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Non-irritant concentrations and performance of ceftaroline skin tests in patients with an immediate beta-lactam hypersensitivity.

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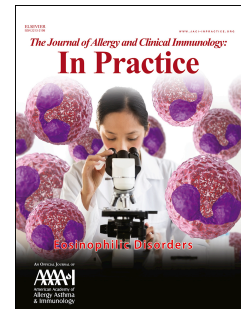
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34 Clinical implication box:

35 The non-irritant concentrations (NICs) of ceftaroline STs have not yet been established. This is the first
36 study to assess the NIC and cross-reactivity between ceftaroline and other beta-lactams.

37 We provide evidence for the NIC to be 2 mg/mL for immediate readings. For delayed readings, the NIC
38 can be set at 20 mg/mL, but the appropriateness of this approach needs to be proven. We question
39 the leaflet of ceftaroline that currently contraindicates its use in all patients with a penicillin,
40 cephalosporin, or carbapenem allergy.

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In a recent multicentric European survey cephalosporins were responsible for 10-40% of β -lactam hypersensitivity reactions.(1) Adverse reactions to ceftaroline, a broad-spectrum, 5th generation parenteral cephalosporin, have been reported in 10 - 20% of inpatients, a fifth of which were suspected hypersensitivity reactions. (2) Establishing the non-irritant concentrations (NICs) for STs is critical to ascertain the optimal balance of sensitivity and specificity, to improve antibiotic stewardship for the patient and to reduce the costs of our health systems. NICs of ceftaroline skin tests (STs) have not yet been established. This prospective study aims at establishing such NICs and the usefulness of ceftaroline STs to assess any cross-reactivity in patients with a documented IgE-mediated allergy to another beta-lactam.

Sixteen patients with STs (immediate readings) or challenge proven immediate beta-lactam hypersensitivity and 14 control individuals were included by trained physicians of the outpatients' clinic of Allergology of the Antwerp University Hospital between June 2020 and January 2021. The local ethics committee approved this study (B300201524055) and patients provided an informed consent in accordance with the declaration of Helsinki. In our hospital, it is standard practice to offer beta-lactam allergic patients subsequent testing for identification of cross-reactive and safe alternative molecules. All patients who chose to participate had additional ST titrations with ceftaroline fosamil. STs with ceftaroline (Zinforo®, GlaxoSmithKline, Middlesex, United Kingdom; neat solution 200 mg/mL) were performed as recommended for other cephalosporins and are described elsewhere.(3-5) Skin prick tests (SPTs) were considered positive when a wheal ≥ 3 mm surrounded by flare was observed. In immediate readings, results were considered positive when there was an increase larger than 3 mm in the initial wheal diameter, accompanied by an erythema ≥ 5 mm compared to the control one. Delayed readings were considered positive when an induration exceeding 5 mm, surrounded by an erythema, was observed. (4, 5) Patients with immediate allergy to (an)other beta-lactam(s) presenting negative or irritative STs (as established in healthy control individuals) underwent a graded intravenous drug challenge (DC) with ceftaroline. Detailed ST methods are described in the article's online repository. The DC protocol is shown in Table E1 in the article's online repository. In patients with positive DCs, and initially negative STs, STs were repeated after 4 weeks.

Patients' characteristics are shown in [Table 1](#).

[Figure 1](#) displays the ST data of all controls and patients with a proven immediate beta-lactam hypersensitivity. In the 14 controls, no wheal and flare were observed in immediate readings of skin prick tests (SPTs) or intradermal tests (IDTs) at concentrations up to 2 mg/mL. However, in 6/14 (42.9%) controls, a wheal and flare ≥ 5 mm was observed for IDTs at 20 mg/mL (1:10 dilution of neat solution). Hence, a concentration of 2 mg/mL was considered as the maximal NIC for immediate-reading of IDTs with ceftaroline. No delayed IDT reactivity was reported. In 6/16 patients with a proven immediate

beta-lactam allergy, a wheal and flare ≥ 5 mm was observed in immediate readings of IDTs with ceftaroline. Based on the findings in controls, IDTs were considered positive, and thus diagnostic, in 2 patients who presented a wheal and flare ≥ 5 mm at a concentration ≤ 2 mg/mL. According to the European guidelines(4, 6), these patients had no DC. In the other four patients, STs were assumed irritant, as wheals and flares were observed only in immediate readings of IDTs at 20 mg/mL. These patients had negative graded DCs. The remaining 10 patients with negative STs had DCs that resulted positive in two. For these patients, STs were repeated after four weeks to exclude negativization of ST results over time, a well-known phenomenon for beta-lactams(7, 8), but remained negative.

Cross-reactivity studies showed a positive ST or DC with ceftaroline in 4/16 patients (Table E2). The two patients with positive STs for ceftaroline (patients #4 and #5) had reacted to penicillin G. Patient #4 showed a positive ST to penicillin G and negative STs to the other tested cephalosporins and aztreonam. Patient #5 showed a positive ST to penicillin G and ceftriaxone and negative STs to cefazolin, cefuroxime, ceftazidime, and aztreonam. Besides, in patient #1 and #7, positive ceftaroline DCs were observed after negative STs. Patient #1, who reacted to amoxicillin (as indicated by a positive DC), showed negative STs and DCs to the other tested cephalosporins and aztreonam. Patient #7, showed positive STs to ceftriaxone, cefuroxime, cefotaxime, and aztreonam, but negative STs and DCs to cefazolin and ceftazidime.

This study provides evidence for the usefulness of STs to assess the cross-reactivity to ceftaroline in patients with a documented IgE-mediated allergy to other beta-lactams. According to the ceftaroline leaflet,(9) its use is systematically contraindicated in patients with penicillin, cephalosporin, or carbapenem allergy. However, the exact reason for this remains elusive.

In our population, the rate of positive STs to ceftaroline in patients allergic to other beta-lactams is relatively low. However, most of our patients had a sensitization against penicillins or the first-generation cephalosporin cefazolin. Further studies enrolling patients with a primary cephalosporin allergy to molecules with side-chains similar to ceftaroline are needed. Based on our data, only for patient #7 similarities in R1 seem to account for cross-reactivity. Specifically, cefuroxime, ceftriaxone, and cefotaxime share an identical branch chain moiety of the R1 structure with ceftaroline, whereas aztreonam and ceftaroline have a similar R1 structure.¹ Regarding the other patients, there were no structural similarities between the responsible beta-lactams and ceftaroline and the involvement of the β -lactam ring in sensitization was excluded on the basis of tolerance to other beta-lactams. Therefore, it seems more appropriate to consider the related patterns of allergy test positivity as a co-sensitization. Based on our findings, it is clear that cross-reactivity is unpredictable by fixed algorithms and that management of a patient with a penicillin allergy requires an individualized approach.

Because of the possibility of coexisting sensitivities to different beta-lactams, prophylactic STs with the beta-lactams concerned would be advisable before their administration via graded DCs to beta-lactam allergic patients needing alternative beta-lactams.

Our data shows that in case of negative STs, 85% of the patients tolerate ceftaroline during DC. Hence we do believe skin tests for ceftaroline are useful in predicting tolerance to this drug in patients with confirmed immediate hypersensitivity to other beta-lactams. Admittedly, calculation of the exact negative and positive predictive value of ceftaroline STs requires a larger population of patients with a history of possibly ceftaroline hypersensitivity who underwent confirmatory STs and, if needed, a DC. On the other hand, the strength of this study relates to its specific inclusion criteria and prospective design including graded DCs as a reference test for ST validation.

In conclusion, by using a titration method in unexposed healthy controls, we provide evidence for the NIC for ceftaroline to be 2 mg/mL for immediate readings. For delayed readings, the NIC can be set at 20 mg/mL. These findings of distinct NICs for immediate and delayed STs parallel our earlier observations with ceftazidime and aztreonam.(3)

This is the first study to assess the cross-reactivity between ceftaroline and other beta-lactams. We question the leaflet of ceftaroline that currently contra-indicates its use in all patients with a penicillin, cephalosporin, or carbapenem allergy and show that cross-reactivity is unpredictable by fixed algorithms and should be assessed by pretreatment STs.

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158 **Table and figure legends**159 **Table 1: patient characteristics and ceftaroline test results**

160 *Culprit (based upon positive skin test or positive drug challenge (DC); Y: year; F= female; M= male;
161 Diagnosis based upon suggestive history + positive skin test or positive DC;; AmX=amoxicillin;
162 AmC=amoxicillin-clavulanic acid; AZ = aztreonam; CFZ= cefazolin; CFT= cefotaxime; CF= ceftazidime;
163 CR= ceftriaxone; CU= cefuroxime; PG= penicillin G;
164 + = positive; - = negative; NP = not performed.
165 **Interval 360 days between index reaction and first skin testing; re-presentation after 10 years still
166 displayed positive penicillin G skin tests, followed by tests for cross-reactive molecules.
167 ° Diagnosis made after positive skin test for amoxicillin-clavulanic acid and negative skin test and
168 challenge for amoxicillin.

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170

171 **Figure 1: flowchart displaying skin test results in patients and control individuals**

172 β -LAB = Beta-Lactam antibiotic; IDT = intradermal tests; DC = drug challenge
173 *Of the 14 patients with negative skin tests, 4 displayed a wheal and flare at 20 mg/mL (considered
174 irritant). All these 4 patients had a negative DC

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Table E1 : protocol IV drug challenge ceftaroline

Preparation: dilute 600 mg powdered drug in 10 mL NaCl 0.9 % = start concentration: 12 mg/mL

Interval	Dose
0 min	12 mg
15 min	60 mg
30 min	180 mg
45 min	348 mg

Note: a drug challenge is performed in day-hospital of the allergology department, under direct supervision of a physician. Before the drug challenge starts and after it ends, each patient is examined by an allergist. Nurses remain at bedside at all times, with a minimum nurse:patient ratio of 1:2.

A drug challenge is considered positive only when objective symptoms can be observed. If symptoms occur, an allergist is attending. Nurses prepare an appropriate dose of epinephrine and antihistamines for the patients' body weight. These emergency medications are readily available at bedside. Emergency equipment is also available.

There is easy access to the Intensive Care Unit (< 1 minute) in case this is necessary.

Patients have to stay under observation for two hours after a negative drug challenge.

Table E2: Cross reactivity in patients with proven ceftaroline hypersensitivity

Pt No	Positive ceftaroline test	Skin testing with other β -LABs								DC with other β -LABs							
		PG	AmC	CFZ	CU	CR	CF	CFT	AZ	PG	AmC	CFZ	CU	CR	CF	CFT	AZ
1	DC ^o	-	- ^o	-	-	NP	-	NP	-	-	+	-	-	NP	-	NP	-
4	ST	+	NP	-	-	NP	-	NP	-	NP	NP	-	-	NP	-	NP	-
5	ST	+	NP	-	-	+	-	Ref	-	NP	NP	-	-	NP	-	Ref	-
7	DC ^o	NP	NP	-	+	+	-	+	+	NP	NP	-	NP	NP	-	NP	NP

β -LAB= Beta-Lactam antibiotic; ST= skin test; DC=drug challenge; PG= penicillin G; AmC= amoxicillin-clavulanic acid; CFZ= cefazolin; CU= cefuroxime; ; CR= ceftriaxone; CF= ceftazidime; CFT= cefotaxime; AZ = aztreonam; NP= not performed.

Note: if skin tests were positive, no DC was performed conform current guidelines.¹ In patient 7, no STs with PG and AmC were performed because of a history of tolerance; Ref=refused by patient

^oST repeated after challenge

Table 1: patient characteristics and ceftaroline test results

PT NO	AGE (Y)	SEX	INTERVAL INDEX REACTION – TESTING (DAYS)	INDEX REACTION	CULPRIT*	CROSS REACTIVE MOLECULES	SKIN TEST CEFTAROLINE (CONCENTRATION; WHEAL/FLARE)	DRUG CHALLENGE CEFTAROLINE
1	37	F	291	Anaphylaxis	AmX		-	+
2	63	M		Anaphylaxis	AmC		-	-
			52					
3	60	M	137	Anaphylaxis	AmX		-	-
4	14	M	64	Anaphylaxis	AmX	PG	+ IDT 2 mg/mL; 6/25	NP
5	60	F	360**	Urticaria Angioedema	PG	CR	+ SPT 0.2 mg/mL; 5/35	NP
6	52	F	152	Urticaria Angioedema	AmX		Irritant IDT 20 mg/mL; 10/30	-
7	42	F	157	Anaphylaxis	CR	CU, CFT, AZ	-	+
8	53	F	Unknown	Undefined rash	Clavulanic acid°		Irritant IDT 20 mg/mL; 5/0	-
9	30	F	29	Anaphylaxis	CU		-	-
10	32	M	214	Urticaria Angioedema	CR		Irritant IDT 20 mg/mL; 5/0	-
11	45	F	40	Anaphylaxis	CFZ		-	-
12	66	F	43	Anaphylaxis	CFZ		Irritant IDT 20 mg/mL; 8/29	-
13	52	F	18	Anaphylaxis	CFZ		-	-
14	73	M	189	Anaphylaxis	CFZ		-	-
15	63	F	41	Anaphylaxis	CFZ		-	-
16	56	F	Not available	Urticaria Angioedema	CFZ		Irritant IDT 20 mg/mL; 8/0	-

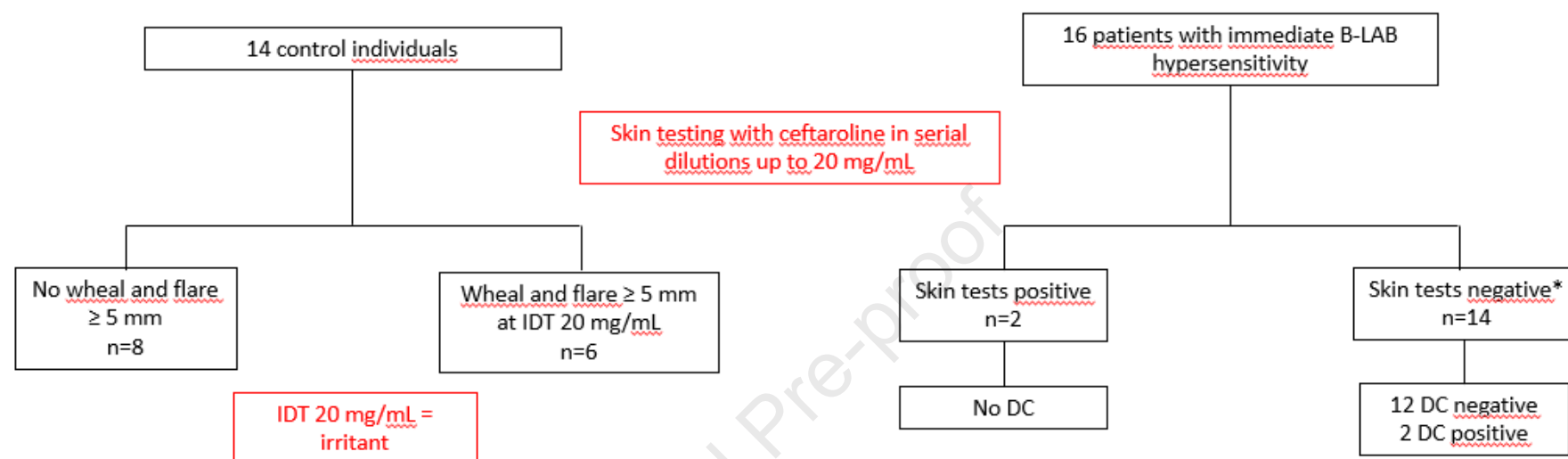
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+ = positive; - = negative; NP = not performed.

**Interval 360 days between index reaction and first skin testing; re-presentation after 10 years still displayed positive penicillin G skin tests, followed by tests for cross-reactive molecules.

° Diagnosis made after positive skin test for amoxicillin-clavulanic acid and negative skin test and challenge for amoxicillin.

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Figure 1



β -LAB = Beta-Lactam antibiotic; IDT = intradermal tests; DC = drug challenge

*Of the 14 patients with negative skin tests, 4 displayed a wheal and flare at 20 mg/mL (considered irritant). All these 4 patients had a negative DC