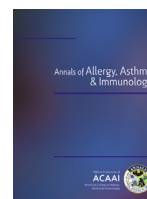




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Skin testing only with penicillin G in children with a history of penicillin allergy

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ABSTRACT

Background: The absence of commercially available penicilloyl-polylysine (PPL) for most of the last decade severely hampered the practice of penicillin allergy evaluation because skin testing without PPL is reported to have a poor negative predictive value (NPV).

Objectives: To determine the safety and NPV of skin testing without PPL using only penicillin G followed by a 3-dose graded challenge to the incriminated penicillin in children with a history of penicillin allergy.

Methods: Patients evaluated for a history of penicillin allergy at the CHU Sainte-Justine Allergy Clinic between December 2006 and December 2009 were skin tested only with penicillin G and underwent a 3-dose graded challenge to the culprit penicillin if the skin test result was negative.

Results: Among 563 patients skin tested to penicillin G, 185 (33%) had a positive skin test result. These patients had a shorter interval between the initial reaction and skin testing compared with patients with a negative skin test result ($P = .03$). A total of 375 of 378 patients (99%) with a negative skin test result were challenged and 18 (4.8%) reacted, translating into a NPV of 95.2% (95% confidence interval [CI], 92.5%–97.1%). Three of 17 patients with a history of anaphylaxis and a negative skin test result reacted to challenge (NPV, 82.4%; 95% CI, 59.0–93.8%). All challenge reactions were mild and resolved promptly with treatment.

Conclusion: Among children with a history of penicillin allergy, skin testing only with penicillin G followed by a 3-dose graded challenge to the incriminated penicillin is safe and yields a good NPV. This approach could be useful when PPL is unavailable.

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Introduction

Approximately 5% of children and 10% of adults report a history of penicillin allergy, although only a few of these patients are truly allergic.^{1–4} Because history is a poor predictor of reactivity, penicillin allergy evaluation that consists of skin tests, often followed by a drug challenge, is key to identify truly allergic and nonallergic patients who can be safely treated with penicillins.^{5,6} The importance of evaluating patients with a history of penicillin allergy is increasingly recognized given that penicillin avoidance is unnecessary for most of them and leads to the use of alternative broader-spectrum antibiotics (vancomycin and fluoroquinolones), which have been associated with additional costs and significant morbidities, such as vancomycin-resistant enterococcus and *Clostridium difficile*-associated diarrhea.^{7–9}

Skin test reagents used for penicillin allergy evaluation include penicilloyl-polylysine (PPL), the major antigenic determinant, and a variety of minor determinants, the most commonly used being

penicillin G.^{6,10} After a negative skin test result, a drug challenge is often performed because, depending on the population studied and skin test reagents used, up to 31% of patients require a drug challenge to identify their allergy.¹¹ A drug challenge may also provide reassurance to patients and parents who might not be convinced that they are not allergic based on negative skin test results and may therefore continue to avoid penicillins.^{12,13}

The lack of commercially available PPL for most of the last decade in North America seriously hampered the practice of penicillin allergy evaluation.^{4,14} Skin testing without PPL is not recommended because up to 75% of patients who have a positive skin test react only to PPL; therefore, only a few allergists who had the capacity to produce their own skin test reagents were apt to perform penicillin allergy evaluation during this time.^{4,6,15} Some groups proposed alternative approaches to palliate the absence of PPL, such as combining penicillin G skin testing with radioallergosorbent testing to PPL followed by 2 graded challenges, but none reached consensus, and in many cases the practice was abandoned.^{4,16,17}

Given the importance of penicillin allergy evaluation, especially in patients with frequent infections and/or a history of allergic reactions to multiple antibiotics, the decision was made at our

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institution to perform penicillin allergy evaluation in the absence of PPL using only penicillin G for skin testing followed, if results were negative, by a 3-dose graded challenge to the penicillin incriminated in the initial allergic reaction. Preliminary results revealing a low reaction rate after a negative penicillin G skin test result led us to adopt this approach as standard practice at our institution until PPL recommercialization.¹⁸ The aim of this study was to determine the safety of this approach and the negative predictive value (NPV) of skin testing solely with penicillin G for predicting an IgE-mediated penicillin allergy.

Methods

Study Cohort

The study was performed at the CHU Sainte-Justine, a large Canadian pediatric university hospital, and was approved by the CHU Sainte-Justine Institutional Review Board. Written informed consent was obtained from parents or legal tutors and/or patients at the time of evaluation. All patients who underwent penicillin skin testing between December 2006 and December 2009 at the CHU Sainte-Justine Allergy Clinic were identified by medical record review. Patients with a history of reaction to any penicillin class antibiotic that was consistent with an IgE-mediated reaction or a delayed nonsevere skin eruption were included. Patients whose history of reaction was to cephalosporins or carbapenems, patients whose history was inconsistent with a hypersensitivity reaction (eg, diarrhea and hallucinations), and those with only a family history of penicillin allergy were excluded. Patients with a history suggestive of serum sickness–like reaction or severe cutaneous adverse reaction (eg, Stevens-Johnson syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis) were not skin tested. Patients were referred by their treating physician. Because of a high referral volume, those with recurrent infections and a frequent need for antibiotics and/or a history of allergy to multiple antibiotics were prioritized for evaluation. Patients were evaluated at the outpatient CHU Sainte-Justine Allergy Clinic, which is located in the CHU Sainte-Justine Hospital, with immediate access to emergency care if needed.

Skin Testing Procedure

All patients were evaluated by 1 of 2 allergists (A.D.R. and L.P.), and skin testing was performed by 1 of 2 experienced nurses. Penicillin G (at a concentration of 10,000 U/mL as recommended⁶) was the only skin test reagent used. A vial of sodium penicillin G (1,000,000 U; Teva Canada Limited, Toronto, Ontario, Canada) was freshly reconstituted daily and diluted in 0.9% saline to a concentration of 10,000 U/mL used for both skin prick tests (SPTs) and intradermal tests (IDTs). SPTs were performed by puncturing the volar surface of the forearm with a 25-gauge needle through a drop of penicillin G. We used 0.9% saline and 2 mg/mL of histamine as negative and positive controls, respectively. If the SPT result was negative, an IDT was performed by planting 0.02 mL of penicillin G, along with 0.9% saline as a negative control, in the volar forearm using a 27-gauge tuberculin syringe. Reading was performed 15 minutes later by the allergist who had evaluated the patient, and the test result was considered positive if it elicited a wheal greater than 5 mm compared with the negative control with a flare reaction for both SPTs and IDTs.

Graded Drug Challenge Procedure

If the skin test result was negative, a 3-dose graded drug challenge was performed to the penicillin incriminated in the allergic reaction (or amoxicillin if the culprit penicillin could not be identified) usually on the day of skin testing. The first dose was 1/100th

of the therapeutic dose (based on body weight), the second dose was 1/10th, and the third consisted of the full therapeutic dose. The 3 doses were administered 20 minutes apart, and the patient was observed for 60 minutes after the last dose. Twenty-minute intervals were chosen because orally administered penicillins are rapidly absorbed¹⁹ and we had previous experience with this protocol.¹² Parents and patients were warned about the possibility of a delayed reaction and asked to contact the allergy clinic if any delayed reaction were noticed. If no immediate or delayed reaction occurred, the child was considered not allergic to penicillin, and parents and treating physicians were informed that the child could receive penicillin in the future without any special precaution. If a reaction occurred during the challenge, the procedure was immediately stopped, treatment was rapidly administered according to symptoms, and the patient was kept under observation until all symptoms resolved.

Statistical Analysis

Comparisons were made for categorical variables using the Fisher exact test when the variable was dichotomous and the χ^2 test when the nominal variable exceeded 2 categories. The Mann-Whitney test was used to compare continuous variables. $P < .05$ was considered significant. The 95% confidence intervals (CIs) was calculated using the Clopper and Pearson method. Statistical analysis was performed with SPSS statistical software, version 19 (SPSS Inc, Chicago, Illinois).

Results

A total of 563 patients with a history of penicillin allergy were skin tested to penicillin G between December 2006 and December 2009 (Table 1). Patients were between 7 months and 21 years of age (median age, 5.8 years) at the time of evaluation, and 51% were female. Twenty-eight percent had a history of atopy and 17% had a history of asthma in line with estimates of the prevalence of these conditions in the pediatric population.^{20,21} Most patients (89%) reported a reaction to amoxicillin (with or without clavulanic acid), 8% to penicillin (penicillin V, penicillin G, or exact penicillin class antibiotic could not be identified), 2% to cloxacillin, 0.7% to ticarcillin–clavulanic acid, 0.5% to ampicillin, and 0.4% to piperacillin–tazobactam. Reactions were classified as urticaria in 38%, maculopapular in 34%, unspecified skin eruption in 10%, and angioedema with or without urticaria in 14%. A history of anaphylaxis (fulfilling the criteria proposed by Sampson et al²²) was documented in 25 patients (4%) of whom 7 were treated with epinephrine. Among 25 patients with anaphylaxis, 24 (96%) had skin symptoms, 24 (96%) had respiratory compromise (1 was intubated), 6 (24%) had persistent gastrointestinal symptoms, and 2 (8%) had cardiovascular involvement (syncope and hypotonia). Twelve patients with anaphylaxis reacted 24 hours or less and 11 more than 24 hours after the start of penicillin treatment; 2 patients could not provide this information. Among patients with a nonanaphylactic reaction, the time to reaction onset was 24 hours or less in 24%, more than 24 hours in 61%, and unknown in 15%.

A positive skin test result was elicited in 185 patients (32.9%); 1 patient had a positive SPT result, and 184 had positive IDT results. Characteristics of skin test–positive and skin test–negative patients are compared in Table 2. The time elapsed between the allergic reaction and the evaluation was shorter in skin test–positive patients than in skin test–negative patients, explaining the younger age at time of evaluation of skin test–positive patients. The age at time of reaction did not differ between skin test–positive (median, 1.5 years) and skin test–negative patients (median, 1.7 years) ($P = .28$). The probability of having a positive skin test result steadily decreased as the time elapsed since the reaction increased: from 38% ($n = 63/165$) in patients with an interval since the reaction of 0.1 to 0.9 years to

Table 1Characteristics of patients evaluated for a history of penicillin allergy^a

Characteristic	Anaphylactic patients (n = 25)	Nonanaphylactic patients (n = 538)		P value
		Time to reaction onset of ≤24 hours (n = 128)	Time to reaction onset of >24 hours or unknown (n = 410)	
Age at time of evaluation, median (range), y	5.9 (0.9–17.4)	5.3 (0.6–20.6)	6.1 (0.7–21.1)	.28
Female sex	16 (64)	61 (48)	212 (52)	.31
Atopy	4 (16)	43 (34)	113 (28)	.16
Asthma	3 (12)	24 (19)	69 (17)	.70
History of allergic reaction to another antibiotic	10 (40)	31 (24)	123 (30)	.22
Family history of penicillin allergy ^b	1 (7)	25 (25)	66 (22)	.18
Culprit penicillin				.26 ^d
Aminopenicillins	23 (92)	112 (88)	378 (92)	
Amoxicillin	19 (76)	89 (70)	344 (84)	
Amoxicillin–clavulanic acid	3 (12)	15 (12)	30 (7)	
Cloxacillin	0	6 (5)	4 (1)	
Ampicillin	1 (4)	2 (2)	0	
Penicillins	2 (8)	16 (13)	32 (8)	
Penicillin ^c	1 (4)	12 (9)	31 (8)	
Ticarcillin–clavulanic acid	1 (4)	3 (2)	0	
Piperacillin–tazobactam	0	1 (0.8)	1 (0.2)	
Type of reaction ^e				
Urticaria	NA	59 (46)	154 (38)	.10
Maculopapular rash	NA	45 (35)	145 (35)	>.99
Unspecified rash	NA	12 (9)	44 (11)	.74
Angioedema	NA	12 (9)	67 (16)	.06
Anaphylaxis	25 (100)	NA	NA	NA ^f
Time elapsed between allergic reaction and evaluation, median (range), y	3.9 (0.17.2–14)	2.0 (0.1–15.5)	2.9 (0.1–17.2)	.17
Time to onset of allergic reaction after start of penicillin treatment				
≤24 hours	12 (48)	128 (100)	NA	NA ^f
25–48 hours	3 (12)	NA	107 (26)	
49–72 hours	2 (8)	NA	49 (12)	
73–96 hours	0	NA	19 (5)	
>96 hours	6 (24)	NA	154 (38)	
Unknown	2 (8)	NA	81 (20)	
Skin test positive to penicillin G	7 (28)	40 (31)	138 (33.7)	.77

Abbreviation: NA, not applicable.

^aData are presented as number (percentage) of patients unless otherwise indicated.^bFamily history of penicillin allergy is defined as the presence of a history of penicillin allergy among parents and/or siblings. Data on family history of penicillin allergy were available for 15 anaphylactic patients, 101 patients with time to reaction onset of 24 hours or less, and 305 patients with time to reaction onset of more than 24 hours or unknown.^cPenicillin indicates penicillin V, penicillin G, or exact penicillin molecule could not be identified (in the latter case challenge was performed with amoxicillin).^dComparison between reaction rate to aminopenicillins and penicillins.^eCategories are mutually exclusive. Patients were categorized for their type of reaction based on their predominant or most severe manifestation.^fA P value was not calculated for these variables because they also served to divide the population into groups.

35% (n = 126/356), 30% (n = 42/139), and 25% (n = 17/68) in patients with an interval of 1 to 4.9 years, 5.0 to 9.9 years, and 10.0 to 17.2 years, respectively. Patients with anaphylaxis and those with a time to reaction onset of 24 hours or less were not more likely to be skin test positive than those with a time to reaction onset of greater than 24 hours or unknown (Table 1).

All patients with a negative skin test result to penicillin G (n = 378) were offered a graded challenge to the incriminated penicillin. One refused and 2 others were lost to follow-up. A reaction occurred in 18 of 375 patients challenged (4.8%), translating into a NPV of 95.2% (95% CI, 92.5%–97.1%) of penicillin G skin testing for predicting an IgE-mediated penicillin allergy. Challenge reactions occurred after 1/100th of the total dose in 3 of 18 patients (17%), 1/10th of the total dose in 4 of 18 patients (22%), and 1 hour or less after the total dose in 11 of 18 patients (61%) (Table 3). All reactive patients had objective skin findings, 2 also had throat symptoms, and 1 was also irritable. Reactions resolved either spontaneously or with one dose of oral antihistamine. One case also developed a delayed macular rash (4 hours after the total dose) and received one dose of corticosteroid. No delayed reactions beyond 4 hours were reported.

The NPV of penicillin G skin testing was compared in the following 3 groups: patients with a history of anaphylaxis, patients with a time to reaction onset of 24 hours or less, and patients with a time to reaction onset of more than 24 hours or unknown (Table 4).

Only the difference in NPV between patients with anaphylaxis and those with a reaction onset of more than 24 hours or unknown was statistically significant ($P = .03$). Patients with a positive challenge result were also more likely to have asthma than patients who did not react to challenge, a finding that was not explained by a higher prevalence of asthma among patients who had anaphylaxis as their initial allergic reaction (Table 5).

Discussion

In a pediatric cohort of 563 patients with a history of penicillin allergy, the results of skin testing only with penicillin G (in the absence of PPL) were positive in 33% and yielded a NPV of 95.2% (95% CI, 92.5%–97.1%) based on challenge outcomes. After a negative penicillin G skin test result, a 3-dose graded challenge to the incriminated penicillin was found to be safe, even in patients with a history of anaphylaxis, because no patient experienced a severe reaction as a result. To our knowledge, this is the first contemporary study in which penicillin skin testing was performed without PPL using penicillin G as the sole skin test reagent.

Although the rate of positive skin test results to penicillin among patients with a history of penicillin allergy is usually reported to be approximately 10%,⁶ this value varies greatly, depending on the population studied. The reported rate of skin test positivity ranges

Table 2Comparison of patients with positive and negative skin test results to penicillin G^a

Characteristic	Positive skin test result (n = 185)	Negative skin test result (n = 378)	P value
Age at time of evaluation, median (range), y	5.3 (0.7–18.1)	6.1 (0.6–21.1)	.03
Female sex	93 (50)	196 (52)	.79
Atopy	60 (32)	100 (26)	.16
Asthma	31 (17)	65 (17)	>.99
History of allergic reaction to another antibiotic	63 (34)	101 (28)	.08
Family history of penicillin allergy ^b	29 (21)	63 (22)	.93
Culprit penicillin			
Aminopenicillins	169 (91)	344 (91)	>.99 ^d
Amoxicillin	145 (78)	307 (81)	
Amoxicillin–clavulanic acid	20 (11)	28 (7)	
Cloxacillin	3 (2)	7 (2)	
Ampicillin	1 (0.5)	2 (0.5)	
Penicillins	16 (9)	34 (9)	
Penicillin ^c	13 (7)	31 (8)	
Ticarcillin–clavulanic acid	2 (1)	2 (0.5)	
Piperacillin–tazobactam	1 (0.5)	1 (0.3)	
Type of reaction ^e			
Urticaria	77 (42)	136 (36)	.07
Maculopapular rash	52 (28)	138 (37)	
Unspecified rash	15 (8)	41 (11)	
Angioedema	34 (18)	45 (12)	
Anaphylaxis	7 (4)	18 (5)	
Time elapsed between allergic reaction and evaluation, median (range), y	2.0 (0.1–16.4)	3.0 (0.1–17.2)	.03
Time to onset of allergic reaction after start of penicillin treatment			
<24 hours	43 (23)	97 (26)	.05
25–48 hours	36 (19)	74 (20)	
49–72 hours	12 (6)	39 (10)	
73–96 hours	10 (5)	9 (2)	
>96 hours	63 (34)	97 (26)	
Unknown	21 (11)	62 (16)	

^aData are presented as number (percentage) of patients unless otherwise indicated.^bFamily history of penicillin allergy is defined as the presence of a history of penicillin allergy among parents and/or siblings. Data on family history of penicillin allergy were available for 139 skin test–positive patients and 282 skin test–negative patients.^cPenicillin indicates penicillin V, penicillin G, or exact penicillin molecule could not be identified (in the latter case challenge was performed with amoxicillin).^dComparison between reaction rate to aminopenicillins and penicillins.^eCategories are mutually exclusive. Patients were categorized for their type of reaction based on their predominant or most severe manifestation.

from 0.8%⁴ to 61.5%²³ and from 2.4%²⁴ to 71%²⁵ in predominantly adult and pediatric cohorts, respectively.^{3,11,15,24–47} Most of these studies used a panel of skin test reagents that included PPL. In those that also used penicillin G at 10,000 U/mL as a separate reagent, 20%³⁹ to 100%⁴⁵ of skin test–positive patients reacted to penicillin G.^{26,37,39,45,48} In our

cohort, given that among 203 patients diagnosed as having penicillin allergy (185 skin test–positive patients and 18 challenge–positive patients), 91% tested positive to penicillin G, the 33% rate of skin test positivity, although higher than the frequently reported mean of 10%, is not unexpectedly high in light of this literature.

Table 3

Characteristics of patients with positive penicillin challenge results

Mean age at time of evaluation, y	Sex	Time elapsed, y ^a	Initial allergic reaction	Time to onset ^b	Culprit penicillin	Challenge reaction
4.2	F	3.0	Anaphylaxis	8 d	Amoxicillin	Urticaria after 1/100th dose (<20 minutes)
2.8	M	0.4	Anaphylaxis	6 d	Amoxicillin	Urticaria after full dose (<1 hour)
0.9	F	0.8	Anaphylaxis	49–72 h	Amoxicillin	Urticaria after 1/10th dose (<20 minutes)
2.8	M	1.8	Urticaria/angioedema	<24 h	Amoxicillin	Urticaria after full dose (<1 hour)
9.2	F	6.7	Urticaria/angioedema	25–48 h	Amoxicillin	Urticaria after 1/100th dose (<20 minutes)
0.9	M	0.2	Urticaria	49–72 h	Amoxicillin	Urticaria and irritability after full dose (<1 hour)
4.0	F	3.0	Urticaria	<24 h	Amoxicillin	Urticaria after 1/10th dose (<20 minutes)
11.0	F	0.4	Urticaria	Unknown	Amoxicillin	Urticaria after full dose (<1 hour)
15.5	M	13.5	Urticaria	49–72 h	Amoxicillin	Urticaria after full dose (<1 hour)
2.8	F	0.8	Urticaria	Unknown	Penicillin ^c	Urticaria after 1/10th dose (<20 minutes)
15.2	F	11.2	Maculopapular rash	<24 h	Ampicillin	Macular rash after full dose (<1 hour)
2.0	M	1.0	Maculopapular rash	<24 h	Amoxicillin	Macular rash after full dose (<1 hour)
9.8	F	6.8	Maculopapular rash	49–72 h	Amoxicillin	Macular rash after 1/10th dose (<20 minutes)
21.1	M	1.1	Maculopapular rash	<24 h	Amoxicillin	Pruritus and throat tightness 1 hour after full dose and macular rash 4 hours after full dose
7.4	M	1.6	Maculopapular rash	49–72 h	Amoxicillin	Urticaria and itchy throat after full dose (<1 hour)
10.9	M	9.9	Maculopapular rash	6 d	Amoxicillin	Macular rash after full dose (<1 hour)
2.5	M	1.5	Undetermined rash	49–72 h	Amoxicillin	Erythema after full dose (<1 hour)
2.6	M	1.9	Undetermined rash	<24 h	Amoxicillin	Urticaria after 1/100th dose (<20 minutes)

^aTime elapsed between allergic reaction and evaluation.^bTime to onset of allergic reaction after start of penicillin treatment.^cThe specific penicillin molecule to which the patient had reacted could not be identified. She was thus challenged with amoxicillin to which she reacted.

Table 4Influence of timing and type of initial reaction on the NPV of penicillin G skin test^a

Type of reaction ^b	Anaphylactic patients (n = 17)	Nonanaphylactic patients (n = 358)		P value
		Time to reaction onset of ≤24 hours (n = 87)	Time to reaction onset of >24 hours or unknown (n = 271)	
Urticaria	NA	35/37 (94.6)	95/98 (96.9)	.61
Maculopapular rash	NA	32/34 (94.1)	100/104 (96.2)	.64
Unspecified rash	NA	7/8 (87.5)	32/33 (97.0)	.37
Angioedema	NA	7/8 (87.5)	35/36 (97.2)	.33
Total [95% CI]	14 (82.4) [56.6–96.2]	81 (93.1) [85.6–97.4]	262 (96.7) [93.8–98.5]	.03 ^c

Abbreviations: CI, confidence interval; NA, not applicable; NPV, negative predictive value.

^aData are presented as number with negative results/number undergoing total challenge (percentage with NPV).^bCategories are mutually exclusive. Patients were categorized for their type of reaction based on their predominant or most severe manifestation.^cP value obtained from a comparison between patients with anaphylaxis and patients with a time to reaction onset of greater than 24 hours or unknown (Fisher exact test). Comparisons between other groups did not reveal a statistically significant difference.

Several factors may have contributed to the higher-than-average rate of skin test positivity in this cohort. The 2 most important factors in this regard are the age at time of evaluation and the time elapsed since the allergic reaction. Sullivan et al²⁵ found that 71% of children younger than 10 years were skin test positive compared with 39% of adults older than 30 years and that

Table 5Comparison of patients with positive and negative challenge results to penicillin^a

Characteristic	Positive challenge results (n = 18)	Negative challenge results (n = 357)	P value
Age at time of evaluation, median (range), y	4.1 (0.9–21.1)	6.1 (0.6–20.6)	.54
Female sex	8 (44)	185 (52)	.63
Atopy	6 (33)	93 (26)	.58
Asthma	7 (39)	57 (16)	.02
History of allergic reaction to another antibiotic	7 (39)	93 (26)	.27
Family history of penicillin allergy ^b	5 (31)	57 (22)	.23
Culprit penicillin			
Aminopenicillins	17 (94)	325 (91)	>.99 ^d
Amoxicillin	16 (89)	290 (81)	
Amoxicillin–clavulanic acid	0	27 (8)	
Cloxacillin	0	7 (2)	
Ampicillin	1 (6)	1 (0.3)	
Penicillins	1 (6)	32 (9)	
Penicillin ^c	1 (6)	29 (8)	
Ticarcillin–clavulanic acid	0	2 (0.6)	
Piperacillin–tazobactam	0	2 (0.6)	
Type of reaction ^e			
Urticaria	5 (28)	130 (36)	.16
Maculopapular rash	6 (33)	132 (37)	
Unspecified rash	2 (11)	39 (11)	
Angioedema	2 (11)	42 (12)	
Anaphylaxis	3 (17)	14 (4)	
Time elapsed since allergic reaction, median (range), y	1.7 (0.2–13.5)	3.1 (0.2–17.2)	.35
Time to onset of allergic reaction after start of penicillin treatment			
≤24 hours	6 (33)	90 (25)	.16
25–48 hours	2 (11)	71 (20)	
49–72 hours	5 (28)	34 (10)	
73–96 hours	0	9 (3)	
>96 hours	3 (17)	93 (26)	
Unknown	2 (11)	60 (17)	

^aData are presented as number (percentage) of patients unless otherwise indicated.^bFamily history of penicillin allergy is defined as the presence of a history of penicillin allergy among parents and/or siblings. Data on family history of penicillin allergy were available for 16 challenge-positive patients and 264 challenge-negative patients.^cPenicillin indicates penicillin V, penicillin G, or exact penicillin molecule could not be identified (in the latter case challenge was performed with amoxicillin).^dComparison between reaction rate to aminopenicillins and penicillins.^eCategories are mutually exclusive. Patients were categorized for their type of reaction based on their predominant or most severe manifestation.

the rate of positive skin test results decreased from 73% to 22% in patients who had reacted within a year of skin testing compared with those who had reacted more than 10 years ago. Other investigators have confirmed this association between skin test positivity and a younger age at time of evaluation and a shorter time elapsed since the reaction.^{26,33,40,48,49} The young age of children in this cohort at the time of evaluation (median, 5.8 years) and the short time elapsed between the reaction and the evaluation (median, 2.6 years) certainly contributed to the higher-than-average rate of skin test positivity observed.

The priority for evaluation given to patients with a history of allergy to more than one antibiotic may have also contributed to the increased rate of skin test positivity. Strom et al⁵⁰ found that patients with a history of reaction to a sulfonamide antibiotic were at increased risk of reacting to penicillin, and Asero⁵¹ found that patients with confirmed antibiotic allergy were more likely to have experienced allergic reactions to multiple antibiotics. In this study, although not statistically significant ($P = .08$), more skin test–positive patients (34%) than skin test–negative patients (28%) reported a history of reaction to more than one antibiotic.

The NPV of penicillin skin testing for immediate IgE-mediated reactions, using a panel of reagents that includes PPL, averages 98% to 99%.^{4,6,10,15,24–26,29–32,38–40,42,48,49} However, recent studies from different groups have found a lower than expected NPV despite the use of PPL and minor determinant mixture (MDM). Bousquet et al¹¹ reported an NPV of 92% among 715 patients who tested negative to PPL, MDM, penicillin G, amoxicillin, ampicillin, and any other β -lactam incriminated by the patient, leading the authors to recommend that drug challenges be performed for all skin test–negative patients. Celik et al³³ found an NPV of 87.5% among 40 patients who tested negative to PPL, MDM, and the culprit penicillin, and Goldberg and Confino-Cohen³⁷ observed an NPV of 95.7% among 94 patients who tested negative to PPL, MDM, penicillin G, ampicillin, and amoxicillin.

In this study, an NPV of 95.2% (95% CI, 92.5%–97.1%) was observed in 375 patients who tested negative to penicillin G despite a higher-than-average prevalence of penicillin allergy (skin test and challenge positive, 36%), suggesting that the absence of PPL had little effect on the NPV. The NPV is known to decrease as the prevalence of the positive outcome increases.⁵² More important, no severe reaction occurred as a result of the challenge procedure in skin test–negative patients despite the fact that 17 of them had a history of anaphylaxis to penicillin. A likely explanation for this finding is that, at least in some populations, the sensitivity of PPL for detecting penicillin allergy has steadily decreased in the last decades.^{11,53} Recently, Bousquet et al¹¹ reported that as little as 5% of skin test–positive patients reacted only to PPL and that 75% of penicillin allergic patients tested negative to PPL and MDM. In comparison, Gadde et al¹⁵ reported in the 1990s that 75% of skin test–positive patients reacted only to PPL. Patients in the latter

study were skin tested to PPL and MDM, which includes penicillin G at a concentration of 10 mM (5,941 U/mL). Because in our cohort 91% of penicillin allergic patients were detected by penicillin G skin testing at 10,000 U/mL, 9%, at most, could have reacted only to PPL (if PPL had detected all challenge-positive patients). Therefore, in our population, PPL sensitivity may be lower than expected, thus explaining the little effect of its absence on the NPV.

As in our cohort, some have reported a lower NPV of penicillin skin testing in patients with a history of anaphylaxis compared with patients with any other history of penicillin allergy. Torres et al.²³ observed an NPV of only 45% among 89 patients with a history of immediate reaction to penicillin (of which 53% had a history of anaphylaxis) and skin test negative to PPL, MDM, amoxicillin, and ampicillin. Ponvert et al.⁴³ challenged 63 patients with a history of anaphylaxis to β -lactams and skin test negative to a large panel of skin test reagents that included, among others, penicillin G (at a concentration of 25,000 U/mL) but neither PPL nor MDM and found an NPV of 79.4%. In contrast, Gadde et al.¹⁵ observed an NPV of 96.4% among 28 patients with a history of anaphylaxis and skin test negative to PPL and MDM compared with 97.4% for the entire cohort.¹⁵ Although it remains unclear whether PPL would have significantly improved the NPV of 82.4% seen in our cohort of 17 patients with a history of anaphylaxis, these data indicate that a cautious approach should be used when challenging skin test-negative patients with a history of anaphylaxis or of an immediate reaction. In that regard, the 3-dose graded challenge starting at 1/100th the target dose used in this study proved to be safe because no severe reaction were elicited.

Another explanation for the small effect of PPL absence on the NPV relates to its positive predictive value (PPV), which ranges from 10%³⁷ to 100%.^{3,26,27,29,30,40,54} This wide variation is explained by the fact that data on the PPV are limited given the risk associated with challenging skin test-positive patients. Only 2 studies intentionally challenged most of the skin test-positive patients in their cohort. Goldberg and Confino-Cohen³⁷ observed 7 reactions among 67 skin test-positive patients challenged (PPV, 10%). Patients with a recent history of penicillin allergy (<3 years) and those with a life-threatening reaction were excluded. In the other study, Caubet et al.³ reported a PPV of 25% among 8 skin test-positive children with a history of delayed nonsevere skin reaction to penicillin. Therefore, if most skin test-positive patients are not truly penicillin allergic (particularly those with a distant nonanaphylactic reaction and those with a delayed-onset reaction), the absence of one reagent (in this instance PPL) is unlikely to have a major effect on the NPV of skin testing. On the basis of these studies, it could be argued that these patients may benefit from being challenged without prior skin testing. This is an issue that deserves further study.

This study has several limitations. It is monocentric and involves young children with a short time elapsed since the reaction who were found to have a higher-than-average rate of positive skin test results to penicillin G. Therefore, the results may not apply to other pediatric populations or adults, especially given that marked differences between cohorts have been reported in the literature.⁶ Because the study was conducted at a time when PPL was unavailable, a direct comparison of the NPV of skin testing only with penicillin G with the NPV of skin testing with PPL and penicillin G was not possible. However, the fact that 375 of 378 skin test-negative patients (99%) were challenged and the large sample size (375 patients were challenged) strengthen the probability that the NPV observed in this cohort (which is comparable to the NPV of penicillin skin testing with PPL reported in the literature) is accurate.

Skin testing to aminopenicillins, which could have detected patients selectively reactive to the amoxicillin or ampicillin side chain, was not performed because of the lack of commercially available intravenous amoxicillin approved for human use in

Canada and because skin testing to ampicillin would likely not detect patients selectively allergic to amoxicillin because their side chain differs.⁶ Moreover, selective allergy to an aminopenicillin side chain appears to be rare in North America, leading at least one group to abandon amoxicillin skin testing.⁴ In this cohort, if we considered all challenge-positive patients as selectively allergic to aminopenicillins (based on a negative skin test result to penicillin G), the prevalence would be 3.2% ($n = 18/563$). In comparison, 33% of patients evaluated had a positive skin test result to penicillin G, suggesting that most patients who reacted to amoxicillin were sensitive to the penicillin core and not the side chain.

Other limitations that can be raised are that the timing of the allergic reactions was not precisely defined and that patients with various types of reactions, ranging from a benign maculopapular rash to anaphylaxis, were evaluated with the same approach. Although knowing the exact timing of reaction onset after drug administration may be invaluable given that reactions starting within an hour are likely to be IgE mediated and that those starting after more than 1 hour are likely to be T-cell mediated,⁵⁵ we found that parents could rarely provide this information. Studies have found that history is often a poor predictor of skin test reactivity and that caution should be exercised before ruling out the possibility of an IgE-mediated allergy in a patient with a history of a benign delayed-onset skin eruption.^{5,6,15,56} In this study, 5 patients with a history of nonurticarial skin eruption starting more than 24 hours after the start of penicillin treatment had an immediate reaction during challenge. Moreover, the timing and the type of allergic reaction did not predict the result of skin testing or the challenge outcome, although patients with a history of anaphylaxis were at an increased risk of reacting to the challenge. These results support the approach used in this study given that the main purpose of penicillin skin testing followed by a 3-dose drug challenge is to rule out an IgE-mediated allergy, which could be life threatening, and to do so in a controlled setting where emergency treatment can be provided in case of reaction.⁶

The diagnostic approach to delayed reactions to penicillins in children is less well established. Delayed reading of IDT and patch test results is of little diagnostic value in these circumstances and was thus not performed.^{3,57} Although 60% of patients reacted more than 24 hours after the start of their initial treatment, no patient had a delayed reaction after challenge. Because studies have found that some delayed reactors can only be identified when given a full course of antibiotics,^{58,59} it is possible that some delayed reactors were missed with the 3-dose challenge. In this study, full-course drug challenges were not performed because they are not standard practice⁶ and because the risk of a benign delayed skin eruption during a subsequent aminopenicillin treatment in children who have tolerated a 3-dose drug challenge is approximately 5% comparable with the general population, suggesting that they are not at increased risk and therefore do not require additional workup.^{12,60} Given the poor performance of skin testing in diagnosing delayed reactions to penicillins in children,^{3,57} it is unlikely that PPL would have increased their detection.

Although PPL in combination with penicillin G and/or other minor determinants remains the preferred skin test regimen, this study found that in the absence of PPL, penicillin allergy evaluation can be safely performed in children using only penicillin G followed by a graded drug challenge to the incriminated penicillin. Future studies directly comparing the NPV of skin testing only with penicillin G to skin testing with PPL and penicillin G are needed to more accurately delineate the effect of PPL on the NPV. Finally, given the changing sensitivity and possibly specificity of penicillin skin test reagents, it might be time to formally evaluate the PPV of skin test reagents currently in use because the costs of falsely labeling someone as penicillin allergic are increasingly recognized.

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