict a clinical reaction. In effect, many patients with
320 detectable IgE antibodies do not display such reactions.⁵¹ Nevertheless, in the present study
321 subjects with positive results to penicillin reagents did not undergo AX challenges.

322 Nine subjects (3.8%) had reacted to two different cephalosporins (Table II). In some of them,
323 this may be due to cross-reactivity between the responsible cephalosporins. For example,
324 ceftriaxone and cefepime have identical R1 side chains, whereas cefuroxime and ceftazidime
325 have R1 side-chain structures similar to that of the aforementioned cephalosporins; cefaclor and
326 cefprozil also share a similar R1 side chain.^{5,15} In other subjects, such as those who had reacted
327 to both ceftriaxone and cefazolin, or to both cefotaxime and cefazolin, coexisting sensitivities
328 can be hypothesized.

329 Concerning *in vitro* tests, our data – together with those of the literature⁵² – indicate that the
330 IgE assay for cefaclor could be used as a complementary test, because skin-test negative,
331 ImmunoCAP-positive cases can be diagnosed.

332 According to the European guidelines,¹⁶⁻¹⁹ in the present study, a specific diagnostic protocol
333 employing skin tests with parent drugs in addition to the classic benzylpenicillin reagents and
334 semisynthetic penicillins was applied to patients with immediate reactions to cephalosporins.
335 To evaluate such subjects, nevertheless, a simpler diagnostic protocol could be applied
336 employing skin tests only with the suspected cephalosporins and, in case of negative results,
337 performing challenges, if there are no contraindications. This could be a time- and cost-
338 effective way to exclude/document hypersensitivity to the suspected cephalosporin. Moreover,
339 if such hypersensitivity is excluded, there is no need for evaluating cross-reactivity.

340 In conclusion, most immediate reactions to cephalosporins are IgE-mediated. Cephalosporin
341 skin testing appears to be a useful tool for evaluating such reactions. However, further studies
342 should be carried out in large samples of subjects with immediate reactions to cephalosporins in
343 order to fully establish the diagnostic value of both *in vivo* and *in vitro* tests.

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FIGURE 1. Allergy test results of the 236 patients.

BP-OL, benzylpenicilloyl-octa-L-lysine; *IDT*, intradermal test; *MD*, sodium benzylpenilloate; *MDM*, minor determinant mixture; *PPL*, penicilloyl-polylysine; *SPT*, skin prick test.

*3 positive in the re-evaluation

[¶]1 positive in the re-evaluation.

[‡]1 positive in the re-evaluation.

Skin tests with the suspected cephalosporin concerned were negative in 11 subjects with histories of immediate reactions to cephalexin (3 subjects), cefixime (3), cephadrine (1), cefoxitin (1), cefpodoxime (1), ceftibuten (1), or cefepime (1).

FIGURE 2. Diagnostic algorithm and results of allergy workup in the 236 patients.

AM, ampicillin; *AX*, amoxicillin; *BL*, β -lactams; *BP-OL*, benzylpenicilloyl-octa-L-lysine; *CAP*, ImmunoCAP; *ceph*, cephalosporins; *CLV*, clavulanic acid; *CH*, challenge with the suspected cephalosporins; *MD*, minor determinant; *MDM*, minor determinant mixture; *pen*, penicillins; *PG*, penicillin G; *PPL*, benzylpenicilloyl-poly-L-lysine; *PV*, penicillin V.

Rectangles in dotted lines include patients positive to both culprit cephalosporins and penicillins or other culprit β -lactams.

FIGURE 3. Results of cephalosporin skin tests of the 236 patients in relation to the time interval between the last cephalosporin reaction and the allergy examination.

TABLE E1. Clinical data and allergy test results of the 14 subjects who refused cephalosporin challenges

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Patient, n	Sex	Age (y)	Drug involved	Type of reaction (Time*, mo)	ImmunoCAP					Skin tests						Challenges
					PG	PV	AM	AX	Cefaclor	PPL/ BP-OL	MDM/ MD	PG	AM	AX	Culprit β-lactam	Culprit β-lactam
28	F	46	Ceftriaxone/AM	Angioedema (240)/Urticaria (148)	-	-	-	-	-	-	-	-	-	-	-/-	ref/ref
29	M	73	Ceftriaxone	An S (3)	-	-	-	-	0.11	-	-	-	-	-	-	ref
33	F	39	Cefodizime	An M (21)	-	-	-	-	-	-	-	-	-	-	-	ref
35	F	52	Cephadrine	Urticaria (300)	-	-	-	-	-	-	-	-	-	-	-	ref
59	F	64	Cefaclor	An M (264)	-	-	-	-	-	-	-	-	-	-	-	ref
95	M	17	Cefaclor	Urticaria (36)	-	-	-	-	-	-	-	-	-	-	-	ref
125	F	38	Cefoxitin/AX	An M (48)/Urticaria (16)	-	-	-	-	-	-	-	-	-	-	-/-	ref/ref
137	M	64	Ceftriaxone/AX+C	An M (18)/An M (2)	-	-	-	-	-	-	-	+	+	+	-/+	ref/np
141	F	43	Ceftriaxone	An M (31)	-	0.2	0.14	-	-	-	-	-	-	-	-	ref
167	F	58	Ceftriaxone	An M (4)	-	-	-	-	-	-	-	-	-	-	-	ref
170	M	61	Ceftriaxone	An M (48)	0.11	0.34	0.33	0.25	0.26	-	-	-	-	-	-	ref
212	F	66	Ceftriaxone	An Mo (23)	15.6	28.7	10.5	0.24	0.98	+	+	+	+	-	-	ref
219	F	58	Cefuroxime/AM	UA (132)/UA (8)	0.14	3.94	0.36	-	0.11	-	-	-	-	-	-/-	ref/np
232	M	66	Cefazolin	An S (4)	-	-	-	-	-	-	-	-	-	-	-	ref

AM, ampicillin; An, anaphylaxis (M, mild; Mo, moderate; S, severe); AX, amoxicillin; BP-OL, benzylpenicilloyl-octa-L-lysine; C, clavulanic acid; F, female; M, male; MD, sodium benzylpenilloate; MDM, minor determinant mixture; np, not performed; PG, penicillin G (or benzylpenicillin); PPL, penicilloyl-polylysine; PV, penicillin V; ref, refused; UA, urticaria-angioedema.

*Time (mo) elapsed between adverse reactions to β-lactams and the allergy examination.

TABLE II. Characteristics of subjects who had reacted to more than one cephalosporin (first 9 subjects) or to both cephalosporins and other β -lactams (subjects 67-220)

[illegible]

AM, ampicillin; An, anaphylaxis (M, mild; Mo, moderate; S, severe); AX, amoxicillin; BPOL, benzylpenicilloyl octa-L-leucine; C, clavulanic acid; F, female; M, male; MD, sodium benzylpenilloate; MDM, minor determinant mixture; np, not performed; PG, penicillin G (or benzylpenicillin); PPL, penicilloyl-polylysine; PV, penicillin V; ref, refused; UA, urticaria-angioedema.

*Time (mo) elapsed between adverse reactions to β -lactams and the allergy examination.

[†]Subjects who underwent re-evaluation after negative challenges.

TABLE III. Clinical data and allergy test results of the 26 subjects with immediate reactions only to cephalosporins and positive results to penicillin reagents

Journal Pre-proof

Patient, n	Sex	Age (y)	Cephalosporin involved	Type of reaction (Time*, mo)	ImmunoCAP					Skin tests					
					PG	PV	AM	AX	Cefaclor	PPL/ BP-OL	MDM/ MD	PG	AM	AX	Culprit
2	F	25	Cefaclor	Urticaria-angioedema (7)	4.49	14.9	0.39	-	2.53	-	-	-	-	-	+
36	F	51	Ceftriaxone	Anaphylaxis severe (1)	1.25	2.3	0.8	0.9	0.22	-	-	-	-	-	+
51	F	59	Ceftriaxone	Anaphylaxis severe (1)	-	-	0.1	-	0.32	-	-	+	-	-	+
52	F	44	Ceftriaxone	Anaphylaxis mild (1)	1.24	0.17	0.19	0.13	0.25	-	-	-	-	-	+
55	F	54	Ceftriaxone	Anaphylaxis moderate (1)	0.16	0.23	1.04	0.21	0.31	-	-	-	-	-	+
58	F	69	Ceftriaxone	Anaphylaxis severe (2)	0.35	0.49	0.87	0.36	0.34	-	-	-	-	-	+
73	F	60	Ceftriaxone	Anaphylaxis mild (1)	0.32	0.55	0.2	0.1	0.15	+	-	-	-	-	+
98	F	33	Ceftazidime	Bronchospasm (3)	0.47	0.17	-	-	-	-	-	-	-	-	+
116	F	77	Ceftriaxone	Anaphylaxis severe (6)	0.21	11.7	1.07	0.79	1.47	-	-	-	-	-	+
138	F	68	Ceftriaxone	Anaphylaxis moderate (3)	0.29	0.36	0.25	0.45	-	-	-	-	-	-	+
153	F	61	Ceftriaxone	Anaphylaxis moderate (18)	-	-	-	-	-	-	+	-	+	+	+
160	F	58	Ceftriaxone	Anaphylaxis severe (1)	0.38	1.67	0.49	-	0.56	-	-	-	-	-	+
162	F	17	Cefaclor	Anaphylaxis mild (120)	-	-	-	-	-	-	-	-	+	+	-
163	F	64	Ceftriaxone	Generalized erythema (1)	-	-	-	-	-	+	-	-	-	-	+
165	M	17	Cefaclor	Urticaria (2)	-	-	-	-	6.19	-	-	-	+	-	+
169	F	36	Ceftriaxone	Anaphylaxis severe (2)	0.3	1.02	2.29	0.37	0.35	-	-	-	-	-	+
175	F	49	Ceftriaxone	Urticaria-angioedema (3)	0.11	0.65	0.28	0.55	0.54	-	-	-	-	-	+
184	F	59	Cefuroxime axetil	Urticaria-angioedema (1)	-	1.16	-	-	-	-	-	-	-	-	+
192	F	39	Cefaclor	Anaphylaxis moderate (2)	-	-	-	-	7.85	-	-	-	+	+	+
203	F	68	Cefonicid	Anaphylaxis mild (84)	0.49	0.41	0.36	0.39	0.55	-	-	+	+	-	+
208	F	58	Ceftriaxone	Anaphylaxis moderate (36)	1.39	1.15	1.25	0.7	0.33	-	-	-	-	-	+
212	F	66	Ceftriaxone	Anaphylaxis moderate (23)	15.6	28.7	10.5	0.24	0.12	+	+	+	+	-	-
221	F	44	Ceftriaxone	Anaphylaxis mild (5)	28.9	33.1	36.2	18	0.19	-	-	+	+	+	+
228	F	62	Ceftriaxone	Anaphylaxis severe (1)	0.46	2.18	0.31	0.27	0.15	-	-	-	-	-	+
229	F	71	Cephalexin	Anaphylaxis moderate (12)	-	-	-	-	-	-	-	-	+	+	-
235	M	67	Ceftriaxone	Anaphylaxis moderate (1)	2.39	2.21	1.57	0.68	0.47	-	-	-	-	-	+

AM, ampicillin; AX, amoxicillin; BP-OL, benzylpenicilloyl octa-L-leucine; F, female; M, male; MD, sodium benzylpenicillate; MDM, minor determinant mixture; PG, penicillin G (or benzylpenicillin); PPL, penicilloyl-polylysine; PV, penicillin V.

*Time (mo) elapsed between the last adverse cephalosporin reaction and the allergy examination.

TABLE IV. Clinical data and allergy test results of the 20 subjects re-evaluated after negative challenges with the responsible cephalosporins

Journal Pre-proof

Patient, n	Sex	Age (y)	Drug involved	Type of reaction (Time*, mo)	Skin tests with culprit β -lactam 1 st evaluation	Skin tests with culprit β -lactam 2 nd evaluation
12	F	23	Ceftriaxone	An Mo (108)	-	+
14	F	32	Ceftriaxone	Urticaria (14)	-	-
16	F	28	Ceftriaxone	Bronchospasm (8)	-	-
31	F	56	Cefazolin	An S (48)	-	+
42	F	18	Cefotaxime	Urticaria-angioedema (12)	-	-
48	M	18	Ceftriaxone/AX+C	Urticaria (7)/Urticaria (9)	-/-	-/-
61	F	68	Ceftriaxone	Generalized erythema with pruritus (12)	-	-
66	F	41	Ceftazidime	Urticaria (196)	-	-
67	F	65	Ceftazidime/Ceftriaxone/AX	An S (60)/An M (24)/An Mo (1)	-/-/+	-/+
86	F	59	Cefprozil	Urticaria-angioedema (240)	-	-
99	F	58	Ceftriaxone	Urticaria (36)	-	-
104	F	43	Ceftriaxone	Urticaria (15)	-	-
118	F	49	Ceftriaxone	Syncope (96)	-	-
129	F	18	Ceftriaxone/Piperacillin	Urticaria (60)/Urticaria (48)	-/-	-/-
134	M	35	Ceftriaxone/Cefazolin	Urticaria (12)/Urticaria (10)	-/-	-/-
144	M	19	Ceftriaxone	Urticaria (36)	-	-
156	M	38	Cefuroxime	Urticaria-angioedema (84)	-	-
178	F	38	Ceftriaxone/AX+C	An M (132)/Urticaria (15)	-/-	-/-
188	F	39	Ceftriaxone	An M (14)	-	+
231	F	56	Cefotaxime	An S (173)	-	+

An, anaphylaxis (M, mild; Mo, moderate; S, severe); AX, amoxicillin; C, clavulanic acid; F, female; M, male.

*Time (mo) elapsed from adverse reactions to β -lactams and the allergy examination.

TABLE I. Clinical data of the 236 subjects with immediate reactions to cephalosporins

Characteristic	All patients (n = 236)
Age (y), mean $\pm$ SD	51.2 $\pm$ 17.6
Women, n (%)	178 (75.4)
Time since last cephalosporin reaction*, median (range) [25th, 75th percentile]	4 (1-360) [1, 14.3]
Family history of allergic disease, n (%)	80 (33.9)
Personal history of allergic disease, n (%)	60 (25.4)
Responsible β -lactams, n (%)	All reactions: 269 [249 to cephalosporins and 20 to other β -lactams]
Ceftriaxone	157 (58.4)
Cefaclor	19 (7.1)
Cefazolin	19 (7.1)
Ceftazidime	17 (6.3)
Cefotaxime	10 (3.7)
Cefuroxime	9 (3.3) [5 axetil]
Cephalexin	3 (1.1)
Cefodizime	3 (1.1)
Cefixime	3 (1.1)
Cefprozil	2 (0.7)
Cefonicid	1 (0.4)
Cefoxitin	1 (0.4)
Cefpodoxime	1 (0.4)
Ceftibuten	1 (0.4)
Cefatrizine	1 (0.4)
Cephradine	1 (0.4)
Cefepime	1 (0.4)
Amoxicillin	14 (5.2) [11 plus clavulanic acid]
Ampicillin	3 (1.1)
Piperacillin	1 (0.4)
Mezlocillin	1 (0.4)
Aztreonam	1 (0.4)
Manifestation, n (%)	All cephalosporin reactions 249
Anaphylaxis	158 (63.4) [56 mild, 42 moderate; 60 severe [¶]]
Urticaria	52 (20.9)
Urticaria and angioedema	21 (8.4)
Generalized erythema with pruritus	9 (3.6)
Angioedema	4 (1.6)
Bronchospasm	4 (1.6)
Syncope	1 (0.4)

*Time (mo) elapsed between the last adverse cephalosporin reaction and the current allergy examination.

[¶]8 with urinary and fecal incontinence; 5 with cardiac arrest; 3 with urinary incontinence; 2 with fecal incontinence; 1 with cardiac ischemia; and 1 with cardiac arrest plus urinary and fecal incontinence.

