

Outpatient penicillin use after negative skin testing and drug challenge in a pediatric population

Matthieu Picard, M.D.,¹ Louis Paradis, M.D.,¹ Mélanie Nguyen, M.D.,¹ Philippe Bégin, M.D., M.Sc.,¹ Jean Paradis, M.D.,² and Anne Des Roches, M.D.¹

ABSTRACT

The practice of elective penicillin skin testing could be compromised by the fact that patients, their parents, or their physicians remain reluctant to reuse penicillin-class antibiotics (PCAs) despite a negative evaluation by an allergist. This study addresses reuse of PCAs in a pediatric population after negative penicillin skin testing and drug challenge and factors associated with its reluctance. All children evaluated for a history of penicillin allergy at the CHU Sainte-Justine Allergy Clinic between January 1998 and June 2000 with negative skin testing and drug challenge were included in the study. A telephone survey was conducted between May and October 2002 to assess the perception of the initial reaction by the parents, subsequent use of antibiotics, and antibiotic-related adverse reactions. Among the 200 children selected, parents of 170 (85%) children completed the survey. Since the allergist evaluation, 130 (76%) children had received antibiotics. PCA was used in 59 (45%) children. Parents of 24 (18%) children refused PCAs because they still feared an adverse reaction. They were more likely to have been very frightened by their child's allergic reaction than other parents whose children had used PCAs ($p = 0.008$). Although elective penicillin skin testing is useful and safe in the pediatric population, a significant proportion of parents still refuse PCAs even though they are needed. Identification of parents that were very frightened by their children's allergic reactions and additional reassurance could improve this situation.

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Penicillin skin testing has been shown to be useful and safe in the adult and pediatric populations.^{1–3} As stated by the American Academy of Allergy, Asthma, and Immunology, skin testing can either be performed electively or at the time antibiotics are required. The usefulness of testing children electively is based on the impracticality of testing them when they are sick and the frequent outpatient need for antibiotics in this population.^{1,4} Risk of resensitization after penicillin skin testing and/or drug challenge has been brought as an argument against elective skin testing although several studies have shown the risk to be minimal.^{1,3,5,6} Another caveat, which has seldom been studied, could be that patients, their parents, or physicians remain reluctant to use the drug despite a negative evaluation by an allergist.

In the adult population, Warrington and colleagues have shown this situation to be prevalent.⁷ In this study, 108 patients with a negative elective penicillin

skin test were surveyed on their subsequent use of antibiotics. Only 29% had taken a penicillin-class antibiotic (PCA) in the following years although 59% had needed an antibiotic therapy. This low use of PCA was explained by the fact that a significant proportion of patients or their physicians were reluctant to use a PCA despite a negative skin test.⁷ Drug challenges had not been performed in this study. Therefore, one could argue that improved PCA reuse could have been achieved by performing drug challenges that would have alleviated the fear of an allergic reaction on subsequent use.

To our knowledge, the issue of PCA reuse and motives associated with subsequent PCA refusal have never been directly addressed in the pediatric population. In this study we investigated the outpatient use of PCA in our center after a negative penicillin skin test and a successful drug challenge. Additionally, factors that could be associated with reluctance to reuse these drugs were examined.

MATERIALS AND METHODS

Children evaluated at the CHU Sainte-Justine Allergy Clinic between January 1998 and June 2000 for a history of penicillin allergy consistent with an IgE-mediated reaction or a benign maculopapular rash and who had a negative penicillin skin test and graded drug challenge were identified by chart review. Children had been referred to our clinic by their general practitioner or pediatrician. They were

From the ¹Division of Allergy and Clinical Immunology, Department of Pediatrics, CHU Sainte-Justine, Montreal, Qc, Canada, and ²Division of Allergy and Clinical Immunology, Department of Medicine, CHUM, Montreal, Quebec City, Canada. Presented as an abstract at the meeting of the American Academy of Allergy, Asthma, and Immunology, March 2004, San Francisco, California.

The authors have no conflicts of interest to declare pertaining to this article. Address correspondence and reprint requests to Anne Des Roches, M.D., CHU Sainte-Justine, Division of Allergy and Clinical Immunology, Department of Pediatrics, 3175 Chemin de la Côte-Sainte-Catherine, Montreal, Qc, Canada, H3T 1C5. E-mail address: a.des.roches@umontreal.ca.

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Table 1 Survey questionnaire

Type of allergic reaction to PCA
Rash (urticarial or maculopapular)
Angioedema
Bronchospasm
Anaphylaxis
Parents' reaction to their child's allergic reaction to PCA
Very frightened and thought the reaction could be life-threatening
Very frightened but did not think the reaction could be life-threatening
Somewhat frightened by the reaction
Not frightened by the reaction
Subsequent need and use of antibiotics by the child
If applicable, the number of courses of antibiotics and the name of each antibiotic taken since the allergist evaluation
If applicable, the reason a PCA was not used despite a need for antibiotics
Parent's refusal because of past allergic reaction to PCA
Physician's preference based on past allergic reaction to PCA
Physician's preference for any other reason
Adverse reaction related to antibiotic use
Child's history of allergic reaction to a non-PCA antibiotic
Family history of allergic reaction to antibiotics
PCA = penicillin-class antibiotic.

all evaluated on an elective basis (when well and not requiring antibiotics).

Several years later, the parents of the children were contacted by phone and, if they accepted, a survey was performed (Table 1). The survey took place between May and October 2002 and was performed by a single surveyor. An information sheet had been sent by mail to the parents before the phone call to encourage them to collect information on their child's antibiotic use.

The protocol at the time consisted of skin testing with penicilloyl-polylysine (PrePen; Hollister-Stier, Taylor Pharmaceuticals, Decature, IL) at a concentration of 6×10^{-5} (PrePen was withdrawn from the Canadian market in 2004 and not recommercialized since) and penicillin G (Novopharm Limited, Toronto, Canada) at a concentration of 10,000 U/mL using the skin prick test followed if negative by an intradermal test. Histamine diphosphate (Galenova, Inc., St. Hyacinthe, Canada) at a concentration of 2 mg/mL and saline were used as positive and negative controls, respectively. Reading was done 15 minutes later and a positive test was defined as a papule of ≥ 5 mm than the negative control with erythema for skin-prick test

and intradermal test. When skin testing was negative, a drug challenge was performed as suggested by the American Academy of Allergy, Asthma, and Immunology in the absence of the minor determinant mixture and because in our experience $\sim 5\%$ of patients react on challenge despite negative skin tests.⁴ It usually took place on the same day and consisted of administering penicillin V oral solution (Wyeth Pharmaceuticals, Montreal, Canada) in graded doses, because it was the most commonly used PCA in our region at the time. Incremental doses ($1/100$, $1/10$, and full dose) were administered at intervals of 20 minutes up to a full dose of 250 mg for children weighing ≤ 27 kg or 500 mg for children weighing > 27 kg or until symptoms occurred. The patient was then observed for 1 hour and 30 minutes. If no reaction had occurred by the end of the observation period, parents were informed that their child was not allergic to penicillin and that the risk of reaction on subsequent exposure was minimal, averaging that of the general population. Hence, they were told that their child could safely receive penicillin in the future. They were also asked to report any adverse reactions occurring in the next 24 hours to document delayed hypersensitivity although this is uncommon. Finally, an explicit letter confirming that penicillin allergy had been ruled out (based on negative skin tests and drug challenge) was sent to the child's physician stating that penicillin could be used without any particular precaution in the future.

Written informed consent at the time of evaluation and oral informed consent at the time of survey were obtained from parents or legal tutor. The study has been approved by our institution review board.

Continuous variables are presented as means and SDs. Categorical variables are presented as frequencies and percentages. Patients were divided in groups according to antibiotic use and comparisons between groups were made using the chi-square test (for categorical variables) and the one-way ANOVA test (for continuous variables). A value of $p < 0.05$ was considered statistically significant. Relative risk was calculated with 95% confidence interval. All statistical analyses were performed with SPSS Statistics 19 software (IBM Corp., Somers, NY).

RESULTS

Among the 200 patients who had a negative penicillin skin test and drug challenge, 170 (85%) completed the survey and 30 refused or were not reached. At least one course of antibiotics had been used in 130 children (76%) after the allergist evaluation. PCA use was reported in 59 children (45%); 60 (46%) had used an antibiotic other than a PCA and 11 (8%) did not remember if the antibiotic they had taken was a PCA.

Characteristics of the patients are shown in Table 2 according to antibiotic use. Age and gender of children

Table 2 Characteristics of the study population according to antibiotic use

	Used PCA (<i>n</i> = 59)	Did Not Use PCA (<i>n</i> = 60)	Do Not Know if Used PCA (<i>n</i> = 11)	Did Not Use Antibiotics (<i>n</i> = 40)	Could Not Be Reached/Refused to Answer (<i>n</i> = 30)
Age (yr)	9.9 ± 4.0	9.7 ± 4.4	7.2 ± 3.2	11.9 ± 4.9*	9.7 ± 4.2
Female gender (%)	32 (54)	30 (50)	5 (45)	20 (50)	11 (37)
Time elapsed since allergist evaluation (mo)	37.9 ± 8.4	38.0 ± 8.4	37.9 ± 9.0	36.2 ± 7.0	N/A
Courses of antibiotics since allergist evaluation	3.9 ± 3.4	3.8 ± 3.3	2.7 ± 3.8	N/A	N/A
Allergic reaction to PCA (%)					
Rash#	54 (92)	53 (88)	10 (91)	36 (90)	N/A
Angioedema	3 (5)	7 (12)	1 (9)	2 (5)	
Bronchospasm	1 (2)	0	0	2 (5)	
Anaphylaxis	1 (2)	0	0	0	
Parents very frightened by their child's allergic reaction§ (%)	28 (47)	30 (50)	5 (45)	17 (43)	N/A
History of allergic reaction to a non-PCA antibiotic (%)	16 (27)	15 (25)	4 (36)	10 (25)	N/A
History of allergic reaction to antibiotics among first-degree relatives (%)	19 (32)	18 (30)	5 (45)	13 (33)	N/A

*Age significantly differed from patients who used antibiotics ($p = 0.004$).

#Urticarial or maculopapular.

§Parents very frightened by their child's allergic reaction (whether they thought the reaction could be life-threatening or not).

PCA = penicillin-class antibiotic; N/A, not applicable.

whose parents could not be reached or refused to answer the survey did not significantly differ from children whose parents completed the survey. Children who had not used antibiotics since the allergist evaluation were found to be significantly older than children who had used antibiotics ($p = 0.004$) but did not differ for other variables.

Among children who took a non-PCA antibiotic, 40% (24/60) did not receive a PCA because their parents still feared an adverse reaction, 15% (9/60) did not because of their physician's unwillingness despite a negative skin test and drug challenge, and 45% (27/60) did not for reasons unrelated to their past allergic reaction.

Parents who refused a PCA were shown to differ from other parents whose children took PCAs in that they had been more frightened by their child's allergic reaction ($p = 0.008$). The relative risk of subsequently refusing PCA in parents who were very frightened by their child's allergic reaction compared with parents who were not was 2.9 (95% CI, 1.2–7.0). A more severe initial reaction (defined as the presence of angioedema, bronchospasm, or anaphylaxis) did not have a statistically significant association with parent's PCA refusal

($p = 0.117$). These children did not differ for any other characteristic (Table 3).

Children whose physicians did not prescribe a PCA because of the past allergic reaction did not differ from other children who used PCAs for any characteristic nor did children who were given non-PCA antibiotics for reasons unrelated to their past allergic reaction.

Among children who took a PCA, five reported an adverse reaction. A rash to amoxicillin was reported in two children. Two patients had a rash to pivampicillin and one had facial angioedema without airway involvement after a second course of penicillin V. One of the patients who had a rash to amoxicillin took the drug again without any reaction. At the time of analysis none of these children had been reevaluated in our institution.

Among the 60 patients who took a non-PCA, one reported a rash with azithromycin and none an adverse reaction to a cephalosporin.

DISCUSSION

Elective penicillin skin testing is a growing practice because studies have shown the negative impact of

Table 3 Characteristics of children whose parents refused PCA

	Refused PCA (n = 24)	Used PCA (n = 59)	p Value
Age (yr)	10.3 ± 4.8	9.9 ± 4.0	0.701
Female gender (%)	13 (54)	32 (54)	0.995
Time elapsed since allergist evaluation (mo)	40.2 ± 9.1	37.9 ± 8.6	0.287
Courses of antibiotics since allergist evaluation	4.6 ± 4.0	3.9 ± 3.4	0.456
Allergic reaction to PCA (%)			
Rash*	19 (79)	54 (92)	0.117#
Angioedema	5 (21)	3 (5)	
Bronchospasm	0	1 (2)	
Anaphylaxis	0	1 (2)	
Parents very frightened by their child's allergic reaction§ (%)	19 (79)	28 (48)	0.008
History of allergic reaction to a non-PCA in the child (%)	10 (42)	16 (27)	0.195
History of allergic reaction to antibiotics among first-degree relatives (%)	7 (29)	19 (32)	0.787

*Urticarial or maculopapular.

#Comparison between rash only and more severe reactions (angioedema, bronchospasm, and anaphylaxis).

§Parents very frightened by their child's allergic reaction (whether they thought the reaction could be life-threatening or not).
PCA = penicillin-class antibiotic.

avoiding β -lactams in all patients with a history of penicillin allergy and the impracticality of performing skin tests only at time of need.⁴ Also, the theoretical risk of resensitization after a negative skin test and/or drug challenge has been shown to be minimal, thus reinforcing the value of this approach.^{1,3,5,6} However, reluctance to reuse a PCAs despite a negative penicillin skin test might compromise this practice and has been shown to be prevalent in the adult population.⁷ In this study, we have found this situation to be also prevalent in the pediatric population despite performing drug challenges in all patients.

However, we show that children do benefit from elective penicillin allergy assessment because a high proportion (76%; 130/170) of these needs to use antibiotics in the following years. Among children who had to use antibiotics, 41% used a PCA without any adverse reaction, showing that almost one-half of these children would have had to avoid PCAs unnecessarily if testing had not been done.

A significant proportion (25%; 33/130) of children did not take a PCA despite a need for antibiotics because either their parents (24/33) or their physician (9/33) was still concerned about the risk of adverse reaction despite negative testing that included drug challenges in all patients. By comparison, in the study by Warrington and colleagues in which only skin testing was performed, more than one-half of patients or their physicians were reluctant to reuse PCAs compared with 25% in this study.⁷ Comparisons between these two studies are

hazardous because it does not account for confounding variables. Nonetheless, it suggests that performance of drug challenges favors PCA reuse. In contrast, Macy and colleagues found PCA reuse in the year following a negative skin test to be similar in patients who had undergone a drug challenge compared with those who had declined one.³ However, in their study the patient made the decision whether they wanted a drug challenge or not and a majority of patients chose to undergo one (146/196), hence introducing a possible bias.

In this study we show that parents who refused PCAs were significantly more likely to have been very frightened by their child's allergic reaction compared with parents whose child had reused PCA. To the contrary, a history of severe adverse reaction to PCAs (defined as the presence of angioedema, bronchospasm, or anaphylaxis) was not a significant predictor of PCA refusal. This shows the subjectivity of the parent's reaction and the importance of addressing this issue during the child's evaluation.

This study was not designed to assess for the physician's viewpoint because only parents were surveyed. However, it is noteworthy that children whose physician was unwilling to prescribe PCAs because of the past allergic reaction did not have a more severe allergic reaction and that their parents were not more likely to have been very frightened by the allergic reaction than children who reused PCAs. Therefore, despite being provided by parents, results on physician's reluctance to prescribe PCAs do not seem to be biased.

Adverse reactions to PCAs were reported in 5 of 59 patients (8.5%). All reactions were benign. Four had their adverse reaction with their first exposure to either pivampicillin or amoxicillin. One patient took the same antibiotic (amoxicillin) again without any reaction. Consequently, three patients experienced a rash that was possibly drug related out of 59 (5.1%) patients on their first exposure to a PCA. These patients were not reassessed by an allergist; therefore, the causative role of the drug could not be confirmed or infirmed. Infections, which are a common cause of cutaneous rash in children, could provide an alternative explanation for these reactions.⁸ It could also be argued that these patients were selectively allergic to the aminopenicillin side-chain because this possibility was not ruled out by our evaluation at the time. However, this particular sensitivity has been shown to be rare in North America.^{9,10} Moreover, the occurrence of a maculopapular rash during a treatment with aminopenicillins averages 5–10% in the general population.⁴ This rate is comparable with the rate observed in our cohort (6.8%; 4/59), suggesting that the reaction risk to PCAs returns to baseline after a negative evaluation. Also, comparable studies have reported a similar rate of adverse reaction to β -lactams after a negative evaluation, varying from 1.8 to 7.6%.^{2,7,11,12}

Angioedema was reported in one patient during a second course of penicillin V after the allergist evaluation. This reaction could represent re sensitization during the first course of penicillin V taken after the drug challenge. However, the patient was not reevaluated in our allergy clinic to confirm this hypothesis.

Data on antibiotic use was collected through a phone survey and was provided by the parents. Therefore, it is subject to recall bias. To palliate this limitation, an information sheet had been sent to the parents before the survey encouraging them to collect information on their child's antibiotic use over the preceding years. This way they had sufficient time to contact their pharmacy and obtain a complete list of antibiotics prescribed if they had any doubts. Overall, 11 parents among 170 participants could not remember if the antibiotic their child had used was a PCA, thus introducing a minor bias.

Study strengths include a high participation rate (85%) and large population size (170 patients completed the survey). It could be argued that children not included in the study because their parents refused to answer or were not reached could have introduced a selection bias. However, their age and gender, which were the sole available variables for analysis, did not differ significantly from children included in the study.

Age differed from the mean only in the group who did not reuse antibiotics. This likely reflects the decreasing need for antibiotics with increasing age.

In conclusion, this study confirms that elective penicillin skin testing is useful and safe regarding PCA reuse in the pediatric population. Almost one-half of children reused a PCA without any adverse reaction in the years after a negative penicillin skin test and successful drug challenge. The rate of adverse reaction to a PCA was not higher in these children compared with the general population. A significant proportion of parents remains fearful toward PCAs and refuses them when needed despite negative testing. These parents can be easily identified at the time the child is evaluated for his/her history of penicillin allergy by asking them if they were very frightened by their child's allergic reaction. Additionally, some physicians still appear to be reluctant to prescribe PCAs despite negative testing. Hopefully, particular attention and additional reassurance aimed at these parents and improved education on penicillin allergy of primary care physicians will help prevent this undesirable situation in the future.

REFERENCES

1. Mendelson LM, Ressler C, Rosen JP, and Selcow JE. Routine elective penicillin allergy skin testing in children and adolescents: study of sensitization. *J Allergy Clin Immunol* 73:76–81, 1984.
2. Pichichero ME, and Pichichero DM. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: Reliability of examination assessed by skin testing and oral challenge. *J Pediatr* 132: 137–143, 1998.
3. Macy E. Elective penicillin skin testing and amoxicillin challenge: Effect on outpatient antibiotic use, cost, and clinical outcomes. *J Allergy Clin Immunol* 102:281–285, 1998.
4. Joint Task Force on Practice Parameters. Drug allergy: An updated practice parameter. *Ann Allergy Asthma Immunol* 105: 259–273, 2010.
5. Solensky R, Earl HS, and Gruchalla RS. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med* 162:822–826, 2002.
6. Bittner A, and Greenberger PA. Incidence of resensitization after tolerating penicillin treatment in penicillin-allergic patients. *Allergy Asthma Proc* 25:161–164, 2004.
7. Warrington RJ, Burton R, and Tsai E. The value of routine penicillin allergy skin testing in an outpatient population. *Allergy Asthma Proc* 24:199–202, 2003.
8. Liu TH, Lin YR, Yang KC, et al. First attack of acute urticaria in pediatric emergency department. *Pediatr Neonatol* 49:58–64, 2008.
9. Macy E, and Burchette RJ. Oral antibiotic adverse reactions after penicillin skin testing: Multi-year follow-up. *Allergy* 57:1151–1158, 2002.
10. Macy E, Richter PK, Falkoff R, and Zeiger R. Skin testing with penicilloate and penilloate prepared by an improved method: Amoxicillin oral challenge in patients with negative skin test responses to penicillin reagents. *J Allergy Clin Immunol* 100: 586–591, 1997.
11. Macy E, Mangat R, and 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* 111:1111–1115, 2003.
12. Demoly P, Romano A, Botelho C, et al. Determining the negative predictive value of provocation tests with beta-lactams. *Allergy* 65:327–332, 2010. □

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