

Systemic reactions during skin tests with β -lactams: A risk factor analysis

To the Editor:

The diagnosis of drug allergy is difficult but is helped by skin testing, which is validated for a few drugs only, such as β -lactams.¹ IgE-dependent β -lactam allergy is first assessed by skin tests—prick tests and then, if negative, intradermal tests.² If skin tests are negative, oral provocation tests may be necessary.^{2,3} Occasionally, some patients can have systemic side effects during skin tests.^{1,2,4} These reactions can occur in nonimmediate hypersensitivity to penicillins,⁵ but the majority have immediate hypersensitivity. The frequency of systemic reactions after β -lactam skin tests, ranging from generalized cutaneous reactions to anaphylactic shock, varies from 0.1% to 2% in tested patients.⁶⁻⁸ Although such tests have been used for decades, the exact risk factors have not been fully analyzed in the literature.

Between September 1996 and December 2004, we included all the patients who had consulted at our allergy clinic (University Hospital of Montpellier, France) with a clinical history suggestive of a β -lactam allergy. We excluded patients who had experienced severe life-threatening skin reactions or drug-induced autoimmune disease.

Skin tests were performed as previously described,² with the major and minor determinants of penicillin PPL (penicilloyl-polylysine) and MDM (minor determinant mixture) (AllergoPharma, Merck, Darmstadt, Germany), penicillin G, amoxicillin, ampicillin, and any other β -lactam suspected from the patient's history if the injectable form was available. Fifteen to 20 minutes after skin prick tests, a wheal larger than 3 mm accompanied by erythema with a negative response to the control saline was considered positive. For intradermal tests, reactions were considered positive when a change in the size of the initial wheal

of 3 mm greater in diameter associated with a flare was observed 20 to 30 minutes after testing with a negative control reagent. A late reading in patients with an unknown chronology or a nonimmediate reaction was made after 24 to 48 hours. Drug provocation tests with the suspected β -lactams were performed only when skin tests were negative and under strict hospital surveillance.³

Patients were not taking any antihistamines or any drugs that could have affected skin tests. Patients on β -blockers were asked to visit their cardiologist to stop the drug 2 days before skin testing. The patients were free of any infectious diseases and fever the day of the tests.

The full-strength concentrations of the β -lactams tested were as follows: 25,000 UI/mL for penicillin G; 25 mg/mL amoxicillin, ampicillin, and amoxicillin + clavulanic acid; 10 mg/mL for other β -lactams; 35 μ g/mL benzylpenicilloyl major determinant; and 1100 μ g/mL minor determinants (AllergoPharma). The test sequence was as follows: (1) prick tests (1/10 concentration and full strength) at intervals of 15 to 20 minutes, and (2) intradermal tests (1/100, 1/10, and full strength concentrations) at intervals of 20 to 30 minutes. The procedure was stopped when a positive skin test was found.

All the information pertinent to drug hypersensitivity was included using the standardized European Network of Drug Allergy (ENDA) questionnaire⁹ in a Drug Allergy and Hypersensitivity Database and using File Maker Pro (Filemaker, Santa Clara, Calif). The analysis was performed by SAS version 8.1 (SAS Inc, Cary, NC).

Qualitative variables such as sex, atopy (defined as at least 1 positive skin test to the common aeroallergens of Montpellier area), asthma, clinical reaction in the history, chronology (time between the last intake of β -lactam and the clinical reaction, separated in 4 classes: <1 hour, 1-6 hours, 6-12 hours, 12-24 hours, $\geq$ 24 hours), results of skin tests, and clinical reaction to skin tests are described in

TABLE I. Description of the patients with generalized reactions during positive skin tests*

Age	Sex	Type of reaction in clinical history	Chronology in clinical history	Reactive ST concentration	Positive ST	Type of reaction after ST	Delay after ST
51	M	A shock	<1 h	Prick (1/1)	PPL, Cfr	Anaphylaxis	<30 min
54	F	Anaphylaxis	<1 h	ID (1/10)	Amp, MDM, PPL, PG	A shock	<1 h
38	M	A shock	<1 h	Prick (1/1)	Amx, Amp	Anaphylaxis	<30 min
58	F	Anaphylaxis	<1 h	Prick (1/10)	Amx, Amp, MDM, PPL, PG, Cfr, Cftm, Cfrd, Cfur, Cfalo	A shock	<15 min
46	F	A shock	<1 h	ID (1/10)	Amx, Amp, Amx+clav, PG	A shock	<1 h
41	F	Urticaria	NA	ID (1/1)	Amx, Amp	G urticaria	14 h
58	F	Urticaria	12 h	ID (1/1)	PPL	G urticaria	<1.5 h
34	F	Anaphylaxis	<1 h	ID (1/1)	Amx	Anaphylaxis	<1.5 h
47	M	A shock	<1 h	Prick (1/10)	Amx, MDM, PG	Anaphylaxis	<15 min
32	F	Anaphylaxis	<1 h	ID (1/1)	Amx, PPL, MDM	A shock	<1.5 h
21	F	Anaphylaxis	<1 h	ID (1/10)	Amx, Amp, PPL, MDM, PG, Cfr	Anaphylaxis	<1 h
45	M	Anaphylaxis	<1 h	ID (1/1)	Amx	Anaphylaxis	<1.5 h
25	F	Macular eruption	NA	Prick (1/1)	Amx, Amp, PPL, PG	G urticaria	<30 min

Amx, Amoxicillin; Amp, ampicillin; A shock, anaphylactic shock; Cfalo, cefalotene; Cfrd, cefradine; Cftm, cefotaxime; Cfr, ceftriaxone; Cfur, cefuroxime; G urticaria, generalized urticaria; ID, intradermal test; MDM, minor determinant mixture; NA, not available; PG, penicillin G; PPL, penicilloyl polylysine; ST, skin tests.

*Chronology: time between last drug intake and clinical reaction; delay: time between the first prick test and reaction after ST.

TABLE II. Comparison between reactors (patients reacting systemically during positive skin tests) and nonreactors (patients who had positive skin test results without systemic reactions during skin tests)

	Reactors	Nonreactors	P*
N	13	135	
Mean age, y (25-75 percentiles)	45 (21-58)	40 (5-82)	.69
Male, %	31	33	1
Patients with asthma, %	15	26	.52
Atopic† subjects, %	31	44	.37
Delay between reaction and skin tests, mo	5.0	17.9	.17
Anaphylaxis in clinical history, %	69	35	.02
Chronology of less than 1 hour‡, %	91	43	.002

*Fisher exact or χ^2 tests for % and Wilcoxon test for other data.

†When at least 1 positive skin prick test to the common aeroallergens of our area was positive.

‡After last drug intake.

frequency (%) and compared with χ^2 or Fisher exact tests. Quantitative variables such as age, time delay (time from initial reactions to skin tests), and delay after skin tests are studied with medians and 25th to 75th percentiles and compared with the Mann-Whitney Wilcoxon test.

Over the past 8 years, we have performed 998 skin tests on patients with a suspected allergy to β -lactams. A total of 147 patients (14.7%) had positive skin tests; among them, 30 had positive prick tests. Thirteen patients (8.8%) showed a systemic reaction during these tests; among them, 5 reacted as early as the prick test step. Their initial clinical history included anaphylactic shock (4 patients), anaphylaxis without hypotension (6), generalized urticaria (2), and maculopapular exanthema (1). The skin test-induced reactions included anaphylactic shock (4 patients) and anaphylaxis (6 patients). The other 3 subjects had generalized urticaria (Table I). All reactions were successfully treated with 40 to 60 mg of prednisolone and 10 mg of an oral H_1 -antihistamine. In case of anaphylaxis, 0.25 μ g of intramuscular epinephrine was injected and repeated if necessary.

Reactors (13 patients reacting systemically during positive skin test) were compared with nonreactors (135 patients who had positive skin test without systemic reactions). We compared age, sex, the presence of asthma, atopy, clinical history of β -lactam allergy (type and chronology), and delay between reaction and skin test. Anaphylaxis in clinical history was more frequent in reactors (69%; $P = .02$, Fisher test) compared with nonreactors (35%). Chronology, defined as the delay between the last drug intake and the reaction, of less than 1 hour was also significantly more frequent in reactors (91%) compared with nonreactors (43%; $P = .002$; Table II).

In the literature, generalized reactions after β -lactam skin testing are rare, from 0.1% to 2% of all tested patients and from 0.7% to 9.4% of positive skin-tested patients.⁶⁻⁸ Our 13 patients with systemic reaction represent 1.3% of

all tested patients and 8.8% of patients with positive skin test result. Therefore, the frequency of generalized reactions is comparable to other published data.

Only 3 generalized reactions after prick tests to β -lactams have been reported since 1963.^{10,11} However, we observed in our study 5 systemic reactions after positive prick tests (4 anaphylactic reactions, 1 generalized urticaria). Atopy was suspected to be a risk factor for severe allergic reactions.¹² In our study, the frequency of atopy was not significantly different between the 2 groups. In practice, patients with a history of anaphylaxis or anaphylactic shock are considered patients at risk during allergy tests. We confirmed that this was indeed a risk factor. Chronology of less than 1 hour was also a risk factor. It had never been searched in other studies.

Considering our results, some precautions during β -lactam skin testing should be taken to prevent these systemic reactions: ready-to-use emergency material, respect for contraindications (β -blockers), starting with low concentrations and gradually increasing, and strict supervision in the hospital during and after (1 hour minimum) skin testing, especially in these patients.

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Seasonal sensorineural hearing loss associated with allergic rhinitis: A case report

To the Editor:

The nasal cavity is anatomically connected to the middle ear by the eustachian tubes, and the middle ear mucosa can be considered an extension of the airways, at least in its inflammatory response.¹ Although mechanisms are not completely clarified, it is well known that inflammation occurring in the nose or paranasal sinuses can result in impairment of the ear function, and that respiratory allergy is a risk factor for otitis media with effusion.² In this sense, conductive hearing loss may complicate the most severe form of rhinosinusitis, mainly because of the eustachian tube involvement.^{3,4} Nevertheless, an effect of allergic rhinitis on the neural system of the ear, although possible in principle, has never been described. We report herein 1 case of documented sensorineural hearing loss provoked by allergic rhinitis in a young adult.

A 33-year-old man, hospitalized for sudden hearing loss, was referred in April 2004 for concomitant rhinoconjunctivitis. The main clinical problem reported on that occasion was the hearing loss with tinnitus. The first episode had occurred in April 1994, when the patient was hospitalized in an ear-nose-throat division because of the abrupt onset of hearing loss. At that time, the ear-nose-throat examination was normal except for a pale nasal mucosa with watery rhinorrhea. Audiometry documented a bilateral sensorineural hearing loss of about 30 dB, but tympanometry was completely normal. Systemic corticosteroids were given for about a week, and the symptoms rapidly remitted. A diagnosis of "sudden idiopathic hearing loss"⁵ was provisionally given. In September 1994, audiometry, tympanometry, and evoked acoustic potential were normal, and the brain computed tomography was negative as well. The same problem invariably relapsed in the subsequent years, always during the springtime, but with variable severity. In May 2000, the patient was hospitalized again because the symptoms (hearing loss and tinnitus) had become almost intolerable. Also on that occasion, no precise diagnosis could be established, and the allergic aspects of the patient were not further investigated. In April 2004, on the occasion of a new episode of troublesome hearing loss, the patient was referred to our unit for consultation. He was apparently well, and the general examination was

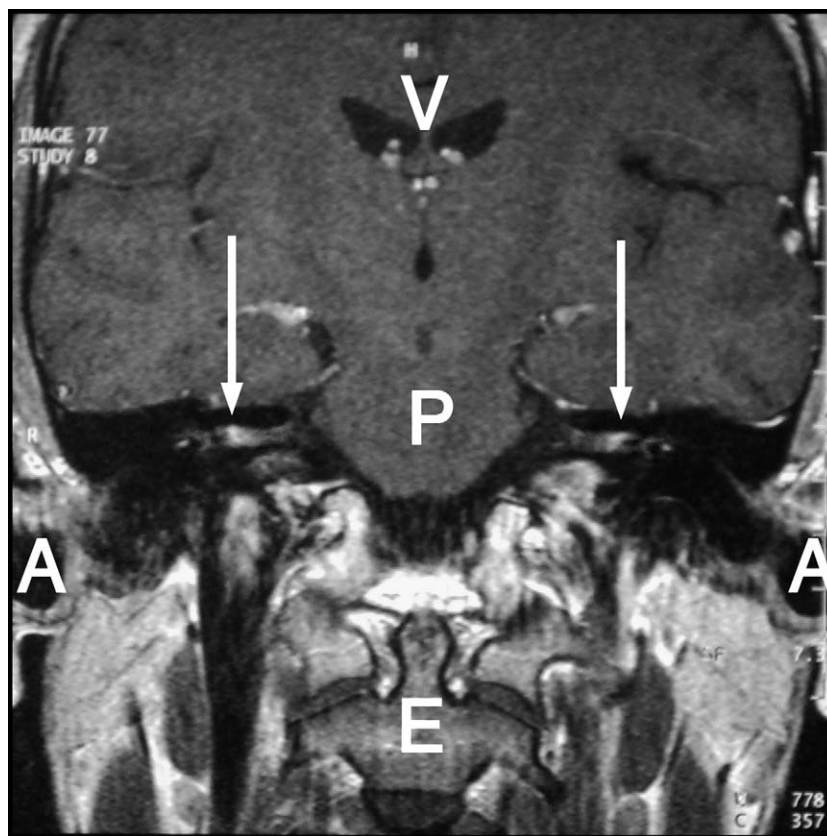


FIG 1. Magnetic resonance imaging of the brain (coronal view). The arrows indicate hyperintense signal of the acoustic nerves within the internal auditory canal. A, Acoustic meatus; E, epistropheus; P, pons; V, ventricula.