Original Article

Oral Challenge without Skin Testing Safely Excludes Clinically Significant Delayed-Onset Penicillin Hypersensitivity

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What is already known about this topic? Penicillins are the drug family most commonly associated with hypersensitivity reactions. Current guidelines recommend negative skin tests before re-administering penicillins to patients with previous nonimmediate reactions.

What does this article add to our knowledge? In patients with a history of nonimmediate reactions to penicillin, we found no relationship between the appearances of late reactions to penicillin challenge and skin test results.

How does this study impact current management guidelines? A 5-day oral challenge without a preceding skin test is safe and sufficient to exclude penicillin allergy after nonimmediate reactions developing during penicillin treatment.

BACKGROUND: Penicillins are the drug family most commonly associated with hypersensitivity reactions. Current guidelines recommend negative skin tests (ST) before re-administering penicillins to patients with previous nonimmediate reactions (NIR).

OBJECTIVE: The objective of this study was to examine whether ST are necessary before re-administering penicillin to patients with NIR.

METHODS: Patients with NIR to penicillins starting longer than 1 hour after last dose administration or starting any time after the first treatment day or patients with vague recollection of their reaction underwent penicillin ST. Disregarding ST results, patients were challenged with the relevant penicillins. One-tenth of the therapeutic dose followed by the full dose was administered at 1-hour interval and patients continued taking the full dose for 5 days.

RESULTS: A total of 710 patients with alleged BL allergy were evaluated. Patients with a history of immediate reaction (52, 7.3%) or cephalosporin allergy (16, 2.2%) were excluded. Of the remaining 642 patients, 62.3% had negative ST, 5.3% positive ST, and 32.4% equivocal ST. A total of 617 (96.1%) patients were challenged. Immediate reaction was observed in 9 patients (1.5%): 1—positive ST, 7—negative ST, and 1—equivocal ST ($P = .7$). Late reaction to the first-day challenge occurred in 24 patients (4%). An at-home challenge was continued by 491 patients. Complete 5-day and partial challenges were well tolerated by 417 (85%) and 44 patients (8.9%), respectively, disregarding ST results. Thirty patients (6.1%) developed mild reactions to the home challenge regardless of their ST results.

CONCLUSION: A 5-day oral challenge without preceding ST is safe and sufficient to exclude penicillin allergy after NIR developing during penicillin treatment. **(J Allergy Clin Immunol Pract 2017;5:669-75)**

Key words: *Beta-lactams; Nonimmediate penicillin allergy; Drug hypersensitivity; Oral challenge*

The dilemma faced by any physician dealing with suspected drug reaction is whether the culprit drug can be re-administered safely. Guidelines for the evaluation of beta-lactam (BL) hypersensitivity reactions have been made by the European Network for Drug Allergy (ENDA).[1] However, these guidelines require 1 or 2 separate sessions of skin tests (ST) in the evaluation of immediate hypersensitivity reactions occurring within 1 hour after the last drug administration. In nonimmediate hypersensitivity reactions, occurring later than 1 hour after the last drug administration, the guidelines require 3 sessions, on separate days, each including ST, late reading of intradermal (ID) tests, and patch testing.[1,2] In both immediate and nonimmediate reactions, the gold standard procedure to determine acute BL tolerance is an oral challenge with a therapeutic BL dose and at least 1 hour of observation to rule out a clinically significant immediate reaction. Obviously, following these guidelines is costly and time consuming. A different approach was presented in a recent study by Mill et al[3] where a direct challenge without prior ST was performed on a large group of children with alleged

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Abbreviations used
BL- Beta-lactams
ENDA- European Network for Drug Allergy
ID- Intradermal
PPL- Penicilloyl-polylysine
ST- Skin tests

amoxicillin allergy. However, a substantial number of the children with a history of immediate reaction reacted to the challenge. The study did not include adults and is also subjected to the limitations of a retrospective work. The commercial penicillin skin-test reagent, penicilloyl-polylysine (PPL), was unavailable in the United States between 2004 and 2010. Consequently, an approach of using partial testing and if negative a divided dose challenge was suggested by different authors.[4] However, a direct challenge disregarding ST results is not a widely accepted practice. Practically, anaphylactic reaction is the major hazard in re-administering BL to a patient with suspected previous hypersensitivity reaction. On excluding rare rashes with potential life-threatening reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-related eosinophilia with systemic symptoms, or acute generalized eczematous pustulosis, all other nonimmediate reactions, although inconvenient, represent no real risk to the patient. Therefore, the ENDA guidelines that at the present time are one of the approaches for diagnosis and the European gold standard for diagnostic evaluation of BL nonimmediate hypersensitivity reactions might not be necessary in everyday life.

To address this question, we prospectively challenged patients with previous nonimmediate reaction to penicillin with the culprit drug followed by a 5-day full therapeutic course, disregarding the precise nature of the initial reaction or the ST results performed before the initiation of the challenge. We similarly evaluated patients with vague or completely no recollection of the hypersensitivity reaction.

METHODS

Patients and skin tests

From June 2011 to April 2015 all subjects referred for allergic evaluation of BL hypersensitivity underwent ID ST with PPL (0.04 mg/mL, 1:10 and 1:1), minor determinants mixture (0.5 mg/mL, 1:10 and 1:1) and amoxicillin (20 mg/mL, 1:10 and 1:1) (all produced by Diater, Madrid, Spain), and penicillin G 10,000 U/mL (Teva, Petach-Tikva, Israel). If the culprit BL was different, patients were also tested ID with the relevant drug: amoxicillin-clavulanic acid 20 mg/mL (Augmentin by GSK, Brentford, UK), cefuroxime 2 mg/mL (Zinnat by GSK), ceftriaxone 2.8 mg/mL (Rocephin by Hoffman-La Roche, Basel, Switzerland), and cefazolin 1 mg/mL (Kefazin by Vitamed, Binyamina, Israel). Histamine phosphate (Histatrol 2.75 mg/mL for ID ST and 0.275 mg/mL for prick ST, by ALK, Washington, NY) and phenol saline (ALK) served as positive and negative control, respectively.

Patients with a history of an immediate reaction starting within 1 hour after the last drug administration were first tested with prick ST. If negative, ID ST were performed, first with the lower concentrations and if negative, higher concentrations were performed. Prick ST was considered positive when the wheal largest diameter was $\geq$3mm of the negative control in the presence of flare. Intradermal ST was considered positive when the wheal largest diameter was $\geq$5 mm of the negative control in the presence of positive flare. Intradermal ST was considered equivocal when the wheal largest diameter was 3 to 4 mm greater than the negative control in the presence of flare.

All other patients—(1) patients with nonimmediate reaction starting longer than 1 hour after the last drug administration; (2) patients with a reaction starting any time after the first treatment day; and (3) patients with no recollection of the hypersensitivity reaction who, for the unknown reason, were "tagged" as penicillin allergic—underwent ID ST with all concentrations simultaneously, without preceding prick ST. In patients who had Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-related eosinophilia with systemic symptoms, or acute generalized eczematous pustulosis, ST were not performed and the patients were excluded from the study and advised to avoid BL.

Oral challenges

Patients who did not have an initial immediate hypersensitivity reaction were invited to participate in the study, regardless of the results of their ST. A challenge was performed with the culprit penicillin. In cases of no recollection of the initial adverse reaction to penicillin, the challenge was performed with amoxicillin. Challenges and ST were performed in the Allergy Unit where trained personnel as well as medications and equipment to treat anaphylactic reactions were present at all times.

According to their weight, patients were given one-tenth of their daily therapeutic dose divided by 2 or 3, according to the number of the daily doses usually administered for the challenged drug. For example, a child weighing 20 kg whose full daily dose of amoxicillin would have been 50 mg/kg $\times$ 20 kg = 1000 mg received 1/10 $\times$ 1000 mg/2 = 50 mg. One hour later, the patients were administered the full daily therapeutic dose divided by 2 or 3 (500 mg for that child) and were observed for 2 hours. Patients were then discharged and instructed to take on that night another full daily therapeutic dose divided by 2 or 3 and to continue taking the same dose, 2 or 3 times a day, for the next 4 days (ie, 500 mg of amoxicillin twice a day). Patients were instructed to stop taking the BL and call the allergy clinic should any adverse reaction develop. Five to seven days after their visit to the allergy clinic, patients were contacted by phone and interviewed about their reactions since the initial visit.

The study was approved by the ethics committee and registered in the National Institutes of Health clinical studies website (No. NCT01520181).

Statistical analysis

Results are expressed as frequencies and percentage, mean, and standard deviation, as appropriate. Differences between groups were analyzed by a χ^2 test for categorical data, a *t*-test for continuous normally distributed variables, and Mann-Whitney for nonnormally continuous parameters (for comparison between 2 groups). Differences among 3 groups were analyzed with the Kruskal-Wallis nonparametric test. P values $<.05$ were considered statistically significant.

Data were analyzed using SPSS-23 software (IBM, NY).

RESULTS

Patients

Seven hundred and ten patients with alleged beta-lactam hypersensitivity were screened (Figure 1). Fifty-two patients (7.3%) had histories of an immediate reaction to BL. Therefore, they were excluded from the oral challenge portion of the study.

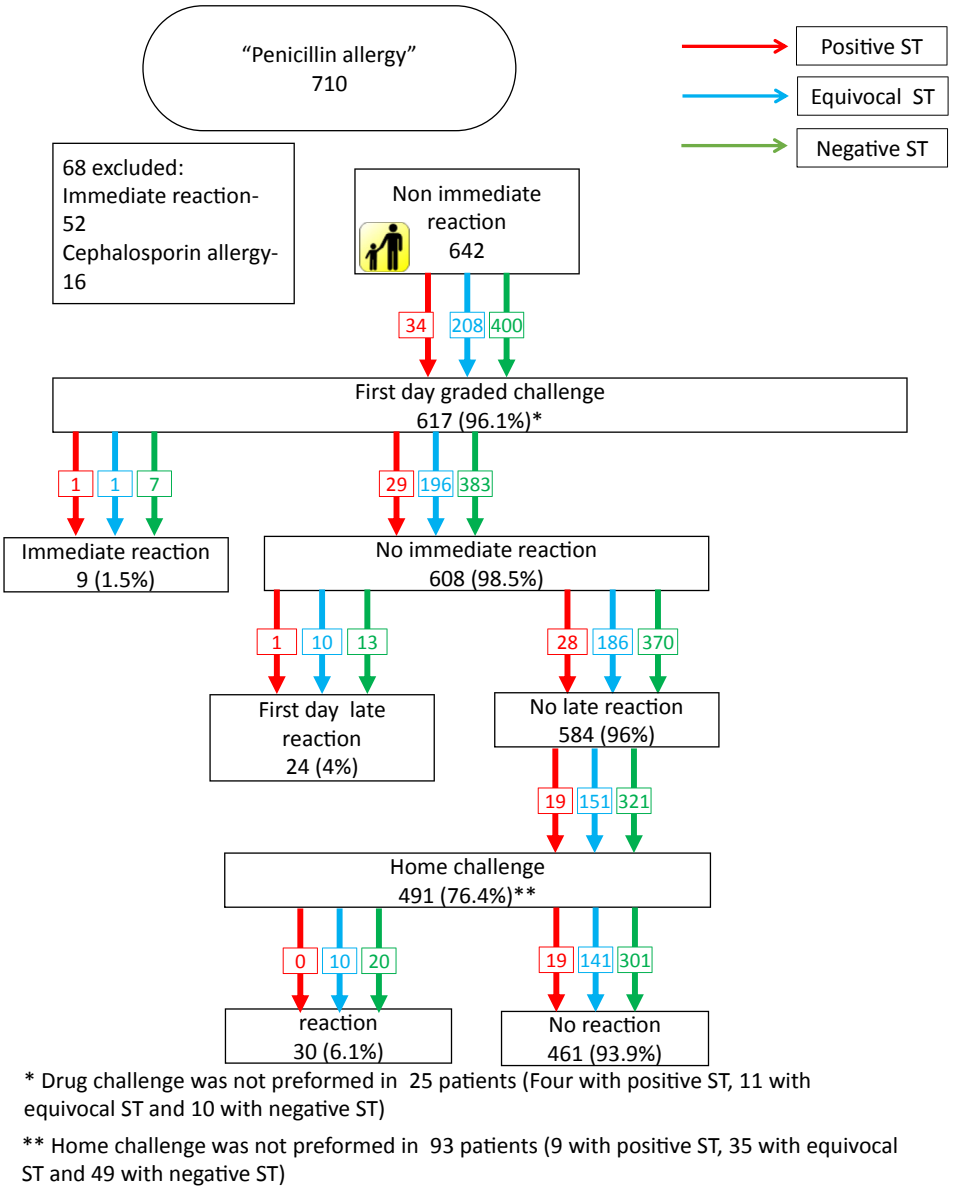

FIGURE 1. Study protocol, skin testing, and oral challenge. ST, Skin test.

Sixteen patients with cephalosporin hypersensitivity were prospectively identified. Because this group was too small to analyze, and because they are potentially different than the penicillin patients, they were excluded from the rest of the results. Six hundred and forty-two patients were eligible for the 5-day oral challenge. Their demographic and clinical data are presented in Table I. Their mean age was 19.9 years, and most of them, 435 (66.6%), were children younger than 18 years. The mean time elapsed from the alleged allergic reaction was 7.1 years (±12.4). The most common culprit penicillin among children was amoxicillin (83.2%) as compared with 31.9% in the adult group. Almost half of the adults (46.3%) could not recall which specific penicillin caused the hypersensitivity reaction. The most common symptom from the penicillin-associated reaction was rash (90%). A total of 31.5% of the patients had either partial or no recollection of the symptoms of the reaction. More than half (55.8%) of the patients could not specify whether the reaction was immediate or delayed and 28.2% did not know when the reaction began during the treatment course (Table I).

Skin tests

Patients underwent ST as described in the Methods section. Skin tests were all negative in 62.3% of the patients, 5.3% had positive ST to at least 1 reagent, and in 32.4% of the patients, the test was equivocal (Table II). As expected, patients with positive ST had a shorter elapsed time since the index reaction than the rest of the patients (10.8 ± 16.6, 19.8 ± 23.5, and 21.2 ± 23.7 months for positive, negative, and equivocal ST, respectively, $P = .05$). When the equivocal group was combined with the positive or the negative group, the new groups were composed of 400 and 242 or 608 and 34 patients, respectively. No systemic reactions were observed after ST even though prick

TABLE I. Demographics and clinical presentation

	All patients N (%)	Children (<18) N (%)	Adults (≥18) N (%)
	642	435 (66.6)	207 (33.4)
Age			
Mean	19.9 ± 23.2	5.2 ± 4.6	48.4 ± 18
Median (min-max)	8 (0.1-83)	4 (0.1-17)	48 (18-83)
Female	330 (51)	171 (39)	159 (77)
Time elapsed since the index reaction (y)			
Mean	7.1 ± 12.4	2.6 ± 4.8	16.5 ± 17
<0.5	192 (29.9)	146 (33.5)	46 (22.2)
0.5-1	111 (17.2)	98 (22.5)	13 (6.3)
1.1-3	86 (13.4)	77 (17.7)	8 (3.8)
3.1-10	96 (15.0)	73 (16.7)	23 (11.1)
>10	115 (17.9)	21 (4.8)	94 (45.4)
Unknown	43 (6.7)	20 (4.6)	23 (11.1)
Culprit drug			
Amoxicillin	428 (66.6)	362 (83.2)	66 (31.9)
Penicillin V	23 (35.8)	6 (1.3)	17 (8.2)
Amoxicillin-clavulanate	66 (10.3)	38 (8.7)	28 (13.5)
Unknown penicillin	125 (19.5)	29 (6.7)	96 (46.3)
Symptoms of the index reaction			
Rash	580 (90)	418 (96)	162 (78.2)
Pruritus	151 (23.5)	86 (19.7)	65 (31.4)
Dyspnea	23 (3.6)	10 (2.3)	13 (6.3)
Gastrointestinal	13 (2.0)	9 (2)	4 (2)
Angioedema	43 (6.7)	20 (4.6)	23 (11.1)
No recollection (complete or partial)	202 (31.5)	103 (23.6)	99 (47.8)
Time interval between the first dose and reaction			
≤24 h	140 (21.8)	101 (23.2)	39 (18.8)
>24 h	321 (50)	238 (54.7)	83 (40.1)
Unknown	181 (28.2)	96 (22)	85 (41)
Time interval between the last dose and reaction			
≤1 h	59 (9.2)	40 (9.2)	15 (7.2)
>1 h	223 (34.7)	175 (40.2)	48 (23.2)
Unknown	360 (55.8)	211 (48.5)	149 (72)

skin testing was omitted. Overall description of the various stages of the study is depicted in Figure 1.

Challenge

The first-day challenge was performed in 617 of 642 patients (96.1%): 91% with amoxicillin, 6% with amoxicillin-clavulanate, and 2.8% with penicillin V. Twenty-five patients (4%) refused oral challenge because of anxiety or refusal to consume antibiotics without an infectious disease. Immediate reactions to the first-day challenge (Table III) were observed in 9 patients (1.5%): 1 with a positive ST, 7 with negative ST, and 1 with equivocal ST ($P = .7$). None of the patients reacted to the low dose of the challenge. All immediate reactions were observed after the higher second dose. These reactions consisted of mild rashes. Three reactions resolved with antihistamines and 6 resolved spontaneously. Late reactions to the in-hospital challenge dose were observed in 24 patients (4.0%). No relationship was found between the appearance of late reactions to the first-day challenge and ST results ($P = .6$). All late reactions consisted of mild rashes and resolved without medical treatment.

Ninety-three of 584 patients (15.9%) who did not develop any reaction to the first-day challenge refused to continue penicillin intake at home after completion of the in-hospital first-day challenge. The complete 5-day challenge was well tolerated by 417 (85%) of the challenged patients not related to ST results ($P = .6$). The partial challenge (2-4 days) that was not completed because of various personal, nonallergic reasons was well tolerated by additional 44 patients (8.9%). Thirty patients (6.1%) had mild, non−life-threatening reactions (mild rashes or pruritus or abdominal discomfort) to the home challenge not related to their ST results ($P = .1$).

DISCUSSION

Beta-lactams are the most prescribed group of antibiotics, with somewhere between 3.6 g and 23 g per 1000 people per day prescribed in Europe.[5] Delayed skin rashes, mostly described as maculopapular or urticarial, are frequently reported in patients administered BL, especially in children. Such rashes are assumed to be a drug-related or viral infection-induced.[6] Most physicians, for fear of a future anaphylactic reaction, state to the patients

TABLE II. Clinical presentation and skin test results

	Total (%)	Negative ST No. (%)	Positive ST No. (%)	Equivocal ST No. (%)
	642	400 (62.3)	34 (5.3)	208 (32.4)
Time elapsed since the index reaction (y)				
Mean		19.8 ± 23.5	10.8 ± 16.6*	21.2 ± 23.7
<0.5	192 (29.9)	118 (29)	13 (38.2)	60 (28.8)
0.5-1	110 (17.1)	66 (16.5)	6 (17.6)	38 (18.2)
1.1-3	84 (13.1)	60 (15)	3 (8.8)	21 (10.1)
3.1-10	100 (15.6)	63 (15.7)	5 (14.7)	32 (15.4)
>10	117 (18.2)	73 (18.2)	3 (8.8)	41 (19.7)
Unknown	39 (6.1)	27 (6.7)	0	12 (5.8)
Culprit drug				
Amoxicillin	428 (66.6)	266 (66.5)	28 (82.3)	134 (63.5)
Penicillin V	23 (3.6)	11 (2.7)	0	12 (5.8)
Amoxicillin-clavulanate	66 (10.3)	42 (10.5)	3 (8.8)	21 (10.1)
Unknown penicillin	125 (19.5)	81 (20.2)	3 (8.8)	41 (19.7)
Time interval between the last dose and reaction				
≤1 h	59 (9.2)	43 (10.7)	3 (8.8)	13 (6.2)
>1 h	223 (34.7)	147 (36.8)	12 (35.3)	65 (31.2)
Unknown	360 (56)	217 (54.2)	18 (52.9)	132 (63.5)
Time interval between the first dose and reaction				
≤24 h	130 (20.2)	94 (23.5)	4 (11.8)	32 (15.4)
>24 h	418 (65.1)	248 (62)	26 (76.5)	144 (69.2)
Unknown	94 (14.6)	61 (15.2)	2 (5.9)	31 (14.9)

*$P = .05$.

TABLE III. Skin test and challenge results

	Total (%)	Negative ST No. (%)	Positive ST No. (%)	Equivocal ST No. (%)
	617	390 (63.2)	30 (4.9)	197 (31.9%)
Immediate reaction to challenge				
No	608 (98.5)	383 (98.2)	29 (96.7)	196 (99.5)
Yes	9 (1.5)	7 (1.8)	1 (3.3)	1 (0.5)
Late reaction to the first-day challenge	608	383	29	196
No	584 (96)	370 (96.6)	28 (96.6)	186 (94.9)
Yes	24 (4.0)	13 (3.4)	1 (3.4)	10 (5.1)
Reaction during days 2-5 of challenge	491	321	19	151
No	461 (93.9)	301 (93.8)	19 (100)	141 (93.4)
Yes	30 (6.1)	20 (6.2)	0	10 (6.6)

ST, Skin test.

that they are allergic to penicillin and ought to avoid BL in the future. Thus, the suspected diagnosis of penicillin allergy is "stuck" to the patient, who in subsequent years may lose recollection of the suspected allergic reaction. Consequently, these patients are frequently denied the optimal antibiotic treatment although the alternative antibiotics prescribed for them may be less effective, more expensive, and associated with more adverse effects.[7]

The rate of positive penicillin ST in patients with a history of penicillin allergy has declined over the years from >10% to ~5%.[8] In accordance with this, 5.3% of our patients had a positive ST to at least one of the tested antigens. On the other hand, the incidence of anaphylactic reactions after BL administration is very low (estimated to be 1:100,000)[9-11] and is specifically low on oral as compared with parenteral administration.[12] In addition, 75% to 86% of fatalities due to penicillin anaphylaxis occurred in patients without a history of allergic reaction.[9,13] Taken together, the incidence of anaphylactic reactions after oral administration of penicillin is expected to be very low even in patients with positive penicillin ST. Probably, this assumption is even more correct in patients whose initial adverse reaction was a nonimmediate one. Delayed reactions after re-administration of penicillin to patients with previous delayed reactions to these antibiotics have been described and seemed to be of minor clinical significance.[14-17]

Indeed, an algorithm constructed by Gruchalla and Pirmohamed[18] suggested that delayed appearance of mild maculopapular cutaneous eruption does not require skin testing and graded challenge with the antibiotic is the preferred option.

However, their suggestion is limited to maculopapular eruptions of mild severity only. On the other hand, based on the ENDA guidelines[1] penicillin re-administration has been recommended only to patients with NIR who had negative ST.

Therefore, we decided to prospectively explore the possibility of performing a simple oral challenge in patients with previous nonimmediate reactions, regardless of both the severity of the eruption and the ST results. Concomitantly, because various studies have used different criteria to define positivity of penicillin ST,[19-21] we also attempted to assess whether a certain method was better than the others. Nevertheless, setting the wheal diameter at either 3 or 5 mm in the presence of flare as the cutoff point for the definition of positive ID test did not change the challenge results. Of note, no systemic reactions were observed after ST even though prick skin testing was omitted.

Other than patients with immediate and nonimmediate reactions, there are an appreciable number of patients who have no first-hand recollection of the allergic response.[22,23] In the present study, 23.6% of the children and 47.8% of the adults had no recollection of the index reaction. Even in patients with positive history and positive ST, 33% (range, 0%-70%) had a vague history of penicillin allergy as shown in a meta-analysis of 30 studies.[24] Considering the prevalence of this clinical situation and the remote possibility of a life-threatening reaction becoming totally forgotten, we decided to include this group of patients as well. Indeed, the vast majority (98.4%) of challenged patients did not have immediate reaction to the challenge. Nine patients (1.6%), most of them with negative ST, developed mild rash. This rate is smaller than the risk in the general population, which is estimated to as high as 5%.[10,25,26]

All late reactions to the first-day challenge that were reported by 4% of the patients also consisted of mild rashes that resolved spontaneously and had no relationship to the ST results.

The current literature presents diverse challenge protocols: Macy et al[4] used a single-dose challenge. This approach is probably very convenient to the patients and excludes immediate reactions. Caubet et al[14] offered their patients first a divided dose and subsequent treatment for 48 hours. The current study aimed to evaluate nonimmediate reactions that mostly appear late in the course of treatment. Accordingly, we used a 5- day challenge protocol as a surrogate to the real life average treatment course.

One weakness of the study is the fact that 15.9% of the patients quit the study after the first-day challenge. This was probable a result of a lack of adequate information given to patients ahead of their scheduled appointment at the allergy clinic. Nevertheless, most of the patients who did not develop any reaction to the first-day challenge (84.1%) continued the challenge at home. Forty-four of the 491 patients (8.9%) stopped their penicillin before completing the full 5-day treatment course. In the minority of them, the reason for treatment discontinuation could be attributed to side effects to the administered penicillin (abdominal pain, nausea). In the rest, the reason was subjective personal and not associated with the drug administration. Overall 30 of 491 patients (6.1%) who continued the challenge had mild rashes during the at-home challenge, again with no relationship to ST results. None of the patients experienced a severe or a life-threatening reaction, and in all of them, the reaction was nothing more than an inconvenient episode.

The current study, performed prospectively on a large group of patients, substantiates the notion that NIR to penicillin are benign phenomena. A history of such a reaction should not be an obstacle to treatment with penicillin in the future. In this group of patients, the "penicillin allergy" tag can be safely removed with a challenge, skipping ST that, as we showed, have no predictive value regardless of the criteria used to assess positivity. The procedure should start with a short graded challenge under medical supervision and continue at home. This convenient protocol can be applied to children as well as adults. It proved to be safe regardless of the time elapsed since the alleged reaction or the culprit penicillin.

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