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Nonirritating skin test concentrations for ceftazidime and aztreonam in patients with a documented beta-lactam allergy

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Clinical Implications

- Our study shows that the maximal nonirritant concentration (NIC) for ceftazidime and for aztreonam is as high as 20 mg/mL for immediate readings of intradermal skin tests (IDTs). For delayed readings of IDT, the NIC is even a 10-fold higher, that is, 200 mg/mL.

Beta-lactam antibiotics (β-LABs) are a predominant cause of immediate and nonimmediate drug hypersensitivity reactions (henceforth designated as IDHRs and NIDHRs). At present, skin tests (STs) with immediate and delayed readings occupy the first place to document such IDHRs and NIDHRs. Therefore, optimizing nonirritant concentrations (NICs) is critical to ascertain the best balance of sensitivity and specificity. Avoiding under- and overdiagnosis should not only improve antibiotic stewardship at the level of the individual patient, but also reduce the costs of our health systems.[1]

This study aims at assessing the NIC for ceftazidime, a third-generation cephalosporin, and aztreonam, a synthetic monobactam, both potentially safe alternative β-LABs in patients with a documented hypersensitivity reaction to penicillin G, amoxicillin (±clavulanic acid), or cefazolin.

For this purpose, we set up a prospective study. All patients were included by trained physicians via the outpatients' clinic of allergology of the Antwerp University Hospital between 2018 and 2020. The local ethics committee approved this study (B300201524055), and patients provided informed consent in accordance with the Declaration of Helsinki.

All patients with an IDHR or NIDHR to penicillin G or amoxicillin (±clavulanic acid) or an IDHR to cefazolin, which was confirmed in our clinic between 2018 and 2020, were systematically offered to participate in this study. Diagnosis of their penicillin G, amoxicillin (±clavulanic acid), or cefazolin hypersensitivity was based on a history complemented by positive STs (immediate and delayed readings), drug-reactive sIgE antibodies, an sIgE-to-tIgE ratio ≥0.002, or a graded drug challenge (DC).[2]

In our hospital, it is standard practice to offer all patients with a beta-lactam allergy subsequent testing for the identification of cross-reactive and safe alternative molecules. All patients who were tested chose to participate, and hence also had additional ST titrations with ceftazidime and aztreonam. Skin testing included skin prick tests (SPTs) and intradermal tests (IDTs) with immediate and delayed readings after 15 minutes and 48 hours, respectively. A 0.9% NaCl solution and histamine (10 mg/mL) were used as negative and positive control. The drugs were diluted in 0.9% NaCl not more than 2 hours before use. For SPTs, a 1-mm lancet (HAL Allergy, Leiden, the Netherlands) was passed through a drop of the drug or the control solution. SPTs were considered positive when a wheal ≥3 mm surrounded by flare was observed. IDTs were performed only when SPTs were negative. For IDTs, 0.02 mL of the reagent solution was injected on the volar side of the forearm, using a disposable 1 mL syringe. Immediate IDT readings were considered positive when the diameter of the wheal, accompanied by an erythema, was at least 3 mm greater than the injection bleb. Delayed IDT readings were considered positive when an induration exceeding 5 mm, surrounded by an erythema, was observed.[3-5] All patients with negative ST results at the recommended end concentration of 2 mg/mL[3] had additional STs with 20 and 200 mg/mL. Graded DCs (cumulative dose of 1 g) were performed irrespective of the outcome of STs with 20 or 200 mg/mL. The DC protocol is shown in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). Challenge tests were performed in our hospital, under direct supervision of a physician and nurses having immediate access to emergency medications and equipment. A DC was considered positive only when objective symptoms could be observed.

As shown in Figure 1, 31 patients with a documented IDHR or NIDHR to penicillin G, amoxicillin (±clavulanic acid), or cefazolin were eligible. Two patients had positive immediate ST readings for aztreonam or ceftazidime at a concentration ≤2 mg/mL. In these patients, the ST was considered diagnostic,[3] leaving 29 patients for further evaluation. Twenty-one of these patients had a complete workup for both aztreonam and ceftazidime, 4 patients were tested only for aztreonam, and another 4 patients only for ceftazidime. Table I shows the patients' characteristics, ST results, and DC outcomes. In 72.4% of our cases (21 of 29), an IDHR was diagnosed. Immediate ST readings were positive in 2, 10, and 5 patients for penicillin G, amoxicillin (±clavulanic acid), and cefazolin, respectively. Four patients displayed a positive sIgE result for 1 or more penicillin determinants. Delayed IDT readings for amoxicillin (±clavulanic acid) were positive in 6 patients. Two patients (patients 6 and 13) had negative serological and STs but experienced a nonimmediate maculopapular exanthema after a challenge with amoxicillin (±clavulanic acid).

As shown in Table I, immediate readings of IDTs for ceftazidime at 20 mg/mL—a 10-fold of the NIC recommended at the start of this study[3]—were negative in all 29 patients. Four of 26 patients demonstrated ST responsiveness at 200 mg/mL, a 100-fold of the recommended NIC. Immediate readings of IDTs for aztreonam at 20 mg/mL were negative in all 29 patients. In contrast, for 200 mg/mL, a positive IDT was observed in 19 of the 26 tested patients. No delayed IDT reactions were

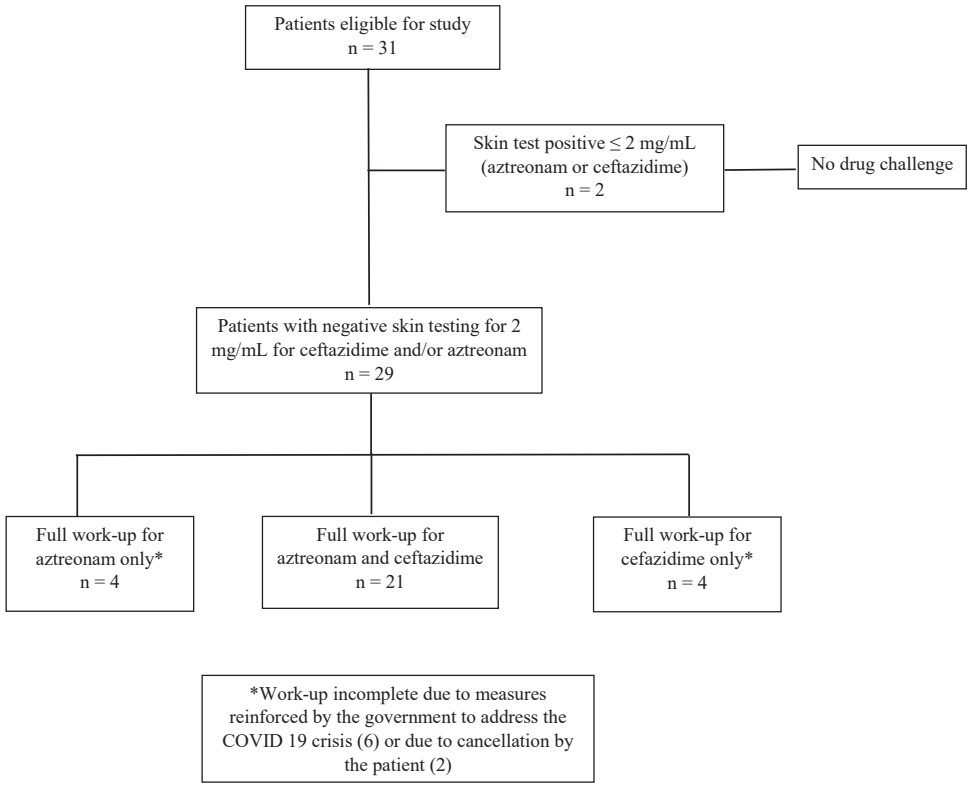

FIGURE 1. Composition of the study population.

observed. All DCs with ceftazidime and aztreonam were uneventful.

The novelty and robustness of this study relates to its inclusion criteria and prospective design including graded DCs in a large series of patients as reference test for validation of NICs. Unlike previous studies that have mainly explored NICs in (unexposed) healthy control individuals,[6,7] we studied NICs in 29 patients with a documented β-LAB hypersensitivity and therefore being at risk for potential cross-reactivity to other β-LABs. This is in line with clinical practice, where correct antibiotic stewardship in patients with a particular β-LAB hypersensitivity implies exploration of cross-reactivity and identification of safe alternatives for the future. Clinical practice does not require us to dichotomize between patients and asymptomatic control individuals.

Our results show that the NICs for ceftazidime and aztreonam, as recommended in the ENDA/EAACI Drug Allergy Interest Group position paper[3] and its update by Romano et al,[8] can further benefit from an assessment in patients who experienced an IDHR or NIDHR to penicillin G and amoxicillin (±clavulanic acid) or an IDHR to cefazolin. In such patients, we endorse the recently proposed NIC of 20 mg/mL for immediate ceftazidime IDTs.[8] For aztreonam, we show that the NIC for immediate IDT readings can be increased up to 20 mg/mL, without false-positives in our series.

At present, the same NICs are recommended for IDHRs and NIDHRs. However, this approach is rather empirical and poorly substantiated. Exploring whether other NICs apply in NIDHRs is an interesting area of research and could improve diagnostic performance STs. Indeed, for intradermal testing for many drugs, the NIC of the sterile intravenous preparation of drug with readings after 15 to 30 minutes might not be similar to that which evokes a T-cell response after 6 to 24 hours.[9] Our results show that for aztreonam and ceftazidime, the NIC for delayed readings can be set at 200 mg/mL, a 10-fold higher than for the immediate readings.

Admittedly, increasing the NIC entails the risk of overdiagnosis. In this respect, a limitation of this study is the small number of included subjects. However, offering a DC as reference test certainly adds rigor to our results and increases confidence in our findings.

During the interpretation of our findings, one should keep in mind that, although STs are extensively used, there are different methods and criteria for positivity worldwide. To establish a positive IDT result, the increase in wheal can be compared with the negative control, with the positive control, or with the injection bleb.[4] Whether our NICs apply to these other protocols remains to be established.

Finally, we show that, although uncommon, cross-reactivity between (amino)penicillins and ceftazidime and aztreonam exists.

In conclusion, by performing DCs irrespective of ST outcomes with 20 and 200 mg/mL, we provide evidence for the NIC for ceftazidime and for aztreonam to be as high as 20 mg/mL for immediate readings. For delayed readings, the NIC can be increased up to 200 mg/mL. Although limited, the risk of

TABLE I. Patients' characteristics, skin test, and challenge results

			Index reactions*			Skin test ceftazidime†		Skin test aztreonam†		Drug challenge	
Patient	Age (y)	Sex (M/F)	Culprit drug	Type of reaction	Symptoms	20 mg/mL	200 mg/mL	20 mg/mL	200 mg/mL	Ceftazidime	Aztreonam
1	53	F	AmC	IDHR	Anaphylaxis	−	−	−	−	−	−
2	72	M	AmC	IDHR	Anaphylaxis	−	−	−	+	−	−
3	67	F	AmC	IDHR	Anaphylaxis	−	−	−	+	−	−
4	20	F	AmC	IDHR	Undefined rash	NP	NP	−	+	−	−
5	33	M	AmC	IDHR	Undefined rash, AO	−	+	−	−	−	−
6	68	F	AmC	NIDHR	Unknown	−	−	NP	NP	−	−
7	43	M	AmC	NIDHR	MPE	−	−	−	+	−	−
8	32	F	AmC	NIDHR	Undefined rash	NP	NP	−	+	−	−
9	31	F	AmC	NIDHR	Undefined rash	−	−	−	+	−	−
10	41	M	AmC	IDHR	Urticaria	−	−	−	+	−	−
11	30	F	AmC	NIDHR	MPE	−	−	−	−	−	−
12	33	F	AmC	NIDHR	Unknown	NP	NP	−	+	−	−
13	42	F	AmC	NIDHR	Undefined rash	−	−	−	+	−	−
14	76	F	AmC	NIDHR	Undefined rash	−	−	−	+	−	−
15	41	F	AmX	IDHR	Unknown	−	−	−	+	−	−
16	25	F	AmX	IDHR	Anaphylaxis	−	−	−	+	−	−
17	56	M	AmX	IDHR	Undefined rash	−	−	NP	NP	−	−
18	54	F	AmX	IDHR	Undefined rash, AO	−	−	−	−	−	−
19	46	F	AmX	IDHR	Undefined rash	−	−	−	+	−	−
20	57	F	AmX	IDHR	Unknown	−	−	NP	NP	−	−
21	38	F	AmX	IDHR	Undefined rash	−	−	−	+	−	−
22	37	F	AmX	IDHR	Unknown	−	−	−	−	−	−
23	62	F	CFZ	IDHR	Anaphylaxis	−	+	−	+	−	−
24	64	F	CFZ	IDHR	Anaphylaxis	−	+	−	+	−	−
25	68	F	CFZ	IDHR	Anaphylaxis	NP	NP	−	+	−	−
26	68	F	CFZ	IDHR	Undefined rash	−	−	−	−	−	−
27	47	F	CFZ	IDHR	Anaphylaxis	−	+	−	+	−	−
28	52	F	PG	IDHR	Vomiting, undefined rash	−	−	NP	NP	−	−
29	54	M	PG	IDHR	Undefined rash	−	−	−	+	−	−

+, positive; −, negative; *AmC*, amoxicillin clavulanic acid; *AmX*, amoxicillin; *AO*, angioedema; *CFZ*, cefazolin; *IDHR*, immediate drug hypersensitivity reaction; *MPE*, maculopapular exanthema; *NIDHR*, nonimmediate drug hypersensitivity reaction; *NP*, not performed; *PG*, penicillin G.
*Based on history complemented by positive skin test results (immediate and delayed readings), sIgE, an sIgE/tIgE ratio ≥0.002, or drug challenge (patients 6 and 13).
†Results refer to immediate readings. Delayed readings resulted negative in all patients.

cross-reactivity between (amino)penicillins and cefazolin and ceftazidime and aztreonam cannot be neglected.

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ONLINE REPOSITORY

TABLE E1. Protocols IV drug challenge aztreonam and ceftazidime

Interval (min)	Dose (mg)
Aztreonam	
Preparation: dilute 1 g of powdered drug in 50 mL NaCl 0.9% = start concentration: 20 mg/mL	
0	20
15	100
30	300
45	600
Ceftazidime	
Preparation: dilute 1 g of powdered drug in 50 mL NaCl 0.9% = start concentration: 20 mg/mL	
0	20
15	100
30	300
45	600

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 2 hours after a negative drug challenge.