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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

To the Editor:

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

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

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

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

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

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

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

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

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

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

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

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

First limitations of our study are the retrospective character and the limited type of cephalosporins tested, belonging exclusively to group A cephalosporins, possibly underestimating allergic risk for other cephalosporins, especially identical side chain-aminocephalosporins. Second, lacking intravenous formulas for 2/4 cephalosporins (i.e cefpodoxime and cefixime) imposed testing by SPT only, possibly reducing sensitivity. Third, 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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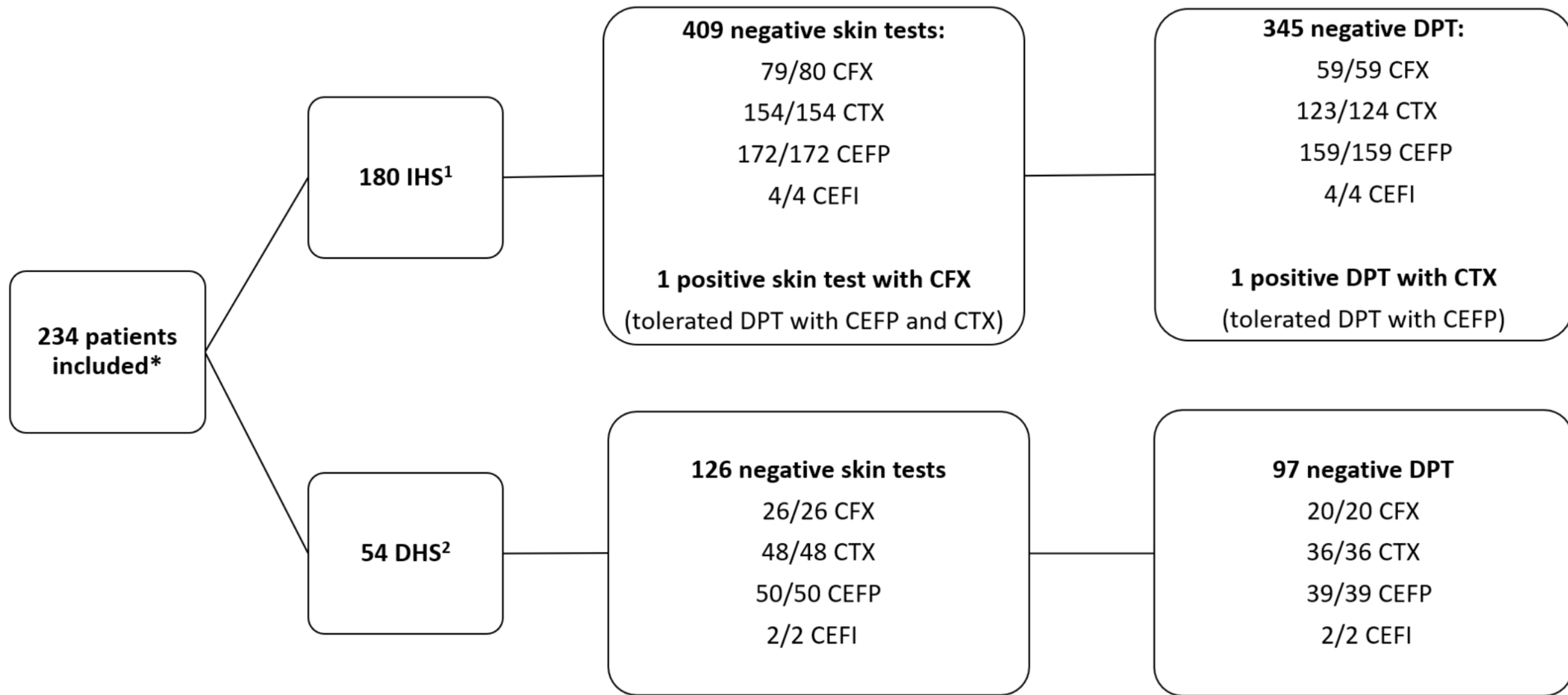
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**Title and legend for Figure 1**

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

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

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



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

		All n=234	<i>Immediate HS (N=180)</i>			<i>Delayed HS (N=54)</i>
			All n=180	Negative skin tests and challenge with 2GC and 3GC <sup>1</sup> (cefepodoxime and/or ceftriaxone and/or cefixime) n=178	Positive skin tests (n=1) and challenge (n=1) with 2GC and 3GC <sup>1</sup> (cefepodoxime and/or ceftriaxone and/or cefixime)	All n=54
<b>Clinical characteristics</b>						
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) <sup>2</sup>	6 (3)	0	7 (13) <sup>3</sup>
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) <sup>4</sup>	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) <sup>5</sup>
	DRESS		-	-	-	2 (4) <sup>6</sup>
	MPE		-	-	-	30 (56)
	FDE		-	-	-	2 (4)
	Bullous drug reaction		-	-	-	1 (2) <sup>7</sup>
	SDRIFE		-	-	-	1 (2)
	Eczematous drug reaction		-	-	-	1 (2)
	Unknown Delayed HS	10 (4)	-	-	-	10 (19)
<b>Penicilline positive skin test results n (%)<sup>8</sup></b>						
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 <sup>1</sup> see detail in Repository Table E2; <sup>2</sup>1 positive for fluoroquinolones, 3 for macrolides (+1 white  
8 beans) 1 for cotrimoxazole, 1 for latex; <sup>3</sup>4 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; <sup>4</sup>33 patients with anaphylactic shock; ; <sup>5</sup> 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; <sup>6</sup> with positive penicillin patch tests for both; <sup>7</sup> with negative penicillin patch  
13 test and positive delayed reading intradermal skin test (IDT). <sup>8</sup>patients 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.