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1 Allergy to third and second generation cephalosporins in confirmed penicillin allergic patients

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27

28 **Clinical implications box (35/40 words)**

29 Clinically-relevant cross-reactivity between penicillins and third and second generation
30 cephalosporins could be between 1% and 2%. In 234 confirmed penicillin-allergic subjects
31 (180 immediate and 54 delayed-type hypersensitivity reactions) we found a cross-reactivity
32 risk below 1%.

33

34 To the Editor:

35 Beta-lactams (BLs) are a major cause of hypersensitivity reactions (HS) to drugs, both
36 immediate (IHR) and delayed (DHR) (1). Historic risk of cross-reactivity to cephalosporins in
37 penicillin-allergic patients (10-30%) was probably overestimated (2,3). Cross-reactivity
38 between penicillins and cephalosporins seems to be related mainly to side-chain similarities
39 (1), as administration of potential identical side-chain first (1GC) and second-generation
40 cephalosporins (2GC) is associated with a HS risk exceeding 30% (1,2), whereas risk with
41 dissimilar side-chain third generation cephalosporins (3GC) can be as low as 1% (2).
42 However, skin testing (ST) followed by a drug provocation test (DPT) of negatively-tested
43 compounds remains the gold standard (1,2).

44 Our objective was to assess allergy to 3GC and 2GC in penicillin-proven allergic patients.

45 We conducted a retrospective study including 234 adults with proven HS to penicillin, based
46 on history according to EAACI criteria (4) and positive ST (immediate or delayed readings) to
47 at least one penicillin, explored for 3GC and 2GC allergy (Online Repository, Tables E3 and
48 E4).

49 The study group has a mean age of 52 years (range 17-93 years) and sex ratio F/M=1.7/1;
50 respectively 180 patients (77%) and 54 patients (23%) with proven IHR and DHR to
51 penicillin (Table 1). Six subjects among 240 evaluated were excluded because of lacking DPT
52 at the time of the work-up (Figure 1).

53 The 234 patients reported 270 HS reactions (196 IHR and 74 DHR) : only one reaction for
54 203 (87%) and more than one for 31 (13%). Anaphylaxis (5), acute or delayed urticaria and/or
55 angioedema and cutaneous adverse drug reaction (CADR) were reported in respectively 118,
56 52 and 49 cases (Table 1). Although most DHR were benign maculopapular drug eruptions
57 (56%), we report 5 severe CADR: two DRESS, two Acute Generalized Exanthematous
58 Pustulosis and one Bullous drug reaction (Table 1).

59 All 234 patients had positive ST with amoxicillin (AX) and/or amoxicillin-clavulanic acid
60 (AX-Clav), as follows: 84 (47%) on skin prick test (SPT) and 96 (53%) on intradermal ST
61 (IDT) among IHR and 8 (15%) positive on patch test and 51 (95%) on delayed reading IDT
62 among DHR respectively (5 positive for both) (Figure 1).

63 In 180 IHR penicillin patients, 409 negative ST were performed with 2GC cefuroxime (n=79)
64 and 3GC (n=330) i.e ceftriaxone (n=154), cefpodoxime (n=172) and cefixime (n=4) (Figure
65 1). Only one patient among 80 (1.3%) IHR tested with cefuroxime (2GC) had positive
66 immediate ST with cefuroxime and negative ST and DPT with cefpodoxime and ceftriaxone
67 (3GC) (Figure 1 and Table E1). Among 54 patients with DHR to penicillin, 126 negative ST
68 with 2GC (n=26) and 3GC (n=100) were performed i.e; ceftriaxone (n=48), cefpodoxime
69 (n=50) and cefixime (n=2) (Figure 1).

70 DPT were performed in all 234 patients: 18 had DPT only with 2GC cefuroxime 15 with one
71 3GC, 140 with two 3GC, 53 with one 2GC and one 3GC and 8 with two 3GC and one 2GC
72 (Table E2). A total of 442 negative challenges were performed with 3GC i.e: ceftriaxone
73 (n=159), cefpodoxime (n=198), cefixime (n=6) and with 2GC cefuroxime (n=79). Only 1/160
74 (0.6%) IHR to penicillin patient challenged with ceftriaxone had positive immediate DPT
75 (with acute urticaria), tolerating subsequent DPT with cefpodoxime, another 3GC, whereas
76 both ceftriaxone ST and post-DPT skin re-tests were negative (Figure 1 and Table E1)
77 Negative predictive value for ceftriaxone ST was 99% for IHR and 100% for DHR.

78 Concerning IHR, we found a very low percentage of positive ST to 2GC (1/106 tested, 0.9%),
79 no positive ST with 3GC (0/232 ST with at least one 3GC) and only one positive DPT to
80 ceftriaxone (0/160 challenges), confirming data on a negligible risk of cross reactivity with
81 C3G and some C2G (6). In line with this, the largest, prospective cohort of IHR to penicillins
82 of Romano *et al.* reports positive ST with cefuroxime (2GC), or ceftriaxone (3GC) in 7/252
83 (2.8%) patients with positive responses in immediate-reading ST to at least one penicillin

84 (mostly aminopenicillin) and negative DPT with afore mentioned molecules in all 244
85 patients, in a study group with a similar percentage of anaphylaxis (70%) as ours (66%) (3).
86 Moreover results for ST to cephalosporins we tested (2/4: cefuroxime, ceftriaxone) and 7
87 other cephalosporins from group A (ceftazidime, cefotaxime, cefepime), group C
88 (cefamandole) and group B aminocephalosporins (cephalexin, cefaclor, and cefadroxil) show
89 the highest risk of cross-reactivity (38%) is related to similar side chain aminocephalosporins
90 (3).

91 As already published, none of the 54 patients with DHR to penicillins cross-reacted with 2GC
92 and 3GC. All of the 97 patients with positive responses in late-reading ST to at least one
93 penicillin evaluated by Buonomo *et al.* had negative DPT with cefixime and ceftriaxone,
94 confirming a low cross-reactivity with penicillins (7), whereas the rate of cross-reactivity
95 upon ST and DPT with similar side-chain aminocephalosporins (cephalexin, cefaclor) was
96 higher (11%).

97 All 4 cephalosporins we tested share the common methoxyimino group on the R1-side chain,
98 belonging to group A cephalosporins based on chemical structure (Figure E1) and present no
99 structural similarities with AX (no amino group) (1). Therefore, positive ST with dissimilar
100 side-chain cephalosporins from group A could be related to coexisting sensitivities (1) or, less
101 likely, to cross-reactions due to sensitization to nuclear structures (3).

102 First limitations of our study are the retrospective character and the limited type of
103 cephalosporins tested, belonging exclusively to group A cephalosporins, possibly
104 underestimating allergic risk for other cephalosporins, especially identical side chain-
105 aminocephalosporins. Second, lacking intravenous formulas for 2/4 cephalosporins (i.e
106 cefpodoxime and cefixime) imposed testing by SPT only, possibly reducing sensitivity. Third,
107 not all cephalosporins investigated are available in other countries, and, last, exclusion of

108 sensitization to clavulanic acid by skin testing with AX was not systematic in AX-Clav ST-
109 positive patients

110 In conclusion, this series of 234 truly penicillin-allergic patients (aminopenicillins) confirms
111 that cross-reactivity between penicillin and dissimilar side chain cephalosporins, like group A
112 cefuroxime, ceftriaxone and cefpodoxime is very low (between 1 and 2%). Should urgent
113 administration of different chemical structure cephalosporins be required, in both IHR or
114 DHR confirmed penicillin allergic patients, it could be undertaken in hospitalized patients
115 under close surveillance, after negative ST.

116

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120

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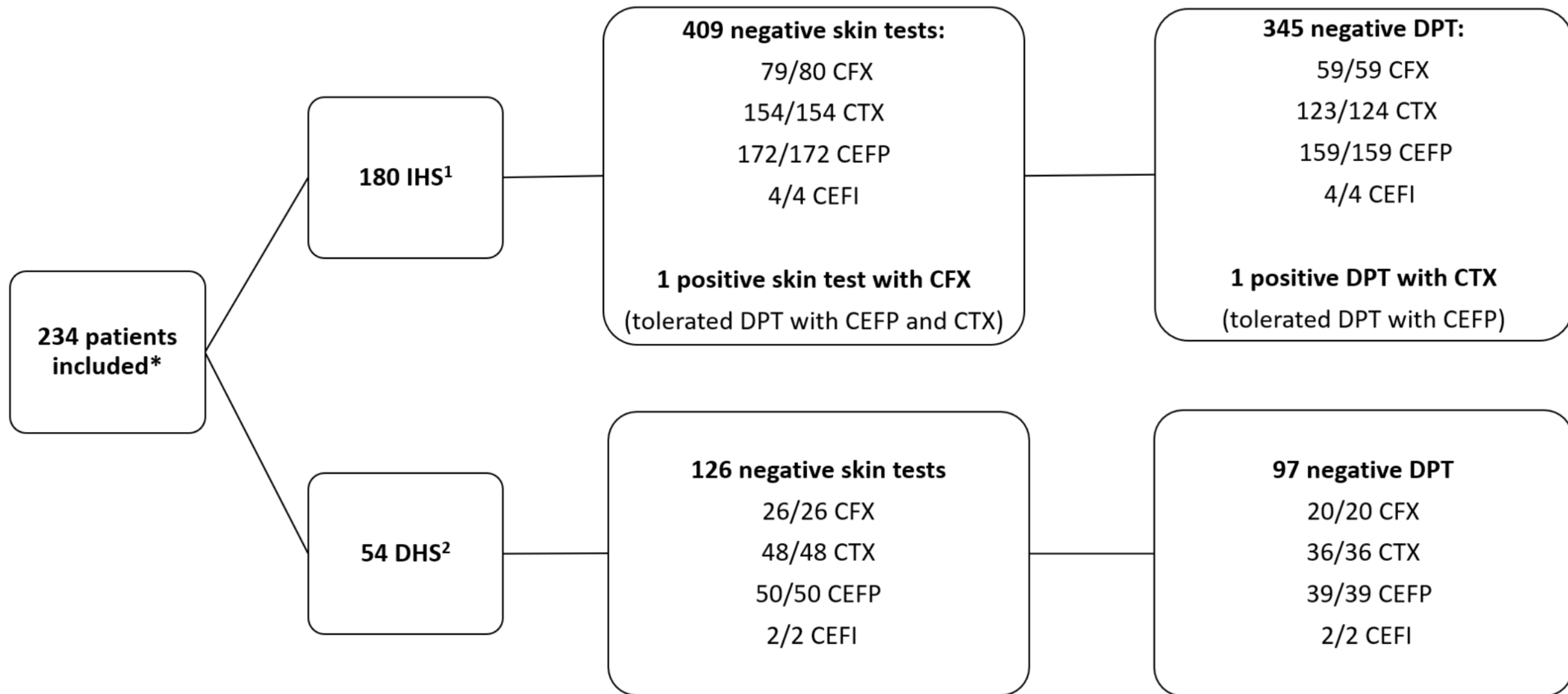
143 **Title and legend for Figure 1**

144

145 **Figure 1.** Results of 2GC and 3GC skin tests and drug provocation tests (DPT) in 234
146 penicillin-allergic patients

147 IHR: immediate hypersensitivity reaction; DHR: delayed hypersensitivity reaction; DPT: drug
148 provocation test; **2GC**: CFX: cefuroxime **3GC**: CTX: Ceftriaxone CEFP: cefpodoxime,
149 CEFI: cefixime,

150 *: 6 patients excluded (lack of DPT); ¹skin tests for penicillin allergy were positive on prick
151 test for 84 (47%) and on intradermal skin test (IDT) for 96 (53%); ²skin tests for penicillin
152 allergy were positive on patch test for 8 (15%) and on delayed reading IDT for 51 (94%). Five
153 patients were positive for both.



1 **Table 1:** Clinical characteristics and results of penicillin allergic population studied

	All n=234	Immediate HS (N=180)			Delayed HS (N=54)	
		All n=180	Negative skin tests and challenge with 2GC and 3GC ¹ (cefepodoxime and/or ceftriaxone and/or cefixime) n=178	Positive skin tests (n=1) and challenge (n=1) with 2GC and 3GC ¹ (cefepodoxime and/or ceftriaxone and/or cefixime)	All n=54	
Clinical characteristics						
Median age (range), y	51 (17-93)	50 (17-88)	50 (17-88)	56 (55-57)	59 (20-93)	
Women, n (%)	147 (63)	109 (61)	108 (61)	1 (50)	38 (70)	
Atopic background, n (%)	69 (29)	52 (29)	52 (29)	1 (50) (+CU)	14 (26)	
Positive skin tests to other allergens, n (%)	13 (6)	6 (3) ²	6 (3)	0	7 (13) ³	
Median time interval (range) between HS reaction and skin testing, months	5 (1-532)	5 (1-532)	5 (1-532)	48	11 (2-429)	
Anaphylaxis, n (%)	118 (50)	118 (66) ⁴	118 (66)	0	0	
Urticaria and/or angioedema, n (%)	52 (22)	47 (26)	45 (25)	2 (100)	5 (9)	
Rash n (%)	11 (5)	11 (6)	11 (6)	0	-	
Unknown Immediate HS, n (%)	4 (2)	4 (2)	4 (2)	0		
Cutaneous adverse drug reaction n=49 (21%)	AGEP	39 (17)	-	-	-	2 (4) ⁵
	DRESS		-	-	-	2 (4) ⁶
	MPE		-	-	-	30 (56)
	FDE		-	-	-	2 (4)
	Bullous drug reaction		-	-	-	1 (2) ⁷
	SDRIFE		-	-	-	1 (2)
	Eczematous drug reaction		-	-	-	1 (2)
Unknown Delayed HS	10 (4)	-	-	-	10 (19)	
Penicilline positive skin test results n (%)⁸						
AX	173 (74)	135 (75)	134 (75)	1 (50)	38 (70)	
AX-Clav	24 (10)	21 (11)	20 (11)	1 (50)	3(6)	
AX and AX-Clav	37 (16)	24 (13)	24 (13)	0	13 (24)	

2 AGEF: Acute Generalized Exanthematous Pustulosis, AX: Amoxicillin, AX-Clav:

3 Amoxicillin-Clavulanic acid; DRESS: Drug Reaction with Eosinophilia and Systemic

4 Symptoms, FDE: Fixed Drug Eruption, MPE: Maculopapular drug eruption, SDRIFE:
5 Symmetrical drug related intertriginous and flexural exanthema, 2GC: second generation
6 cephalosporins, 3GC: third generation cephalosporins

7 ¹ see detail in Repository Table E2; ²1 positive for fluoroquinolones, 3 for macrolides (+1 white
8 beans) 1 for cotrimoxazole, 1 for latex; ³4 positive for macrolides, 2 for cotrimoxazole, 1 for
9 fluoroquinolones; for extra information on skin tests procedures, see the Online repository and
10 repository table E4; ⁴33 patients with anaphylactic shock; ; ⁵ with positive penicillin patch test
11 for one and negative penicillin patch test with positive delayed reading intradermal skin test
12 (IDT) for the other; ⁶ with positive penicillin patch tests for both; ⁷ with negative penicillin patch
13 test and positive delayed reading intradermal skin test (IDT). ⁸patients were tested either with
14 AX or with AX-Clav, depending on the culprit penicillin; 16% tested for both AX and AX-
15 Clav were positive.