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ORIGINAL ARTICLE

Drug Allergy, Insect Sting Allergy, and Anaphylaxis

Resensitization in suspected penicillin allergy

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Abstract

Background: The diagnosis of allergic reactions to penicillins (AR-PEN) is very complex as there is a loss of sensitization over time, which leads to negative skin tests (STs) and specific IgE in serum, and even to tolerance to the drug involved. However, STs may become positive after subsequent exposure to the culprit drug (resensitization), with the risk of inducing potentially severe reactions. The exact rate of resensitization to penicillins is unknown, ranging from 0% to 27.9% in published studies.

Objectives: To analyze the rate of resensitization in patients with suggestive AR-PEN by repeating STs (retest) after an initial evaluation (IE).

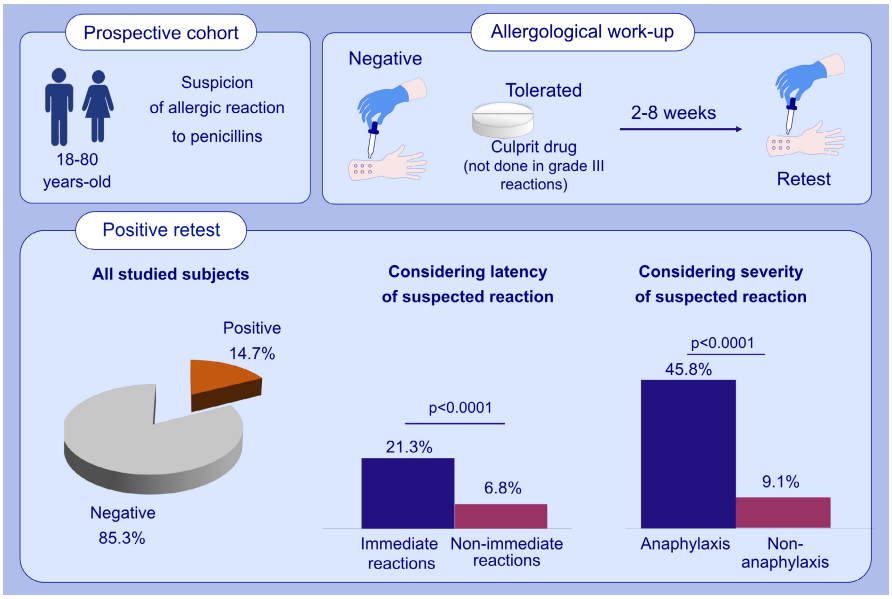
Material and Methods: Patients with suspected AR-PEN were prospectively evaluated between 2017 and 2020. They underwent STs, and a randomized group also underwent a drug provocation test (DPT) with the culprit. Only patients with negative STs and/or DPT were included. All included cases were retested by STs at 2–8 weeks.

Results: A total of 545 patients were included: 296 reporting immediate reactions (IRs) and 249 non-immediate reactions (NIRs). Eighty (14.7%) cases had positive results in retest (RT+): 63 (21.3%) IRs and 17 (6.8%) NIRs ($p < 0.0001$). The rate of RT+ was higher in anaphylaxis compared with all other reactions (45.8% vs 9.1%, $p < 0.0001$). The risk of RT+ was higher from the fifth week after IE (OR: 4.64, CI: 2.1–11.6; $p < 0.001$) and increased with the patient's age (OR: 1.02; CI: 1.01–1.04; $p = 0.009$).

Conclusions: Due to the high rate of resensitization, retest should be included in the diagnostic algorithm of IRs to penicillins after an initial negative study, especially in anaphylaxis, to avoid potentially severe reactions after subsequent prescriptions of these drugs.

KEYWORDS
anaphylaxis, drug provocation test, penicillins, resensitization, skin test, specific IgE

Inmaculada Doña, Lucia Guidolin, Patrizia Bonadonna and María José Torres equally contributed to this work.



GRAPHICAL ABSTRACT

We demonstrate that 14.7% of patients with a suspicion of allergic reactions to penicillins and negative allergological study has positive retest. The rate of resensitization has shown to be higher in immediate and severe reactions. Retest should be included in the diagnostic algorithm of allergic reactions to penicillins after an initial negative study before considering the patient as non-allergic.

1 | INTRODUCTION

Penicillins are the most common cause of drug-induced allergic reactions.[1,2] Penicillin allergy can be manifested as a variety of symptoms, ranging from reactions non-compatible with allergy and mild allergic symptoms (widespread erythema, urticaria, or periorbital edema) to severe anaphylaxis (circulatory failure, cardiac and/or respiratory arrest, and death).[2–4]

The approach for the diagnosis of reactions to penicillins is complex. As it has been proposed by the European Academy of Allergy and Clinical Immunology (EAACI), the first step includes a detailed clinical history. However, information provided by the patient is very often inaccurate, mainly when patients are referred after a long delay and when information about the nature of the symptoms and the suspected antibiotic is incomplete. Therefore, in vitro and skin tests (STs) are usually required, and, if negative, a drug provocation test (DPT) should be considered.[2]

Importantly, many patients who have a history compatible with penicillin allergy yield negative STs and even tolerate the suspected antibiotic in DPT.[5–8] Evidence suggests a loss of specific IgE (sIgE) to penicillins after avoiding the exposure to the drug that induced the allergic reaction[9] and become ST-negative.[10,11] sIgE to penicillin and/or to amoxicillin (AX) in serum was not detected in 50% of patients 3 years after the reactions, and in no patient after 4 years.[9] Concerning basophil activation test, in 60% of patients, negativization occurred after 18 months.[9] Regarding STs, it has been reported that up to 30% of patients with an IgE-mediated hypersensitivity to penicillins may become ST negative within 1 year, and more than 60% within 5 years.[10,11]

However, they can still become ST positive after subsequent exposure to the culprit drug. It has been reported subjects with a suspected allergy to penicillins and negative allergy tests, in which a conversion to ST positivity occurred when they were re-evaluated.[5–8,12] This phenomenon is defined as resensitization. This represents an important problem as patients may be misdiagnosed as non-allergic; thus, being exposed to a risk of suffering a potential severe reaction after subsequent intake of a penicillin.

The exact rate of resensitization to penicillins is not known and figures range widely among different studies, from 0% to 27.9%.[7,13–19] The variable resensitization rate reported in different studies can be attributed to disagreement methodology, relatively small sample sizes in most studies, and failure to perform STs to confirm resensitization in some of the patients who had a suspected adverse reaction after initial negative STs. Therefore, according to this evidence, there is no consensus about whether resensitization should be ruled out routinely or not. While several studies support that the resensitization phenomenon is rare,[13,16–18] others support the need for skin retesting after DPT in order to rule out resensitization.[2,6,20–22] Therefore, it is necessary to assess the need for skin retesting in patients who have a suspected allergy to penicillins and negative allergy tests and to agree on its inclusion after having completed the routine diagnostic workup.

The aim of our study was to determine the rate of resensitization in a group of patients with suggestive reported allergic reaction to penicillins, by repeating STs after an initial evaluation (IE). We also aimed to analyze the potential factors associated with resensitization phenomenon.

2 | METHODS

2.1 | Study design

We prospectively evaluated patients with a suspicion of allergic reactions to penicillins referred to the Allergy Unit of the Hospital Regional Universitario de Málaga (Málaga, Spain) and the Allergy Unit of the Azienda Ospedaliera Universitaria Integrata di Verona (Verona, Italy) between 2017 and 2020.

Reactions were classified into IRs or NIRs if they occurred less or more than 6 h after the drug intake. For IRs, the grading system for generalized allergic reactions of Ring and Messmer was used.[23]

Patients were assessed at two points in time: at an IE, and between 2 and 8 weeks later in a retest evaluation (RE).

In the IE, the allergological work-up[24] included an exhaustive clinical history according to the European Network on Drug Allergy questionnaire,[25] followed by STs. In a randomized group of patients with negative STs and reporting IRs grade I and II and NIRs DPT with the culprit drug was carried out. Only patients giving negative results in STs and/or DPTs were included in this study.

All patients were retested by performing STs at an RE (Figure 1).

The two participating centers followed the same protocol for testing patients throughout the study period.

Inclusion criteria: Patients, aged 14–80 years, with a suspicion of allergic reaction to penicillins and negative STs or DPT at IE.

Exclusion criteria: Patients with a positive STs and/or DPT to penicillins in the IE; patients <18 years and patients >80 years; pregnancy; underlying diseases that contraindicated STs and/or DPTs (uncontrolled pulmonary or cardiovascular diseases, severe atopic dermatitis, chronic urticaria); patients taking beta-blockers with impossibility of suspending them for allergological work-up; patients with psychosomatic disorders.[26]

2.1.1 | Skin test

Regarding IRs, skin prick test (SPT) and, if negative, intradermal test (IDT) were carried out as previously described.[24,26] The reagents were: benzylpenicilloyl-octa-L-lysine (BP-OL) (Diater, Madrid, Spain) at 0.04 mg/ml, equivalent to an $8.64{\cdot}10^{-5}$ molar (M) concentration of the benzylpenicilloyl (BPO) moiety; minor determinant (MD) (Diater, Madrid, Spain) at 0.5 mg/ml, equivalent to a concentration of $1.5{\cdot}10^{-3}$ M of sodium benzylpenilloate; amoxicillin (AX) (Diater, Madrid, Spain) at 20 mg/ml; clavulanic acid (CLV) (Diater laboratories, Madrid, Spain) at 20 mg/ml; and ampicillin (AMP) (Normon, Madrid, Spain) at 20 mg/ml.

Regarding NIRs, delayed reading-SPT and IDT were performed[26,27] using the same reagents as described for IRs. Readings were performed at 48 h.

2.1.2 | Drug provocation test

DPT with the culprit was performed in a single blind, placebo-controlled manner at incremental doses with a minimum 30-min interval between each, reaching the total cumulative dose. Patients were monitored during DPT procedures and for 2 h after the last dose. Complete equipment for cardiopulmonary resuscitation was immediately available.[24,27,28]

2.1.3 | Statistical analysis

Description of quantitative variable was performed including the median and interquartile range. Differences between qualitative variables were analyzed by Chi-square test (no-related samples). Comparisons between quantitative variables by Mann–Whitney U test (no-related samples). In order to establish the characteristics associated with resensitization, a logistic regression analysis was performed. The following variables were analyzed: sex, age, time interval between drug intake and onset of the reaction, symptoms manifested after administration of the penicillin, drugs involved, number of episodes, time interval between the drug reaction and the allergological work-up in the IE, time interval between the IE and the RE, and the tests performed in the IE (ST or DPT). All statistical analyses were carried out using the software package GRAPHPAD PRISM v7. A $p < 0.05$ value was considered statistically significant.

2.1.4 | Ethical issues

The study was conducted according to the principles of the Declaration of Helsinki and approved by the institutional review board (Malaga Provincial Research Ethics Committee) (PI18/00095). All the participants were informed about the study and gave the corresponding informed consent.

3 | RESULTS

3.1 | Demographic and clinical characteristics of patients included in the study

We evaluated a group of 914 patients reporting a clear suspicion of allergic reactions after a penicillin administration (Figure 1). From those, we excluded 369 patients: 304 because they were confirmed as allergic to penicillin in the IE as they had positive STs ($N = 252$) or DPTs ($N = 52$); and 65 because the allergological work-up could not be performed due to contraindications for STs and/or DPTs (28 had cardiac diseases, 18 had uncontrolled asthma, five were taking beta-blockers with impossibility of suspending them, seven had chronic urticaria, four were pregnant, two had psychosomatic disorders, and one had Steven–Johnson syndrome).

Finally, a total of 545 patients reporting a clear clinical history of allergic reactions to penicillins were included. From those, 368 (67.5%) were female, with a median age of 34 (interquartile range 18–50) years old at the reaction. A total of 112 (20.5%) had atopy, 31 (5.7%) had family history of drug allergy. A total of 296 (54.3%) cases reported IRs and 249 (45.7%) were NIRs.

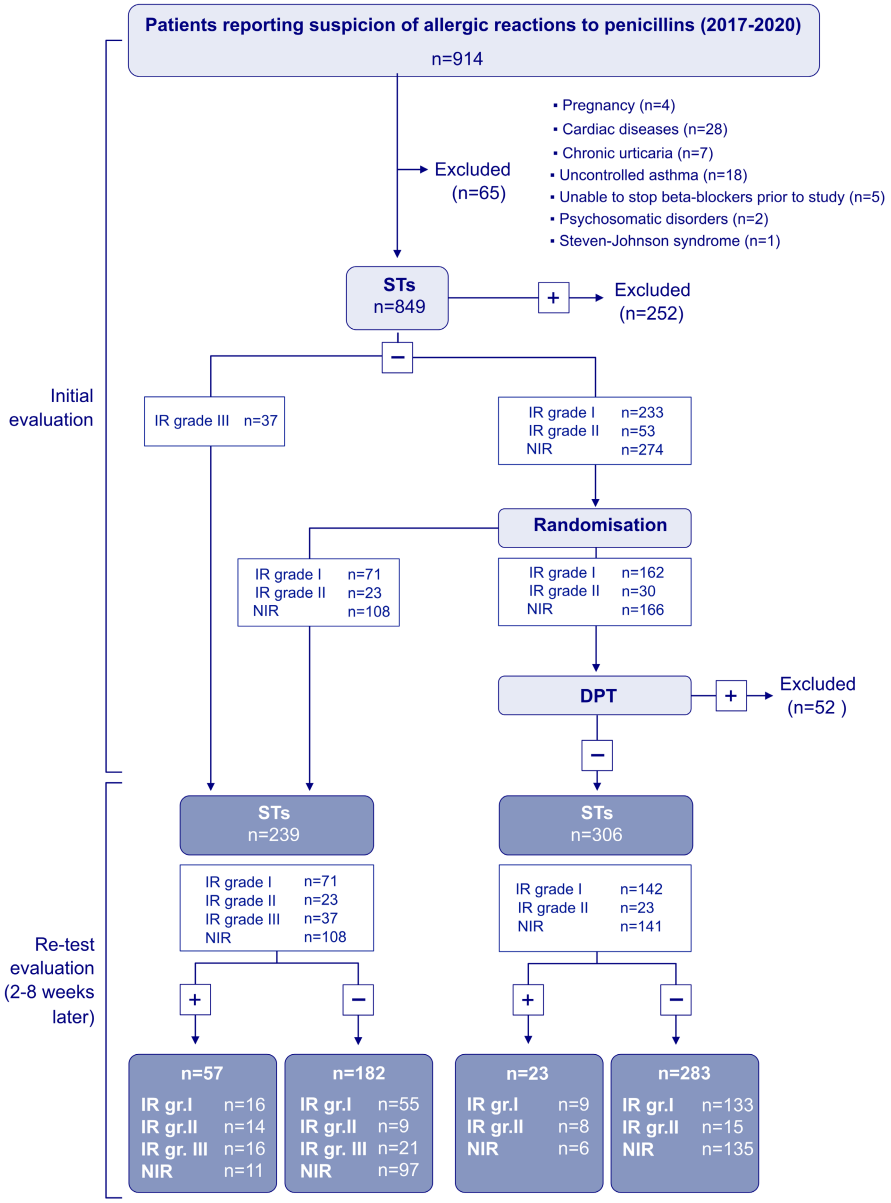


FIGURE 1 Flow chart of the patients evaluated in the study

Regarding the symptoms experienced after the penicillin intake, most patients reported urticaria/angioedema (332; 60.9%), followed by maculopapular exanthema (MPE) (91; 16.7%), anaphylaxis (83; 15.2%), isolated respiratory symptoms (10; 1.8%), and isolated gastrointestinal symptoms (2; 0.4%). The remaining 27 (4.9%) cases reported unspecific symptoms such as anxiety, isolated uneasiness, and paresthesia. Most IRs were grade I (213; 71.9), a total of 46 (15.5%) and 37 (12.5%) were grade II and grade III, respectively. No patient reported grade IV reactions.

Most reported reactions were induced by AX (308; 56.1%) and the combination AX-CLV (196; 36%), followed by penicillin (32; 5.9%), ampicillin (8; 1.5%), and piperacillin-tazobactam (1; 0.2%).

Most cases reported one reaction (507; 93%). A total of 33 (6%) subjects reported two episodes, and 5 (0.9%) reported three or more reactions.

The comparison of patients reporting IRs and NIRs showed no differences regarding age, gender, familiar history of drug allergy, and atopy. Patients reporting NIRs experienced a higher median of reactions ($p = 0.006$) and reported most frequently urticaria/angioedema and MPE compared to IRs ($p < 0.0001$). All patients manifesting anaphylaxis reported IRs. In addition, IRs induced by penicillin were more common than NIRs ($p = 0.004$) (Table 1).

3.2 | Initial evaluation

Patients were evaluated 24 (12–72) months after the last penicillin-induced reaction. All of them had negative STs. Patients reporting grade I and II IRs, and NIRs were randomized into two groups depending on whether DPT with the culprit penicillin was carried out ($N = 306$) or not ($N = 239$). All patients in whom DPT was performed tolerated the drug involved in the reaction.

Comparison of both groups of patients in which only STs were performed and those in which DPT with the culprit followed STs

TABLE 1 Demographic and clinical characteristics of patients included in the study

	Total *N* = 545	Immediate reactions *N* = 296	Non-immediate reactions *N* = 249	*p*
Age (median; IQR; years old)	34; 18–50	35; 19–50	33; 18–50	0.8223
Gender (*N*; % of females)	368; 67.5	199; 67.2	169; 67.9	0.8734
Familiar history of drug allergy (*N*; %)	31; 5.7	16; 5.4	15; 6.02	0.7561
Atopy (*N*; %)	112; 20.5	67; 22.6	45; 18.1	0.1891
N° of episodes (median; IQR)	1; 1–1	1; 1–1	1; 1–2	0.006171
Suspected drug (*N*; %)				
Penicillin	32; 5.9	26; 8.8	6; 2.4	0.004623
Amoxicillin	307; 56.3	160; 54	147; 59	
Amoxicillin-clavulanic acid	197; 36.2	103; 34.9	94; 37.7	
Ampicillin	8; 1.5	6; 2	2; 0.8	
Piperacillin-tazobactam	1; 0.2	1; 0.3	-	
Reported symptoms in reaction (*N*; %)				
Anaphylaxis	83; 15.2	83; 28	-	<2.2e-16
Urticaria/angioedema	332; 60.9	158; 53.4	174; 69.9	
MPE	91; 16.7	22; 7.4	69; 27.7	
Gastrointestinal symptoms	2; 0.4	1; 0.3	1; 0.4	
Respiratory	10; 1.8	9; 3	1: 0.4	
Others	27; 4.9	23; 7.8	4; 1.6	
Severity grade for immediate reactions				
I	213; 39.1	213; 71.9	-	NA
II	46; 8.4	46; 15.5	-	
III	37; 6.7	37; 12.5	-	
Time interval drug intake-reaction (median; IQR; minutes)	30; 10–210	30; 10–60	2880; 480–4320	NA
Time interval reaction–IE (median; IR; months)	24; 12–72	24; 12–72	24; 24–84	0.879
Tests performed at IE (*N*; %)				
Only STs	216; 41.4	131; 44.3	108; 43.4	0.836
DPT with the culprit	306; 58.6	165; 55.7	141; 56.6	
Time interval IE-RE (median; IQR; days)	34; 28–46	33; 28–44	35; 30–47	0.07595
Positive STs at RE (*N*; %)	80; 14.7	63; 21.3	17; 6.8	0.00000203
SPT	49; 61.2	36; 57.1	13; 76.5	0.1466
IDT	31; 38.7	27; 42.9	4; 23.5	
SPT to BP-OL	9; 1.7	7; 2.4	2; 0.8	0.187
SPT to MD	6; 1.1	4; 1.4	2; 0.8	0.6915
SPT to amoxicillin	39; 7.9	28; 10.8	11; 4.5	0.02561
SPT to clavulanic	3; 3.3	2; 2.8	1; 4.8	0.5449
SPT to ampicillin	3; 20	3; 25	-	1
IDT to BP-OL	3; 0.6	2; 0.7	1; 0.4	1
IDT to MD	1; 0.2	1; 0.4	-	1
IDT to amoxicillin	19; 4.6	15; 7.2	4; 1.7	0.1686
IDT to clavulanic acid	13; 14.4	13; 18.6	-	0.0372
IDT to ampicillin	6; 50	6; 54.5	-	1

Note: Comparison of patients reporting IRs and NIRs.

Abbreviations: BP-OL: Benzylpenicilloyl-octa-L-lysine. DPT: Drug provocation test. IDT: Intradermal test. IE: Initial evaluation. IQR: Interquartile range. MD: Minor determinant. MPE: Maculopapular exanthema. NA: Not applicable. RE: Re-test evaluation. SPT: Skin prick test. ST: Skin test.

showed no differences regarding age, gender, atopy, familiar history of drug allergy, number of experienced episodes, the percentage of IRs and NIRs, and time interval between reaction and the study in the IE. Regarding the symptoms reported after the penicillin intake, the percentage of patients reporting anaphylaxis was higher in the group in which only STs were performed at the IE, compared with the group in which DPT with the culprit was performed (25.1% vs. 7.5%; $p < 0.0001$) (Table 2).

Similar results are observed when patients reporting IRs and NIRs were analyzed separately (Table S1).

3.3 | Retest evaluation

Patients were retested by STs 34 (28–46) days after the IE, being positive in 80 (14.7%) cases: 63 (21.3%) IRs and 17 (6.8%) NIRs ($p < 0.0001$). Regarding IRs, 36 cases yield positive results in SPTs (27 to AX, 7 to BP-OL, 4 to MD, 3 to ampicillin, 2 to CLV, and 1 to cefuroxime), and 27 in IDT (14 to AX, 13 to CLV, 6 to ampicillin, 2 to BP-OL, and 1 to MD and to ceftriaxone, respectively). Regarding NIR, 11 cases yield positive results in SPTs (11 to AX, 2 to BP-OL, 2 to MD, and 1 to CLV) and 4 in IDT (4 to AX, and 1 to BP-OL).

Comparison of demographic and clinical characteristics of patients with positive (RT+) and negative (RT−) retests showed that the age in RT+ was higher than RT− ($p = 0.001$); reactions manifested as anaphylaxis were more frequent in RT+ while urticaria/angioedema, MPE and reactions manifested as non-specific symptoms were more frequent in RT− ($p < 0.0001$). The rate of RT+ in patients reporting penicillins-induced anaphylaxis was higher than in patients reporting symptoms other than anaphylaxis (45.8% vs 9.1%; $p < 0.0001$). The percentage of patients who underwent only STs in IE was higher in RT+ than in RT− ($p < 0.0001$) (Table 3). No differences were found when comparing the time interval between reaction and IE, nor the time interval between IE and RE in both RT+ and RT− (Table 3).

The logistic regression analysis showed that the risk of having RT+ was higher if only STs were performed at IE (OR: 4.45; CI: 2.22–9.41; $p < 0.001$) and increased with the patient's age at the time of reaction (OR: 1.02; CI: 1.01–1.04; $p = 0.009$). It was also observed that the likelihood of having RT+ increased in patients from the fifth week after IE (OR: 4.64, CI: 2.07–11.6; $p < 0.001$). On the contrary, the risk was lower when the reported penicillin-induced reactions were urticaria/angioedema (OR: 0.16, CI: 0.08–0.34; $p < 0.001$), MPE (OR: 0.11; CI: 0.03–0.39; $p < 0.001$), and non-specific symptoms (OR: 0.11; CI: 0.02–0.5; $p = 0.01$).

Similar results were found when comparing RT+ and RT− in IRs (Table 4). Furthermore, RT+ rate was higher in severe IRs compared with milder IRs (Grade III: 43.2%; Grade II: 47.8%; Grade I: 11.7%; $p < 0.0001$). Logistic regression analysis performed in patients with IRs showed that the probability of having a RT+ increased in patients from the fifth week after IE (OR: 4.19, CI: 1.73–11.3; $p = 0.003$). Furthermore, the risk of having a RT+ was higher in the group of patients in whom only STs were performed at IE (OR: 3.2; CI: 1.46–7.29; $p = 0.004$) and increased in association with increasing patient age at the time of reaction (OR: 1.02; CI: 1.01–1.04; $p = 0.032$). On the contrary, the risk for having RT+ was lower when the reported penicillin-induced reaction was urticaria/angioedema (OR: 0.23, CI: 0.1–0.51; $p < 0.001$), and other non-specific symptoms (OR: 0.07; CI: 0–0.38; $p = 0.013$).

Regarding NIRs, no differences were found when comparing demographic and clinical characteristics of RT+ and RT− patients (Table 4). Logistic regression analysis performed in patients with NIRs showed that the risk of having a RT+ was higher if only STs were performed at IE (OR: 19.5; CI: 3.26–3.78; $p = 0.007$), and increased with the patient's age at the time of reaction (OR: 1.04; CI: 1–1.09; $p = 0.036$) and with the number of episodes presented (OR: 11.2; CI: 1.72–83.7; $p = 0.011$). As with IRs, the likelihood of having RT+ also increased in patients from the fifth week after IE (OR: 17, CI: 1.83–537; $p = 0.042$).

4 | DISCUSSION

In this study, we aimed to analyze the resensitization phenomenon in patients attending our clinics because of a suspicion of penicillins allergy. We found a rate of resensitization of 14.7%. The reported rate of resensitization among published studies ranges widely: between 0% and 27.9%.[7,13–19] The variable resensitization rates reported among studies can be attributed to different factors. First of all, inclusion criteria for patients assessed. Studies including pediatric patients reported a lower rate of resensitization[8] compared with adults.[14,19] In our study, the median age of our patients was 34 (18–50) years old, detecting a rate of resensitization higher than those reported in studies including children.[8,29] The different rate of resensitization in pediatric and adult population may be explained by the fact that in children most skin eruptions occurring during penicillin treatment are likely to be caused by underlying viral infections, although they are clinically indistinguishable from allergic reactions.[30] This means that the majority of children will not react on subsequent exposures to the culprit drug. Additionally, there are findings that reported no resensitization in adult patients.[18]

Secondly, most published studies analyze IRs together with NIRs. In our study, we included a large sample of patients ($N = 545$) in which we analyzed separately IRs and NIRs, detecting that the rate of resensitization reached up to 21.3% in IRs, whereas in NIRs, this figure is much lower (6.8%). The higher rate of resensitization in IRs may be explained by the available evidence stating that in IRs the sensitivity tends to disappear over time if the culprit drug is avoided,[9] whereas NIRs it may be a long-lasting condition.[27]

In our study, almost 7% of NIRs showed RT+. It is important to take into account that the differentiation between IRs and NIRs is based on clinical history, being the cut-off value in the time interval between the drug intake and the onset of the reaction of 6 h.[31] However, the information obtained by the clinical history is often not reliable, and the latency for the reaction appearance may not reflect exactly the time elapsed. Moreover, the clinical manifestations in IRs and NIRs may be indistinguishable, being in some cases,

TABLE 2 Comparison of demographic and clinical characteristics of patients in which at the IE only STs were performed and those in which DPTs with the culprit were performed following negative STs

	Tests performed at IE		
	Only ST *N* = 239	ST and DPT *N* = 306	*p*
Age (median; IQR; years old)	35; 22–50	33; 16–50	0.07882
Gender (*N*; % of females)	160; 66.9	208; 68	0.7992
Atopy (*N*; %)	49; 20.5	63; 20.6	0.9396
N° of episodes (median; IR)	1; 1–2	1; 1–1	0.08553
Suspected drug (*N*; %)			
Penicillin	7; 2.9	25; 8.2	<2.2e-16
Amoxicillin	45; 18.8	262; 85.6	
Amoxicillin-clavulanic acid	184; 77	13; 4.2	
Ampicillin	3; 1.3	5; 1.6	
Piperacillin-tazobactam	-	1; 0.3	
Reported symptoms in reaction (*N*; %)			
Anaphylaxis	60; 25.1	23; 7.5	0.000001342
Urticaria/angioedema	128; 53.6	204; 66.7	
MPE	35; 14.6	56; 18.3	
Gastrointestinal symptoms	2; 0.8	-	
Respiratory	4; 1.7	6; 2	
Others	10; 4.2	17; 5.6	
Severity grade for immediate reactions			
I	71; 54.2	142; 86.1	3.233e-13
II	23; 17.5	23; 13.9	
III	37; 28.2	-	
Time interval drug intake-reaction; (median; IQR; minutes)	24;12–84	24; 12–60	0.7584
Immediate reactions (*N*; %)	131; 54.8	165; 53.9	0.836
Non-immediate reactions (*N*; %)	108; 45.2	141; 46.1	
Interval time reaction–IE (median; IQR; months)	24; 12–84	24; 12–60	0.7584
Interval time IE-RE (median; IQR; days)	32.5; 28–41	35; 30–52	0.001824
Positive STs at RE (*N*; %)			
SPT	30; 52.6	19; 82.6	0.01274
IDT	27; 47.4	4; 17.4	
SPT to BP-OL	4; 1.7	5; 1.6	0.9344
SPT to MD	1; 0.4	5; 1.6	0.1882
SPT to amoxicillin	26; 12.8	13; 4.3	0.002885
SPT to clavulanic acid	3; 5.5	-	0.2708
SPT to ampicillin	3; 42.9	-	0.07692
IDT to BP-OL	2; 0.9	1; 0.3	0.5809
IDT to MD	1; 0.4	-	0.4345
IDT to amoxicillin	15; 9.7	4; 1.4	0.001701
IDT to clavulanic acid	11; 20.8	2; 5.4	0.04154
IDT to ampicillin	5; 62.5	1; 25	0.5455

Abbreviations: BP-OL: Benzylpenicilloyl-octa-L-lysine. DPT: Drug provocation test. IDT: Intradermal test. IE: Initial evaluation. IQR: Interquartile range. MD: Minor determinant. MPE: Maculopapular exanthema. NA: Not applicable. RE: re-test evaluation. SPT: Skin prick test. ST: Skin test.

difficult to differentiate between IRs and NIRs. In our study, 13 cases who reported urticaria/angioedema or MPE 8 h after penicillin intake gave positive results in STs at RE. In addition, although IRs are known to be induced by an IgE-mediated response, there are some controversies for NIRs, especially for those occurring up to 24 h after drug intake.[32] In this group of cases, it has been reported that there seems to be an overlap between IgE-mediated and T-cell-mediated mechanisms.[33,34]

TABLE 3 Comparison of demographic and clinical characteristics of patients giving positive or negative results in the re-test

	RT+ *N* = 80	RT− *N* = 465	*p*
Age (median; IQR; years old)	41; 29.7–52.2	32.5; 17–49	0.001
Gender (*N*; % of females)	50; 62.5	318; 68.4	0.299
Familiar history of drug allergy (*N*; %)	4; 5	27; 5.8	0.7736
Atopy (*N*; %)	15; 18.8	97; 20.9	0.7652
N° of episodes (median; IR)	1; 1–2	1; 1–1	0.2839
Suspected drug (*N*; %)			
Penicillin	8; 10	24; 5.2	0.001218
Amoxicillin	30; 37.4	277; 59.6	
Amoxicillin-clavulanic acid	40; 50	157; 33.7	
Ampicillin	2; 2.5	6; 1.3	
Piperacillin-tazobactam	-	1; 0.2	
Reported symptoms in reaction (*N*; %)			
Anaphylaxis	38; 47.5	45; 9.7	1.028e-13
Urticaria/angioedema	30; 37.5	302; 64.9	
MPE	6; 7.5	85; 18.3	
Gastrointestinal symptoms	-	2; 0.4	
Respiratory	4; 5	6; 1.6	
Others	2; 2.5	25; 5.4	
Severity grade for immediate reactions			
I	25; 39.7	188; 80.1	0.000000002401
II	22; 34.9	26; 11.1	
III	16; 25.39	21; 9	
Interval drug intake-reaction (median; IQR; minutes)	37; 11.25–90	32.5; 17–49	0.5792
Immediate reactions	63; 78.8	233; 50.1	0.00000203
Non-immediate reactions	17; 21.2	232; 49.9	
Interval time reaction–IE (median; IQR; months)	36; 12–96	24; 12–48	0.07154
Tests performed at IE (*N*; %)			
Only STs	57; 71.2	182; 39.1	0.00000008977
DPT with the culprit	23; 28.7	283; 60.9	
Time interval IE-RE (median; IQR; days)	31.5; 30–42	35; 28.47	0.8427

Abbreviations: BP-OL: Benzylpenicilloyl-octa-L-lysine. DPT: Drug provocation test. IDT: Intradermal test. IQR: Interquartile range. MD: Minor determinant. MPE: Maculopapular exanthema. NA: Not applicable. RT+: Positive in re-test. RT−: Negative in re-test. SPT: Skin prick test. ST: Skin test.

The analysis of potential factors leading to a conversion of STs into positive showed that the severity of the reported reaction is associated with a higher resensitization rate. Although most published studies included only or mainly skin reactions,[8,14,15,19] in a previous reported study[5] anaphylaxis had been associated with RT+, showing a resensitization rate of 31%. In our study we included 83 cases reporting anaphylaxis, being the resensitization rate up to 45.8%. In contrast, the rate of resensitization was much lower in milder reactions (9.1%). In addition, logistic regression analysis showed that the risk of having RT+ was lower in reactions manifested with symptoms other than anaphylaxis. It is important to take into account that anaphylaxis is known to cause false-negative STs in the early post-onset period, as it has been described in postoperative patients,[35,36] and this fact may influence the higher rate of resensitization observed in cases reporting anaphylaxis. However, in our study, the interval time between reaction and IE was 36 (12–96) months and no differences were found when comparing this interval in cases reporting anaphylaxis and those reporting other milder entities.

The fact that the RT+ rate is higher in anaphylaxis reinforces the recommendation of performing a retest in patients with severe reactions even if they had tolerated a therapeutic administration of

TABLE 4 Comparison of demographic and clinical characteristics of patients giving positive or negative results in the re-test in both IRs and NIRs

	Immediate reactions			Non-immediate reactions		
	RT+ *N* = 63	RT− *N* = 233	p	RT+ *N* = 17	RT− *N* = 232	p
Age (median; IQR; years old)	42; 29.5–52	32; 17–47	0.003099	40; 33–53	33; 17–50	0.204
Gender (*N*; % of females)	24; 61.9	160; 68.7	0.3641	11; 64.7	158; 68.1	0.7721
Familiar history of drug allergy (*N*; %)	4; 6.3	12; 5.2	0.7089	-	15; 6.5	0.2795
Atopy (*N*; %)	13; 20.6	54; 23.2	0.6689	2; 11.8	43; 18.5	0.4838
N° of episodes (median; IQR)	1; 1–1	1; 1–1	0.2613	2; 2–2	1; 1–2	0.09816
Suspected drug (*N*; %)						
Penicillin	7; 11.1	19; 8.2	0.005621	1; 5.9	5; 2.2	0.1237
Amoxicillin	22; 34.9	138; 59.2		8; 47.1	139; 59.9	
Amoxicillin-clavulanic acid	33; 52.4	70;30		7; 41.2	87; 37.5	
Ampicillin	1; 1.6	5; 2.1		1; 5.9	1; 0.4	
Piperacillin-tazobactam	-	1; 0.4		-	-	
Reported symptoms in reaction (*N*; %)						
Anaphylaxis	38; 60.3	45; 19.3	0.000000003552	-	-	0.4104
Urticaria/angioedema	18; 28.6	140; 60.1		12; 70.6	162; 69.8	
MPE	2; 3.2	20; 8.6		4; 23.5	65; 28	
Gastrointestinal symptoms	-	1; 0.4		-	1; 0.4	
Respiratory	4; 6.3	5; 2.1		-	1; 0.4	
Others	1; 1.6	22; 9.4		1; 5.9	3; 1.3	
Time interval drug intake-reaction (median; IR; minutes)	30; 10–60	25; 8.7–33.7	0.2161	480; 480–2400	2880; 510–4320	0.4409
Time interval reaction–IE (median; IQR; months)	36; 12–96	24; 12–48	0.07154	24; 12–72	24; 12–96	0.678
Tests performed at IE (*N*; %)						
Only STs	46; 73	85; 36.5	0.0000002219	11; 64.7	97; 41.8	0.07856
DPT with the culprit	17; 27	148; 63.5		6; 35.3	135; 58.2	
Time interval IE-RE (median; IQR; days)	31; 29.7–39	33; 28–46	0.6106	37; 31–72.7	35; 29–47	0.1883
Positive STs at RE (*N*; %)						
SPT	36; 57.1			13		
ID	27; 42.9			4		
SPT to BP-OL	7; 12.3			2; 11.8		
SPT to MD	4; 6.9			2; 11.8		
SPT to amoxicillin	28; 51.1			11; 68.8		
SPT to clavulanic acid	2; 6.2			1; 16.7		
SPT to ampicillin	3; 37.5			-		
ID to BP-OL	2; 3.9			1; 9.1		
ID to MD	1; 1.9			-		
ID to amoxicillin	15; 46.1			4; 40		
ID to clavulanic acid	13; 43.3			-		
ID to ampicillin	6; 75			-		

Abbreviations: BP-OL: Benzylpenicilloyl-octa-L-lysine. DPT: Drug provocation test. IDT: Intradermal test. IE: Initial evaluation. IQR: Interquartile range. MD: Minor determinant. MPE: Maculopapular exanthema. NA: Not applicable. RE: Re-test evaluation. RT+: Positive in re-test. RT−: Negative in re-test. SPT: Skin prick test. ST: Skin test.

the involved drug during DPT.[2,31] However, in these cases, it would be advisable to start testing with higher dilutions due to the risk of systemic reaction.[2]

It has been previously reported that resensitization may occur not only after drug administration, but also after non-therapeutic exposure to the drug, and even after inadvertent exposure.[37] Later,

it was reported that repeated skin testing may influence the maintenance of positivity in in vitro tests for detecting sIgE in IRs.[9] In order to verify how the intensity of the reexposure to the drug had any influence on the rate of repositivization, at IE we randomized patients into two groups: those in which DPT was performed after STs and those in which only STs were performed. We found that the rate of resensitization was higher in the group in which only STs were performed at IE. This may be due to the higher percentage of anaphylaxis in this group, as DPT was not carried out in grade III IRs. However, analyzing the rate of resensitization in patients reporting penicillin-induced anaphylaxis, we did not find statistical differences when comparing patients in whom only STs were performed at IE and in those in whom DPT followed STs. Therefore, it seems that the rate of resensitization may be related to the severity of reaction more likely than to the tests performed at IE. This agrees with previously reported data in cephalosporins-induced reactions.[38]

Another issue is whether those patients with RT− are really non-allergic. In fact, the logistic regression analysis showed that the risk of having RT+ was lower when the reported penicillin-induced reactions were manifested as non-specific symptoms, among others. Additionally, it is not known if they may become allergic after subsequently exposure to penicillins. It has been reported that up to 16% of subjects who showed tolerance to penicillins in the DPT reacted after repeated testing. In fact, up to three evaluations have been reported to be needed to produce positive STs in some cases.[7,12] Even one patient was rediagnosed as allergic to penicillin after a fifth course of AX, although STs were not repeated to confirm this diagnosis.[8] Conversely, it has been reported that resensitization after more than two antibiotic courses of 10 days of penicillin is extremely rare.[13,16] In our study we do not know the percentage of cases with RT who finally tolerated the culprit penicillin as we did not assess tolerance to the culprit drug after the RE. Our aim was to analyze the rate of resensitization and the factors that influence it, but not to evaluate the prevalence of allergy after negative retests.

As it has been previously described that sensitization decreases over time,[9] we aimed to analyze the influence of time on resensitization.[10] Therefore, we analyzed the time interval between reported reaction and IE, and between IE and RE. Although no differences were found when comparing RT+ and RT−, logistic regression analysis showed that the likelihood of having a RT+ increased in patients from the fifth week after IE. Therefore, it would be advisable to perform retest after this time to find the most optimal resensitization rate.

A limitation of the study may be the lack of inclusion of in vitro tests in the allergological approach at IE. Therefore, patients with positive results in the in vitro tests and negative STs could have been included in the study even though they would have been diagnosed as allergic at IE. However, we did not include in vitro tests in order to harmonize study protocols in both participating centers. Moreover, in vitro tests have been reported to be less sensitive than STs.[39]

In summary, the data obtained in this study contribute to the improvement of the knowledge about the accuracy and predictive value for penicillin-allergy diagnostic work-up. Although nowadays there is no consensus about whether resensitization should be ruled out routinely or not, considering the results obtained in this study, it is advisable to retest patients in strong suspicion of allergic reactions to penicillins and negative allergological tests before considering the patient as non-allergic. This is especially important in severe reactions, as patients may be wrongly labelled as non-allergic even after a tolerated DPT with the culprit. The inclusion of retest in these cases it is important to avoid potentially severe reactions after the subsequent prescriptions of penicillins.

AUTHORS CONTRIBUTION

ID, LG, PB, and MJT designed the study. ID and MJT performed the statistical analysis. ID, LG, PB, and MJT wrote the manuscript. All authors contributed to data collection and interpretation of the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. All authors have given final approval to the version to be published. Research is part of their daily activities. All the authors had full access to all the data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Doña I, Blanca-López N, Torres MJ, et al. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. *J Investig Allergol Clin Immunol*. 2012;22(5):363-371.
2. Romano A et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams–an EAACI position paper. *Allergy*. 2020;75(6):1300-1315.

3. Torres MJ, Blanca M, Fernandez J, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy*. 2003;58(10):961-972.
4. Brockow K, Ardern-Jones MR, Mockenhaupt M, et al. EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. *Allergy*. 2019;74(1):14-27.
5. Moreno E, Laffond E, Muñoz-Bellido F, et al. Performance in real life of the European network on drug allergy algorithm in immediate reactions to beta-lactam antibiotics. *Allergy*. 2016;71(12):1787-1790.
6. García Núñez I, Barasona Villarejo MJ, Algaba Mármol MA, Moreno Aguilar C, Guerra Pasadas F. Diagnosis of patients with immediate hypersensitivity to beta-lactams using retest. *J Investig Allergol Clin Immunol*. 2012;22(1):41-47.
7. Lopez-Serrano MC, Caballero MT, Barranco P, Martinez-Alzamora F. Booster responses in the study of allergic reactions to beta-lactam antibiotics. *J Investig Allergol Clin Immunol*. 1996;6(1):30-35.
8. Hershkovich J, Broides A, Kirjner L, Smith H, Gorodischer R. Beta lactam allergy and resensitization in children with suspected beta lactam allergy. *Clin Exp Allergy*. 2009;39(5):726-730.
9. Fernández TD, Torres MJ, Blanca-López N, et al. Negativization rates of IgE radioimmunoassay and basophil activation test in immediate reactions to penicillins. *Allergy*. 2009;64(2):242-248.
10. Blanca M, Torres MJ, García JJ, et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. *J Allergy Clin Immunol*. 1999;103(5 Pt 1):918-924.
11. Romano A, Gaeta F, Valluzzi RL, Zaffiro A, Caruso C, Quaratino D. Natural evolution of skin-test sensitivity in patients with IgE-mediated hypersensitivity to cephalosporins. *Allergy*. 2014;69(6):806-809.
12. Matheu V, Perez-Rodriguez E, Sanchez-Machin I, Garcia-Robaina JC, de la Torre Morin F. Importance of repeat testing in the diagnosis of penicillin allergy. *Br J Dermatol*. 2006;154(1):198.
13. Dorman SM, Seth S, Khan DA. Risk of allergic reactions to recurrent intravenous penicillin administration in penicillin skin test negative patients. *J Allergy Clin Immunol Pract*. 2018;6(1):196-200.
14. Parker PJ, Parrinello JT, Condemi JJ, Rosenfeld SI. Penicillin resensitization among hospitalized patients. *J Allergy Clin Immunol*. 1991;88(2):213-217.
15. Pichichero ME, Pichichero DM. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. *J Pediatr*. 1998;132(1):137-143.
16. Solensky R, Earl HS, Gruchalla RS. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med*. 2002;162(7):822-826.
17. Macy E, Mangat R, Burchette RJ. Penicillin skin testing in advance of need: multiyear follow-up in 568 test result-negative subjects exposed to oral penicillins. *J Allergy Clin Immunol*. 2003;111(5):1111-1115.
18. Bittner A, Greenberger PA. Incidence of resensitization after tolerating penicillin treatment in penicillin-allergic patients. *Allergy Asthma Proc*. 2004;25(3):161-164.
19. Goldberg A, Confino-Cohen R. Skin testing and oral penicillin challenge in patients with a history of remote penicillin allergy. *Ann Allergy Asthma Immunol*. 2008;100(1):37-43.
20. Torres MJ, Romano A, Celik G, et al. Approach to the diagnosis of drug hypersensitivity reactions: similarities and differences between Europe and North America. *Clin Transl Allergy*. 2017;7:7.
21. Dona I, Romano A, Torres MJ. Algorithm for betalactam allergy diagnosis. *Allergy*. 2019;74(9):1817-1819.
22. Torres MJ, Adkinson NF Jr, Caubet JC, et al. Controversies in drug allergy: beta-lactam hypersensitivity testing. *J Allergy Clin Immunol Pract*. 2019;7(1):40-45.
23. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet*. 1977;1(8009):466-469.
24. Torres MJ, Romano A, Mayorga C, et al. Diagnostic evaluation of a large group of patients with immediate allergy to penicillins: the role of skin testing. *Allergy*. 2001;56(9):850-856.
25. Demoly P, Kropf R, Pichler WJ, Bircher A. Drug hypersensitivity: questionnaire. EAACI interest group on drug hypersensitivity. *Allergy*. 1999;54(9):999-1003.
26. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy*. 2002;57(1):45-51.
27. Romano A, Blanca M, Torres MJ, et al. Diagnosis of nonimmediate reactions to beta-lactam antibiotics. *Allergy*. 2004;59(11):1153-1160.
28. Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy*. 2003;58(9):854-863.
29. Mendelson LM, Ressler C, Rosen JP, Selcow JE. Routine elective penicillin allergy skin testing in children and adolescents: study of sensitization. *J Allergy Clin Immunol*. 1984;73(1 Pt 1):76-81.
30. Caubet JC, Kaiser L, Lemaître B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol*. 2011;127(1):218-222.
31. Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy*. 2014;69(4):420-437.
32. Bircher AJ, Scherer Hofmeier K. Drug hypersensitivity reactions: inconsistency in the use of the classification of immediate and nonimmediate reactions. *J Allergy Clin Immunol*. 2012;129(1):263-264.
33. Terrados S, Blanca M, Garcia J, et al. Nonimmediate reactions to betalactams: prevalence and role of the different penicillins. *Allergy*. 1995;50(7):563-567.
34. Gómez E, Blanca-Lopez N, Salas M, et al. Induction of accelerated reactions to amoxicillin by T-cell effector mechanisms. *Ann Allergy Asthma Immunol*. 2013;110(4):267-273.
35. Soetens F, Rose M, Fisher M. Timing of skin testing after a suspected anaphylactic reaction during anaesthesia. *Acta Anaesthesiol Scand*. 2012;56(8):1042-1046.
36. Orihara M, Takazawa T, Nagumo K, Sakamoto S, Horiuchi T, Saito S. Interpreting the results of early skin tests after perioperative anaphylaxis requires special attention: a case report and review of literature. *J Anesth*. 2020;34(4):624-629.
37. Blanca M, Garcia J, Vega JM, et al. Anaphylaxis to penicillins after non-therapeutic exposure: an immunological investigation. *Clin Exp Allergy*. 1996;26(3):335-340.
38. Romano A, Valluzzi RL, Caruso C, Zaffiro A, Quaratino D, Gaeta F. Evaluating immediate reactions to cephalosporins: time is of the essence. *J Allergy Clin Immunol Pract*. 2021;9(4):1648-1657.
39. Mayorga C, Celik G, Rouzaire P, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI drug allergy interest group position paper. *Allergy*. 2016;71(8):1103-1134.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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