

Prevalence of Skin Test Reactivity in Patients with Convincing, Vague, and Unacceptable Histories of Penicillin Allergy

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ABSTRACT

Penicillin (PCN) allergy has been vastly overdiagnosed, and too many people are incorrectly labeled as allergic to PCN, which affects their health by preventing the use of β -lactam antibiotics. This investigation explores whether taking a careful history can eliminate the need for some to carry the PCN allergy label. A retrospective study of a focused history and PCN skin testing was done in a consecutive sample of a suburban allergy population of 319 patients who had a positive history of PCN allergy. The patients were divided into three groups based on PCN history: convincing, vague, and unacceptable. The convincing group had patients with impressive histories of PCN allergy likely to be immunoglobulin E-mediated. The vague group had unimpressive but plausible histories of PCN allergy. The unacceptable group were those patients with the PCN-allergic label who were either never exposed to PCN or the PCN reaction was too far-fetched to be believable. Out of 319 patients with a positive PCN allergy history, 135 (42.3%) patients were classified as convincing, 150 (47%) patients were classified as vague, and 34 (10.7%) patients were classified as unacceptable. Positive PCN skin tests were found in 19 of 135 (14.1%) patients in the convincing group, in 10 of 150 (6.7%) patients in the vague group, and 0 of 34 (0%) patients in the unacceptable group. The finding that 6.7% of

patients with a vague PCN allergy history had positive skin tests suggests that skin testing is necessary in this group. The PCN-allergic label in the unacceptable group had been unchallenged by 33 primary care physicians and 9 allergists. This study suggests that physician acceptance of unwarranted PCN-allergic labels is not uncommon, and that such labels can be removed without skin testing. (Allergy and Asthma Proc 26:59–64, 2005)

Approximately 10% of the population relate a history of penicillin (PCN) allergy.^{1,2} In the United States ~28 million people have a label of being allergic to PCN and potentially compromise their health by taking other antibiotics that are less effective, have more side effects, are more expensive,³ and may lead to the development of resistant organisms (e.g., vancomycin-resistant bacteria).² Many studies have shown that only 10–15% of those people who relate a history of PCN allergy are actually allergic to PCN.³ Therefore, PCN allergy is overdiagnosed and large numbers of people are needlessly denied the benefits of this efficacious class of antibiotics. In 1984, Mendelson *et al.*⁴ made a breakthrough with the problem of overdiagnosis of PCN allergy when they introduced the idea of elective PCN skin testing in the office setting with pediatric patients. When patients with a PCN-allergic label are electively skin tested, most who are found to be skin test negative can have the PCN-allergic label discarded.

In evaluating patients with a positive history of PCN allergy, the history itself may assume more prominence because there has been a tendency to skin test less in the past few years,⁵ and at times it has been difficult to obtain benzyl penicilloyl-polylysine (BPL) and the chemicals needed to formulate the PCN reagents. This study examines

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the association of PCN skin test reactivity with the history of PCN allergy, where there has been a lack of consistency in terminology, and particularly focuses on vague histories. Solensky *et al.*, in a literature review of positive PCN allergy histories, consolidated disparate definitions into two useful groups, “convincing” histories that are likely to be immunoglobulin E (IgE)-mediated and “vague” histories that are unlikely to be IgE-mediated.⁶ Investigators have used various terms to describe vague PCN allergy histories including “questionable,”⁷ “invalid,”⁸ “uncertain,”⁹ “atypical,”¹⁰ and “remote.”¹¹ This study differentiates vague histories of PCN allergy that are unimpressive but plausible (termed “vague”) and those that are unbelievable (termed “unacceptable”), as defined by inclusion criteria, and investigates whether taking a careful history of PCN allergy can allow some PCN-allergic labels to be discarded.

METHODS

Patients

The patients in this study were seen in a suburban allergy practice from 1986 to 2002. If the patient gave a history of PCN allergy on the initial workup for other problems, a detailed history of PCN allergy was taken followed by PCN skin testing and an oral PCN challenge if the skin tests were negative. The study was done retrospectively and included 319 consecutive patients with a positive PCN allergy history with <20% declining participation for various reasons. In addition, to investigate the prevalence of a positive history of PCN allergy in this population, a retrospective chart review was done (excluding patients referred for antibiotic adverse reactions) on all consecutive patients seen in the general allergy practice from January 1998 through 2002.

PCN Allergy History

All histories were performed by the principal investigator. The patient or patient's parent was asked about clinical features of the reaction, age at the time of reaction, type and amount of PCN, route of PCN administration, time between exposure until reaction, illness for which PCN was given, other medications used when the reaction occurred, who observed the reaction, history of β -lactam exposure before and after the reaction, and history of other drug reactions.

PCN Skin Test Reagents

The major determinant, BPL, was purchased as PrePen from Hollister-Stier Laboratories (Spokane, WA). Potassium PCN G (PG) was obtained from Pfizer Laboratories (New York, NY), and amoxicillin was obtained from the Bristol-Myers Squibb Co. (Princeton, NJ). The minor PCN determinant reagents of PG and penicilloate (P) each had a concentration of 1×10^{-2} M.

A solution of 1 million U of potassium PG was made fresh on the day of skin testing by mixing PCN with 8.0 cc

of sterile NaCl solution, and a dilution of 0.5 cc of this PG solution with 9.5 cc of sterile NaCl solution also was made fresh before use in skin testing. Sodium hydroxide solution was prepared by dissolving 9.1 g of NaOH in distilled water to make a 0.114 N NaOH solution, which was sterilized by autoclaving and sterile filtration. A vial of 1 million U of potassium PG was mixed fresh on the day of skin testing with 8.0 cc of sterile NaOH solution by shaking to make P/PG stock solution. After 5 minutes of incubation at room temperature, the P/PG skin test reagent was immediately prepared by diluting 1 cc of the P/PG stock solution with 9 cc of ice-cold sterile NaCl solution. The reagent was still cold when used and was prepared fresh before each skin testing.

Procedures for PCN Skin Testing and Challenge

Patients were off antihistamines for 72 hours before PCN skin testing. Patients were skin tested on the volar aspect of the forearm by the prick (puncture) technique using simultaneously all three PCN reagents (BPL, PG, and P/PG) with diluent and histamine controls. If the wheal response was $\geq 3 \times 3$ mm with surrounding erythema in 15 minutes, the response was considered positive. If the prick test was negative, 0.01–0.02 mL of each reagent was injected intradermally in duplicate in the volar aspect of the forearm. The intradermal tests with all three PCN reagents, diluent, and histamine controls were placed simultaneously and read after 15 minutes. If the wheal was 3×3 mm greater than the initial bleb with surrounding erythema, the test was considered positive. All skin tests were performed by a trained allergy nurse and were read by the principal investigator. If the intradermal test was negative, the patient was given an oral challenge with PCN V-K, 250 mg, and observed in the office for 1 hour. Vital signs (blood pressure and pulse) were taken before the challenge and after the 1-hour observation period. In addition to the PCN tests, four patients were skin tested using the same technique with prick and intradermal tests to amoxicillin at 5 mg/mL, and with negative tests, three patients were challenged with oral amoxicillin, 250 mg, and observed for 1 hour, and the fourth patient was orally desensitized/challenged in the hospital.

Classification of Patients

The PCN history-positive patients were initially placed into two groups: convincing and vague. The vague history patients, defined as unlikely to have had IgE-mediated PCN reactions, were further subdivided into “vague” and “unacceptable” history categories. A convincing history of PCN allergy was defined as likely to be IgE mediated if it included at least one of the following: symptoms of airway obstruction, dyspnea, laryngeal edema, dizziness, unconsciousness, pruritic urticaria/angioedema, pruritic upper airway, explosive time-related vomiting and/or diarrhea, and skin eruptions with a pruritic component. The vague category included patients with a history of skin eruptions

TABLE I

PCN Skin Test Results in Categories of History-Positive Patients					
	Number of Patients	Percent of Patients	Positive Skin Tests	Percent of Positive Skin Tests	Reagents Positive in PCN Skin Test Reactions
Convincing history PCN allergy	135	42.3	19	14.1	8 BPL 5 PG 2 BPL + PG 2 BPL + P 2 PG + P
Vague history PCN allergy	150	47	10	6.7	6 BPL 2 BPL + PG 1 BPL + P 1 P
Unacceptable history PCN allergy	34	10.7	0	0	
Total positive history PCN allergy	319	100	29	9.1	

without pruritus, pruritus of the skin without an eruption, fever, vague breathing symptoms, vague gastrointestinal symptoms, vague central nervous system (CNS) symptoms, vague joint symptoms, unknown reactions from 0 to 6 years old told to the patient by family members, and a faded memory of the adverse PCN reaction. In the few instances when the patient cited symptoms of more than one organ system, the predominant organ system was designated. The unacceptable history of the PCN group were patients who carried the PCN-allergic label who had either never been exposed to PCN or the purported PCN reaction was grossly inappropriate such as vaginitis 1 month after exposure to PCN.

Statistics

Statistical analysis was performed with the SAS program for windows. The chi-square test was used. The Yates correction was used to make the chi-square test more stable.

RESULTS

The classification of 319 PCN history-positive patients and their PCN skin testing results are shown in Table I. The study population included 104 male patients and 215 female patients ranging in age from 1.4 to 83 years with 7.8% being below the age of 11 years and 18.8% being below the age of 21 years, and there was an overall mean age of 39.5 years. Of the 319 patients who carried a PCN-allergic label, 184 (57.7%) patients had a history of PCN allergy unlikely to be IgE-mediated, which was divided into 150 (47%) patients in the vague group and 34 (10.7%) patients in the unacceptable group. Of the 78 patients who declined participation in the study, 31 (39.7%) patients had convincing histories, 38 (48.7%) patients had vague histories, and 9 (11.5%) patients had unacceptable histories.

There were no adverse reactions to the PCN skin tests and no positive reactions to the prick puncture test, but one patient had a borderline reaction to this test, which was confirmed as positive with an intradermal test. The time from index reactions to skin test positivity in the convincing group was six patients less than 1 year, six patients 1–5 years, and seven patients >5 years, and in the vague group two patients <1 year, two patients 1–5 years, and six patients >5 years. Out of the 290 patients who had negative PCN skin tests there were 288 oral challenges with PCN V-K performed. Thirteen patients reported adverse reactions to the challenges including face itching, trunk itching, lower-lip tingling and numbness, increase in postnasal drip, heart racing, heart racing with lightheadedness, minor chest pain, increase in nasal secretions, feeling cold, headache, throat tightness, heartburn, and fatigue. These reactions ceased within 15–75 minutes without any objective findings.

Using the chi-square test comparing positive skin tests in the vague group versus the unacceptable group, there is no significant difference ($p = 0.20$). A comparison of positive skin tests in acceptable histories (convincing plus vague groups) versus unacceptable histories (unacceptable group) was significant ($p = 0.025$).

The prevalence of a positive history of PCN allergy in this population was obtained from 1025 consecutive patients with various general allergy presentations. Of these 1025 patients, 911 (88.9%) patients had a negative history and 114 (11.1%) patients had a positive history of PCN allergy. Most of these 114 history-positive patients were the same subjects as those included in the study group of 319 PCN history-positive patients. Of those patients who recalled the type of PCN in the index adverse reaction, 61 patients identified amoxicillin; 53 of these 61 patients had

TABLE II

PCN Skin Test Results in Groups of Patients with a Vague History of PCN Allergy				
Symptomatic Organ System, Other Groups	Number of Patients	Percent of Patients	Positive Skin Tests	Reagents Positive in PCN Skin Test Reactions
Skin	99	66	8	4 BPL 2 BPL + PG 1 BPL + P 1 P
Joints	4	2.7		
Respiratory	3	2		
CNS	6	4		
Gastrointestinal	10	6.7		
Unknown reaction (0–6 years)	16	10.7	2	2 BPL
Faded memory	9	6		
Other	3	2		

negative skin tests to the major and minor determinants, and 4 of these 53 patients with convincing histories of amoxicillin reactions also had negative amoxicillin skin tests. There were 17 patients who identified ampicillin in the index reactions and all 17 had negative skin tests to the major and minor determinants. Of the four patients who had negative amoxicillin skin tests, three had negative amoxicillin challenges. The fourth patient, a 5-year-old boy with an amoxicillin allergy history of wheezing, angioedema, and urticaria was orally desensitized/challenged to amoxicillin in the hospital over 4 hours with a cumulative dose of 400 mg, and he tolerated the procedure well except for one fleeting hive on the chest noted after 45 minutes.

Patients who were placed in the vague category are shown in Table II, broken down into groups of affected organ system as reported by the patient, and other groups. Of the 150 patients in the vague category, the largest group was the skin organ system with 99 patients, and 8 of these patients had positive PCN skin tests. In the skin symptom group, 88 were patients with polymorphous skin eruptions who did not have a memory of pruritus, 7 patients had large local skin reactions to PCN injections, and 4 patients had PCN-associated pruritus without skin lesions. The next largest vague group was 16 patients who were later told by their family that they had a PCN reaction before they were 7 years old and thus too young to remember the event themselves. In 10 of the 16 of these purported reactions, the patient had no specific information about why they had a PCN-allergic label, and 6 patients were told by their family what the alleged PCN reaction was. There were 10 patients in the vague gastrointestinal group with 5 of these patients reporting reactions that were predominantly nausea, 3 patients reporting reactions that were predominantly vomiting, and 2 patients reporting reactions that were predominantly diarrhea. There also was a group of nine patients who didn't remember the reason for their PCN-allergic label. Two of these nine patients said they knew at one time but subse-

TABLE III

Patients with an Unacceptable History of PCN Allergy

Number of Patients	Reason for PCN-Allergic Label
5	History of inhalant allergy and/or asthma
7	Family history of PCN allergy
2	History of mold allergy
6	Headache with PCN
3	Vaginitis with PCN
3	Psychological symptoms (anxiety and/or depersonalization) with PCN
3	Pain with PCN injections
4	Oral symptoms (toothache, sore gums, and/or tongue burning) with PCN
1	Leg weakness with PCN

quently forgot the circumstances of being labeled PCN allergic. In the six vague CNS reaction groups, three that were associated with oral PCN were described as convulsions. Of the four joint system reactions, three were characterized by joint pain and swelling and one was a possible serum sickness reaction with fever, malaise, and joint symptoms. In the group listed as "other," two patients carried a PCN-allergic label because they had a positive PCN skin test without having had an adverse PCN reaction, and one patient was told by a previous physician to consider himself allergic to PCN because his mother had a PCN reaction when he was in utero.

The data for the 34 patients in the unacceptable history of PCN allergy category are shown in Table III, listing the reasons that they carried the PCN-allergic label. In this group, there were 13 male patients and 21 female patients, and the ages ranged from 16 to 69 years with a mean age of 44.5 years. Of the 34 patients in the unacceptable group, 33 patients had been seen by at least one primary care physician and 9 patients had undergone prior consultations with

allergists. All of the physicians who had prior contact with the patients in the unacceptable history group either advocated or did not challenge the PCN-allergic labels.

DISCUSSION

The findings in this investigation suggest that a portion of those patients with a history of PCN allergy and labeled allergic to PCN can have this label removed without skin testing. Solensky *et al.*⁶ and Puchner and Zacharisen¹² stated that all subjects with vague histories of PCN allergy should be skin tested. The findings in this study support their position for the majority of patients who have a history unlikely to be IgE mediated but not for a subgroup of patients with histories that are classified in this study as unacceptable. A history of PCN allergy unlikely to be IgE mediated covers a wide spectrum, and in this report outliers are identified who appear to carry incorrectly a PCN-allergic label.

The results in this study of the prevalence of unacceptable histories of PCN allergy and skin testing in these patients are consistent with previous reports. Green *et al.*⁸ reported that of 1042 patients with positive histories of PCN allergy, 107 (10.3%) of the histories were judged to be “invalid,” with 4 of these 107 having positive PCN skin tests. Gadde *et al.*⁹ reported that out of 776 patients with a positive history of PCN allergy, the histories besides those of anaphylaxis, urticaria, or exanthem left 227 “other” (29.2%) and 57 “uncertain” (7.3%). In their report, positive PCN skin tests were found in 4 of the 227 (1.8%) patients in the “other” group, and in 1 of the 57 (1.7%) patients in the “uncertain” group. Van Dellen and Gleich¹³ reported that 15 out of 123 positive PCN allergy histories were “local or uncertain” reactions, and 1 of these 15 had a positive skin test. Van Arsdel *et al.*¹⁰ reported that out of 85 PCN history-positive patients, 17 (19.8%) patients were in a group of “atypical or could not recall” history, and all of the 17 patients in this group had negative PCN skin tests. Warrington *et al.*¹¹ reported that in a cohort of 53 patients with a “remote” history of PCN allergy, all 53 patients had negative PCN skin tests. In addition, Tripp and Brown¹⁴ reported, without PCN skin testing, that of 326 patients relating a positive history of β -lactam allergy, 43 (13%) patients had inappropriate allergic labels, which the investigators felt should be removed by history alone.

At least 8.5–9% of the population¹⁵ incorrectly believe that they are allergic to PCN and therefore are denied the health benefits of this important class of antibiotics. It was thought in the 1970s and 1980s that the overdiagnosis of PCN allergy could be addressed by PCN skin testing, but the early enthusiasm for using this approach seems to have diminished.^{5,12} Also, the lack of commercially available PCN reagents probably has added to the decline of PCN allergy skin testing. The concern with the few anaphylactic deaths that have occurred with oral PCN^{16,17} has undoubtedly contributed to the continuing inflated number of those

labeled PCN allergic and the overreporting of adverse PCN reactions by patients, parents, and physicians. The history of an adverse reaction to PCN has potential inaccuracies that also can contribute to the inflated number of these reported reactions. Factors that confound the history include declining hypersensitivity, underlying illness, other medications taken at the same time, lack of a temporal association between taking PCN and symptoms, fading memory of the nature of a skin eruption, and, in some individuals, perhaps an underlying fear of anaphylaxis. These difficulties often are not applicable to many who relate unacceptable histories of PCN allergy. For example, a patient’s potentially faded memory does not play any role when an allergy to PCN history is based on having a personal history of atopy, having a family history of PCN allergy, or on a previous reaction to PCN that clearly is unassociated such as headache or vaginitis.

The unacceptable history of PCN allergy essentially is an incorrect history that, for the patients in this study, was not challenged and in many cases was advocated by their prior physicians. The finding that none of these physicians challenged the PCN-allergic label is consistent with other reports that inappropriate allergy to PCN labels often are not discarded.^{11,14,18,19} Although limited, there are some data available that physicians may be able to use for guidance in discerning whether a patient’s history of PCN allergy is acceptable or not. There is evidence that a personal^{20–22} or family^{20,23} history of allergy is not associated with an increase in PCN IgE antibodies. In addition, according to the Drug Hypersensitivity Practice Parameter,²⁴ family history is not a valid history of PCN allergy.

A potential limitation of this study was the atypical population of suburban allergy patients. However, the prevalence of a positive history of PCN allergy in 11.1% of a large (1025 patients) consecutive sampling of this population is similar to that in other populations.^{1,2,18} Another potential limitation of this study was the relatively small sample size. A study with a larger sample may reflect a small percentage of positive skin tests in the unacceptable history group, because even patients with negative histories of PCN allergy have been found to have a low percentage of positive skin tests.^{25,26}

Although there have been deaths from PCN without prior histories of reactions,²⁷ a careful history can contribute to the evaluation of the risk of PCN anaphylaxis and the decision of whether or not to skin test. A convincing history is a risk factor for anaphylaxis and there is general agreement that patients with this history should be skin tested. The approach to the patient who does not have a convincing history is less certain. If the history is vague, the data in this study that 6.7% of these patients had positive PCN skin tests suggest that skin testing is necessary to avoid missing the few potential PCN reactors in this group where there is a low risk for IgE-mediated reactions. In the vague group, the limited data suggest that there is less risk with adverse PCN reaction histories that are based on gastrointestinal, CNS,

joint, or respiratory symptoms than with histories that are based on skin symptoms, but a larger study is needed to clarify this. The most common PCN allergy history was in the vague group, which can present a conundrum. It would seem that a vague history would not reflect IgE-mediated allergy, but the finding that 6.7% of this group had positive skin tests suggests that some histories are inaccurately understated and can not be ignored. The most common vague symptoms were skin related, and the unique difficulties with recalling skin reactions may be a reason for understating the PCN history. The finding that there were no positive PCN tests in the 34 patients with unacceptable histories suggests that this group is less likely to have IgE antibodies and can be distinguished from those in the vague category. With PCN histories that are unacceptable, removing the PCN-allergic label and treating with PCN is not riskier than giving PCN to anyone without a PCN-allergic label.

In summary, the most common category of those patients with a positive PCN allergy history was the vague group where 10 of 150 (6.7%) patients had positive PCN skin tests, suggesting that skin testing patients with vague histories is necessary to avoid missing patients at risk for PCN reactions. It was found that 34 (10.7%) patients of a population of 319 subjects labeled allergic to PCN had unacceptable positive histories of PCN allergy because either they never had an exposure to PCN or the history was unbelievable. The PCN-allergic label in these 34 patients had not been removed by 33 primary care physicians and 9 allergists. The findings suggest that physician acceptance of this particular subgroup of those patients labeled allergic to PCN is not uncommon and that these patients can, without skin testing, have this label removed. This may help to lessen the overdiagnosis of PCN allergy and therefore avoid the unnecessary withholding of PCN treatment for a number of patients who have been labeled incorrectly as allergic to PCN.

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