

Risk Assessment of Immediate Systemic Reactions from Skin Tests with β -Lactam Antibiotics

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Key Words

Anaphylaxis · Hypersensitivity · β -Lactams · Penicillin · Risk assessment · Skin tests

Abstract

Background: Some clinical studies have demonstrated that skin tests for β -lactam antibiotics may cause more adverse reactions than skin tests for common allergens. **Objective:** To assess the risk of systemic reactions from penicillin skin testing, based on a pre-test categorization of patients, in order to establish an appropriate strategy for preempting and dealing with cases. **Methods:** A case series of 175 patients with a suspected allergy to penicillin was reviewed, and patients were classified as having a low or high probability of allergic sensitization to penicillin, according to their clinical history. For every group, the rate and the increase in the relative risk (RRI) of systemic reactions by skin testing were calculated. The results were compared to those reported in the available literature. **Results:** In our case series of 175 patients, 52 were classified as having a high probability of being allergic to penicillin, according to their clinical history. Five systemic reactions to skin testing were observed, and these

were exclusively in this group (9.61%, RRI = 479). In agreement with the literature, patients with a high likelihood of penicillin allergy showed an increase of up to 10% in the occurrence of systemic reactions at skin testing; in patients who had had severe allergic reactions, this figure was up to 20%. **Conclusions:** The RRI of systemic reactions by skin testing is proportional to the pre-test probability of a true immediate hypersensitivity reaction to β -lactam antibiotics. In the present case series, only patients with high pre-test probability were at risk, and this group should therefore be skin tested and monitored in a hospitalization regimen, where resuscitation staff and access to an emergency room are immediately available.

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Introduction

Skin tests are unanimously recommended as the first-line approach to diagnosing allergic sensitization to penicillin and other β -lactams [1–4]. Several studies have consistently suggested that this practice carries a higher risk of systemic reactions, as compared to skin tests with

standardized common food- or aeroallergens. This is especially true for patients with a clinical history of generalized or severe adverse reactions [1, 5–10]. When performing skin tests for penicillin and other β -lactams, established safety procedures must be adopted, and ready access to emergency treatment should be available [1–3].

In Italy, most allergists perform skin tests only in day hospitals, since the Italian Society of Allergy and Clinical Immunology [11] recommends that skin tests with penicillin and its derivatives be carried out only in a hospitalization regimen.

Nonetheless, the magnitude of the risk is largely variable across studies [5–10, 12], and very severe reactions or death have only been reported anecdotally [13–18]. Thus, it seems that the routine hospitalization of patients who undergo skin tests for antibiotics is a result of authorities being overly precautionary, rather than a necessary safety or organizational requirement. Naturally, this has economic consequences in terms of resource allocation.

Based on these considerations, we carefully reviewed the available data in the literature, and studied a case series of patients with a clinical history of adverse reactions to β -lactams, in order to assess whether a reliable *ex ante* assessment of the clinical risk – and, as a consequence, a more appropriate level of organizational and logistic requirements – were feasible.

Methods

Case Series and Risk Assessment

Prior to skin testing, consecutive patients referred to our allergy unit because of a suspected allergic reaction to β -lactams were assigned to different groups according to their risk level. Patients with typical manifestations of delayed allergy [4] – such as maculopapular exanthema, fixed exanthema, erythema multiforme, Stevens-Johnson syndrome or DRESS (drug rash with eosinophilia and systemic symptoms) – were excluded. The main criterion to diagnose a true immediate hypersensitivity reaction (in all likelihood IgE-mediated) has been the time of onset of clinical manifestations after the drug intake, unrelated to severity. An onset time of <1 h was mandatory to include a patient into the subgroup with a high probability of having a positive skin test to penicillin.

The basic requirement for allocating patients in the high probability group was:

- systemic symptoms (accurately reported or diagnosed by physicians in an emergency room) with immediate onset (≤ 1 h): anaphylactic shock, generalized urticaria-angioedema, generalized pruritus with or without rash, and respiratory complaints.
- Other confirmatory anamnestic data were:
- increasing severity of symptoms with repeated doses and/or repeated courses of therapy;

- no other potential culprit drugs;
 - repeated episodes to the same antibiotic class.
- Criteria to include patients in the subgroup with a low probability of allergic sensitization to penicillin were either:
- subjective symptoms only (e.g. general malaise);
 - clinical manifestations with delayed onset (≥ 3 h, including mild or subjective cardiovascular and/or respiratory symptoms);
 - self-reported history of adverse reaction to penicillin or other β -lactams with vague, poorly documented symptoms;
 - gastroenteric symptoms with delayed onset (≥ 3 h), not followed by systemic manifestations.
- Other supporting data were:
- concomitant intake of other potential culprit drugs (especially NSAIDs);
 - clinical history of a previous tolerance of an antibiotic belonging to the same class.

Patients not allocable to these subgroups were classified as intermediate [19].

Since it was an observational study, no institutional review board approval was required, but a written informed consent was obtained anyway from all study participants.

Informed anamnestic data were collected by the drug hypersensitivity questionnaire of the European Network of Drug Allergy/European Academy of Allergology and Clinical Immunology (ENDA/EAACI) [20].

Skin Tests

Patients were skin tested according to ENDA/EAACI guidelines [3]. Briefly, skin tests were performed in all patients, using the major determinants of penicillin-polylysine, the minor determinant mixture (MDM) (Kit DAP; Diater Laboratories, Madrid, Spain), penicillin G, ampicillin, amoxicillin and any other suspected β -lactam, if available in injectable form. Skin tests were performed on the volar forearm at the recommended concentrations [2, 3]: 25,000 UI/ml for penicillin G; penicillin-polylysine 5×10^{-5} mmol/l; MDM 2×10^{-2} mmol/l; ampicillin and amoxicillin 20 mg/ml; 1–2 mg/ml for most cephalosporins.

Skin prick tests were carried out using a prick lancet with a 1-mm point, (Stallergen Italia, Milan, Italy). If negative, intradermal tests were performed with 0.02 ml of the solution using a tuberculin-type syringe. Tests were read and scored according to ENDA/EAACI guidelines [3].

In patients reporting previous severe reactions, skin tests were carried out starting with a 1,000-fold dilution, gradually increasing at logarithmic steps, until a positive response was elicited or the maximum concentration was reached.

The rates of positive skin tests and adverse events were carefully recorded in order to quantify the relative increase in the clinical risk (RRI). Signs and symptoms triggered by skin testing were defined as systemic or anaphylactic according to the revised nomenclature suggested by the World Allergy Organization [21, 22]. The results of the case series were compared with the data published in the literature.

Literature Analysis

The available literature (within Medline and Embase) concerning the prevalence of systemic reactions by skin testing with common respiratory and food allergens and β -lactams was searched by cross-referencing the keywords ‘skin test’, ‘penicillin’,

Table 1. Prevalence of systemic reactions in penicillin skin testing

	n	Positive skin tests	Systemic reactions	Fatality	ARI, %	RRI	NNH
Suspected allergy to penicillins	175	38 (21.71)	5 (2.86)	0	2.84	142	35
Vague history of allergic reactions	74	1 (1.35)	0	0	0	0	0
Doubtful history of allergic reactions	49	2 (4.08)	0	0	0	0	0
True history of allergic reactions	52	35 (67.31)	5 (9.61)	0	9.59	479	10

Figures in parentheses are percentages.

‘systemic reactions’ and ‘anaphylaxis’. Further searches were made starting from the references quoted in the screened articles. Only those studies reporting suitable information about the clinical aspects and epidemiological relevance of the adverse events were retained. Case reports were not considered.

The risk of systemic reactions by skin testing with penicillins, according to published data, was compared to the risk in allergic patients tested for common respiratory and food allergens [5, 23, 24]. When possible, the prevalence of general reactions was gauged separately for different groups of patients and sorted by different criteria of selection: (1) patients with no history of adverse reactions to penicillins or general population not screened; (2) patients with history of suspected adverse reactions to penicillin or other β -lactams; (3) patients with true allergic sensitization to penicillins proved by positive skin tests; (4) patients with history of anaphylaxis or severe systemic allergic reactions [21, 22] (group at higher risk of systemic reaction by skin testing) [3].

Statistical Analysis

The statistical significance of the observed differences among subgroups was computed by the Fisher’s exact test. To quantify risks of systemic reactions from skin testing, the following indices were calculated:

- *Absolute Risk Increase (ARI)*. The absolute arithmetic difference in the rate of adverse events between experimental and control patients, calculated as: experimental event rate – control event rate.
- *Relative Risk Increase (RRI)*. The proportional increase in rate of adverse events between experimental and control patients, calculated as: (experimental event rate – control event rate)/control event rate.
- *Number Needed to Harm (NNH)*. The number of patients who, when receiving the experimental treatment, would result in 1 additional patient being harmed (compared with controls). This was calculated as: 100/ARI.

Results

175 (116 females, age range 11–69 years, mean age 44 years) referred to our allergy unit for suspected hypersensitivity to penicillin were studied. According to the afore-

mentioned criteria, 74 of them were classified as having a low probability of positive skin tests, 52 as a high probability, and 49 were classified as intermediate. The skin tests were positive in 1.35% (1/74) of the low-probability group, in 4.08% (2/49) of the intermediate group, and in 67.31% (35/52) of the high-probability group (table 1). No local or systemic adverse reaction was seen in those patients with low or intermediate probability. In contrast, systemic reactions occurred in 5 patients (9.61%) in the high-probability group. All of them had clear-cut positive skin test reactions, the size of which were not related to severity of the systemic reaction (mean diameters: 6–9 mm). Four of these developed mild to moderate systemic reactions (3 urticaria with angioedema and 1 generalized itching with cutaneous rush), and 1 had an anaphylactic shock after the intradermal test with the MDM (table 2). The increase in the RRI of having a systemic reaction during the skin test in patients with a high-probability history was 479, with an expected systemic reaction every 10 patients tested. On the basis of these results, it can be deduced that the prevalence of sensitization proved by skin test positivity and, consequently, the risk of systemic reactions in the patients with a vague history and low probability of allergic sensitization to β -lactams is altogether similar to the risk of the patients with a negative history selected from the general population. In contrast, when an allergic sensitization is very likely and/or systemic reactions are reported, the risk of a systemic reaction from penicillin skin testing is remarkably high.

These results are in general agreement with the available literature, which is summarized in table 3. In particular, the rate of systemic reactions during the skin test with common allergens ranges between 0.02 and 0.002%, with higher values reported in older studies where intradermal skin tests were used [5, 23, 24]. Nonetheless, as skin tests with β -lactams usually include an intradermal test, we assumed a prevalence of 0.02% of systemic reac-

Table 2. Systemic reactions induced by skin testing with penicillin determinants

Patient	Culprit drug	Clinical reaction	Determinant	Dose	Skin test	Clinical presentation
1	amoxicillin	anaphylaxis	amoxicillin	20 mg/ml	prick	urticaria-angioedema
2	not mentioned	anaphylaxis	MDM	2×10^{-2} mmol/l	intradermal	systemic pruritus and shock
3	amoxicillin	urticaria-angioedema	amoxicillin	20 mg/ml	intradermal	urticaria-angioedema
4	amoxicillin	anaphylaxis	amoxicillin	2 mg/ml	prick	systemic pruritus and rash
5	amoxicillin	urticaria-angioedema	amoxicillin	20 mg/ml	intradermal	urticaria-angioedema

Table 3. Prevalence of systemic reactions by penicillin skin testing in different clinical-epidemiological studies

Author	Patient allergies	n	Syst. reactions	Fatality	ARI, %	RRI	NNH
Valyasevi et al. [5]	common allergens	15,189	3 (0.02)	0	0.02	–	5,000
Lin et al. [23]	common allergens	10,400	2 (0.02)	0	0.02	–	5,000
Liccardi et al. [24]	common allergens	55,105	1 (0.002)	0	0.002	–	50,000
Green et al. [7]	no history of penicillin allergy	1,229	0	0	0	0	0
	penicillin (anamnestic)	1,718	3 (0.02)	0	0	0	5,000
	penicillin skin test positive	412	3 (0.73)	0	0.71	35	141
Sullivan et al. [8]	penicillin (anamnestic)	740	4 (0.54)		0.52	26	192
	penicillin skin test positive	469	4 (0.85)		0.83	41	120
Sogn et al. [12]	no history of penicillin allergy	600	0	0	0	0	0
	penicillin (anamnestic)	825	0	0	0	0	0
	penicillin skin test positive	146	0	0	0	0	0
Gadde et al. [9]	no history of penicillin allergy	4,287	3 (0.07)		0.05	2.5	2,000
	penicillin (anamnestic)	776	9 (1.16)		1.14	57	88
	penicillin skin test positive	128	12 (9.37)		9.35	467	11
	penicillin, severe reactions	52	10 (18.2)		18.18	909	6
Valyasevi et al. [5]	penicillin (anamnestic)	1,383	1 (0.07)	0	0.05	2.5	2,000
Valyasevi and Van Dellen [6]	penicillin (anamnestic)	1,710	2 (0.12)	0	0.10	5	1,000
	penicillin skin test positive	86	2 (2.32)	0	2.30	43	115
Torres et al. [1]	penicillin skin test positive	290	32 (11.03)		11.01	550	10
Co Minh et al. [10]	penicillin (anamnestic)	998	13 (1.30)		1.28	64	78
	penicillin skin test positive	147	13 (8.84)		8.82	441	11

Figures in parentheses are percentages.

tions for common allergens to calculate the indexes for risk of adverse events (ARI, RRI and NNH). Concerning β -lactams, systemic reactions to the skin test were also observed in patients with a negative clinical history [9], at a frequency greater than in control subjects tested with common respiratory and food allergens, although the

difference was not significant (0.07%, $p = 0.125$). It is reasonable to assume that this reflects the presence in the general population of sensitized subjects with no history of allergy to β -lactam antibiotics.

The rate of systemic reactions is significantly higher in patients skin tested because of a positive history of an ad-

verse reaction to penicillin, irrespective of the severity, although there is a wide variability across studies (0.07–1.30%, $p < 0.0001$) [5, 6, 8–10].

When only the patients with positive results of penicillin skin tests were considered – as the systemic reactions are normally connected with positive skin tests – the risk of systemic reactions appears remarkably increased (2.32 to 11.03%) compared to patients sorted only by positive clinical history [1, 6, 9, 10].

The prevalence of systemic reactions is still higher in patients with positive skin tests and a history of anaphylaxis (18.20%), with 1 predicted adverse event per 6 patients skin tested [9].

Discussion

Skin tests are the first-line diagnostic method to assess *in vivo* IgE-mediated sensitization to inhalant/food allergens and drugs.

The diagnosis of hypersensitivity reactions to β -lactams antibiotics is based on the collection of a detailed history, skin testing and specific IgE dosing [2]. Skin tests, including intradermal tests, are well standardized [2, 3] and used worldwide to diagnose and study allergies to β -lactam antibiotics. Determination of specific IgE antibodies is in general less sensitive and more expensive [2].

On the whole, skin prick tests are considered a safe diagnostic procedure, and systemic reactions have been reported more frequently with intradermal testing [25]. Systemic reactions are usually mild to moderate in severity and can be controlled by following the recommended therapy in the international guidelines [26].

In the past, few fatalities have been reported – and most of these were associated with biological products no longer used – but a number of fatalities from penicillin skin testing are known to have occurred. At least 3 cases of death during the early development of penicillin skin testing [14, 27, 28] and 1 recent case due to a non-standardized intradermal test [18] have been recorded. Moreover, the existence of another 5 cases not reported in the literature has been highlighted [6, 15].

Of course, the recent case of death due to inappropriate use of skin testing [18] stresses the point that only well-trained allergists should manage the diagnostic work on drug hypersensitivity reactions, so that they can effectively prevent and treat possible systemic life-threatening reactions.

A large clinical-epidemiological study has suggested that the overall risk of inducing severe anaphylactic reac-

tions by skin testing with common allergens is about 0.02% [5]. The subsequent advances in the standardization of extracts and diagnostic methods have further reduced the rate of reactions with commercial standardized extracts to $<0.002\%$ [24], with latex or fresh food being the more likely to cause adverse events [29–32]. As far as penicillin is concerned, the rate of systemic reactions by skin tests is apparently higher than for common allergens. Some clinical-epidemiological studies have shown that when skin tests are performed in a large population with no history of allergic reactions to penicillin, positive responses are observed in 1.7% and systemic reactions in 0.07% of cases [9]. The RRI in those patients is therefore slightly higher than in patients sensitized to common allergens.

The prevalence of systemic reactions in patients skin tested because of a history of suspected allergy to penicillin or other β -lactams has been assessed in the literature with a variety of results (ranging from 0.02 to 1.3% of cases), which implies a RRI between 0 and 64 times, with an adverse reaction expected every 550 patients skin tested. It is likely that this variability depends on the different selection criteria for patients. However, in patients with a proved penicillin allergy, selected *ex post* by skin test positivity, the incidence of systemic reactions increases remarkably – up to 11.02 and 18.20% in patients with previous severe adverse reactions [1, 9]. The relative risk of systemic reactions increased from 50 to about 500 times, with an adverse event expected about every 10 patients skin tested for penicillin and β -lactams.

A set of recommendations and safety procedures to be adopted when performing tests – including a facility for continuous monitoring of each patient's condition – has been established. As a general rule, intravenous access and immediate availability of emergency treatment should be available, and it is recommended that skin tests are performed in a hospital setting [2, 3, 10, 11, 16, 33]. Allergists who deal with penicillin skin testing are aware of the risk of systemic reactions. Most allergists (at least in Italy) only perform skin tests with penicillin in a day hospital regimen [11], since the safety procedures suggested by some papers cannot be applied in an ambulatory setting [34, 35].

In the present study, a case series of patients was divided into 3 subgroups according to the probability of having an allergic IgE-mediated sensitization to β -lactam antibiotics. In patients identified as having a low probability of allergy reactions, there was no systemic reaction; thus, the risk of adverse events appears comparable to that of patients sensitized to common allergens

or of the population without a history of allergic reactions to penicillins. Therefore, it is reasonable to suppose that in such patients skin tests could be performed in an ambulatory setting, complying with the usual safety conditions required for such procedures.

Conversely, in patients with a high probability of having an allergic sensitization, adverse reactions occurred with a frequency that is equivalent to that reported in the literature for patients with true penicillin allergy, and diagnosed ex post by skin testing results. As such, the criteria we adopted to establish the high or low probability in our sample were reliable for screening the patients with true immediate hypersensitivity (very likely IgE-mediated) reactions to penicillin. For these patients, the risk of adverse systemic reactions by skin testing with penicillin and cephalosporin is particularly high, as compared to tests performed with common allergens.

Hence, it is necessary to perform the procedure in a highly controlled setting, like a day hospital, with continuous patient monitoring and immediate access to an emergency room.

As a general rule, the use of day hospitals for non-invasive diagnostic purposes is not appropriate, and the regulatory authorities nowadays require evidence when deciding how to best allocate such resources. The improper use of hospitalization leads to both a notable lengthening of waiting lists (depending on bed availability) and a remarkable increase in costs.

Although the data are preliminary, and require further confirmation in larger populations, the aforementioned criteria would allow a more appropriate allocation of resources – i.e. allocating the patients at lower risk to an ambulatory hospital setting – resulting in less organizational requirements and less costs.

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