Penicillin allergy: prevalence of vague history in skin test-positive patients

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Objective: Penicillin (PCN) skin testing is a reliable tool for predicting which patients can safely receive the antibiotic. Depending on the study, 7% to 76% of patients who have a history of PCN allergy have positive PCN skin tests. Many physicians approach patients who have a vague history of PCN allergy less cautiously than they approach those who have a convincing history suggestive of an IgE-mediated reaction. We reviewed the published literature to determine how many patients who had a history of PCN allergy and who were skin test-positive had a vague history of allergy.

Data Sources: By cross-referencing the keywords "penicillin" and "skin test," an Ovid MEDLINE search for English language studies published from 1966 to 1998 was performed.

Study Selection: Studies in which history positive/skin test-positive patients were identified, and which contained documentation of the type of previous reaction in these patients, were included in the analysis. The MEDLINE search revealed 295 English language articles, of which 27 fulfilled the inclusion criteria. Three additional studies published prior to 1966 (and therefore not available through MEDLINE) also were found, bringing the total to 30. A "convincing" history was defined to be one likely to be IgE-mediated (such as anaphylaxis, urticaria, angioedema or pruritic rash). A "vague" history was one unlikely to be IgE-mediated (such as maculopapular rash, GI symptoms, or an unknown reaction).

Results: Overall, 347/1063, or 33%, of history positive/skin test-positive patients had a vague PCN allergy history, with a range of 0% to 70% among the 30 studies.

Conclusion: A large proportion of patients who have PCN-specific IgE antibodies, as determined by skin testing, have vague PCN allergy histories. These results therefore, indicate that, like patients with convincing histories, patients with vague allergic histories should undergo PCN skin testing prior to PCN administration.

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INTRODUCTION

Physicians know that many patients who are labeled "penicillin (PCN) allergic" can safely receive the antibiotic. Penicillin skin testing was developed in the 1960s after the relevant immunogenic determinants had been elucidated, and it remains the most accurate method of detecting the presence or absence of PCN-specific IgE antibodies. The high negative predictive value of the test is especially useful because it indicates that more than 98% of patients who have a history of PCN allergy but who are skin test negative can safely receive the antibiotic.[1] The reported rate of positive skin tests in history-positive patients varies between 7% to 76%,[2] with most recent studies reporting rates less than 20%.[3–5] The wide variation is likely due to differences in patient selection and differences in factors such as the type of allergic history (vague or convincing), the length of time elapsed since the reaction occurred, the skin test reagents, the skin testing techniques, and the methods of skin test interpretation. Most studies have found that patients who have a convincing history of an IgE-mediated PCN reaction have higher rates of positive PCN skin tests than those who have a vague history.[4,6–8] It also has been found that patients who have a vague history of allergy consistently have higher positive skin test rates than normal nonallergic controls.[4,6,7] We have observed that many allergists and non-allergists approach patients who have a vague history of PCN allergy less cautiously than those who have a convincing history. In this study, we reviewed the published literature to determine what proportion of history positive patients who had positive skin tests had vague histories of PCN allergy.

METHODS

An Ovid MEDLINE literature search was performed for the years 1966 to 1998, by cross-referencing the keywords "penicillin" and "skin test." Studies published prior to 1966 were located by searching the references of the publications obtained via MEDLINE. Inclusion criteria for analysis were as follows: (1) English language articles, (2) studies in which patients with a history of PCN allergy were skin tested with penicilloyl-polylysine (PPL) and/or one or more minor antigenic determinants, and (3) documentation of the type of previous PCN reaction experienced by skin test positive patients. Exclusion criteria were as follows: (1) studies in which investigators chose not to skin test those patients who had a vague history of PCN allergy (ie, one not consistent with an IgE-mediated mechanism), (2) studies in which skin testing was performed on a group of patients with a particular history of PCN allergy

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only (such as those with a history of a delayed rash), and (3) studies with overlapping patient populations (ie, by investigators at the same institution).

We defined a vague history to be one unlikely to be IgE-mediated, such as a maculopapular rash (without pruritis) or isolated GI symptoms. Reactions listed as "unknown" also were included in the category of vague history. A convincing history, on the other hand, was considered to be one likely to be IgE-mediated, such as anaphylaxis, angioedema/urticaria, pruritic rash, or bronchospasm. A few of the authors did not specify the types of reactions, but rather divided them into vague and convincing groupings themselves.[6,7,9,10] The classification criteria used by these authors were essentially the same as the ones used by us.

RESULTS

The MEDLINE search using the above noted keywords resulted in 426 publications, 295 of which were in English. Of these, a total of 27 met the inclusion criteria and were included in the analysis. Searching the references of these articles, three additional studies prior to the year 1966 were found and also analyzed. Hence, a total of 30 studies, ranging from the years 1964 to 1998 were included in the analysis. Table 1 presents the 30 studies and their characteristics. As shown, of a total of 1,063 PCN skin test-positive patients, 347, or 33%, had a vague history of PCN allergy. Among individual studies, the percent of skin test-positive patients who had a vague history of PCN allergy ranged from 0% to 70%. Fifteen studies skin tested adults-only; five skin tested both adults and children; six skin tested children-only; and four authors did not comment on the ages of the participants. Because the studies span four decades and the PCN skin testing procedure still is not standardized today, the skin tests were not performed in a uniform manner. Some authors used a higher concentration of Penicilloyl-polylysine (PPL) than is used today, or injected a larger volume than the usual 0.02 to 0.03 mL used today. The criteria used to evaluate skin reactions also varied. Since minor

Table 1. List of Publications, PCN Skin Test Results, and Number of Vague Histories in Skin Test-Positive Patients

First Author and (Reference #)	Year	Reagents Used*	Subjects	# of Patients Skin Tested	# of Positive Skin Tests	# Vague History	% Vague History
Budd[15]	1964	PPL, Pen G	adults	27	7	3	43
Finke[18]	1965	PPL, Pen G	adults	120	44	18	41
Resnik[19]	1965	PPL	adults	15	5	1	20
Levine[16]	1966	PPL, Pen G, PC	adults	68	51	18	35
Idsoe[20]†	1968	PPL, Pen G	?	329	173	75	43
Rosh[21]	1968	PPL, Pen G	children	73	10	7	70
Levine[22]	1969	PPL, Pen G, PC, PN	adults	90	12	4	33
Bierman[23]	1969	PPL, Pen G	children	160	16	4	25
VanDellen[8]	1970	PPL, Pen G, PC, PN	?	123	43	11	26
Wide[24]	1971	PPL, Pen G	adults	54	9	0	0
Adkinson[6]	1971	PPL, Pen G, PC, PL	adults	169	43	15	35
Green[7]	1977	PPL, Pen G	?	1042	147	56	38
Warrington[25]	1978	PPL, Pen G, PC, PL	adults/children	253	29	15	52
Tuchinda[26]	1980	PPL, Pen G	children	25	16	6	38
Jarisch[27]	1981	PPL, Pen G	adults/children	50	15	0	0
Mendelson[9]	1984	PPL, Pen G, PC, PL	children	233	19	7	37
VanArsdel[28]	1986	PPL, Pen G, PC, PN	adults	97	12	0	0
Stark[29]‡	1987	PPL, Pen G, PC	adults	428	43	11	26
Borish[30]	1987	PPL, Pen G, PC, PL	adults/children	N/A	11	2	18
Blanca[31]	1989	PPL, Pen G	adults	N/A	14	3	21
Kwong[32]	1992	PPL, Pen G, PC, PL	adults	32	2	0	0
Silviu-Dan[33]	1993	PPL, Pen G, PC, PL	adults/children	112	11	4	36
Gadde[4]	1993	PPL, Pen G, PC, PL	adults	776	55	12	22
Audicana[34]	1994	PPL, Pen G, PC	adults	N/A	16	2	13
Romano[35]	1995	PPL, Pen G, PC	adults	195	29	0	0
Khoury[36]	1996	PPL, Pen G, PC, PL	?	N/A	44	27	61
Romano[37]	1997	PPL, Pen G, PC	children	84	4	0	0
Lisi[38]	1997	PPL, Pen G, PC	adults	101	27	12	44
Macy[5]	1997	PPL, Pen G, PC, PL	adults/children	348	60	11	18
Pichichero[10]	1998	PPL, Pen G, PC, PL	children	241	80	20	25
TOTAL				**5245**	**1063**	**347**	**33%**

* PC = penicilloate; PL = penilloate, PN = penicilloyl-N-propylamine.
† Original data are from deWeck and Blum.[39]
‡ Data is pooled from Stark,[29] Sullivan,[40] and Wendel.[41]

PCN antigens other than penicillin G were elucidated later than the major determinant, some of the earlier studies used only PPL and penicillin G in their skin testing. Overall, 19 out of 30 studies used a minor determinant other than penicillin G in skin testing.

DISCUSSION

Oftentimes physicians approach patients who have a vague history of PCN allergy less cautiously than they approach patients who have a history consistent with an IgE-mediated mechanism. We decided to review the literature to determine what proportion of history positive patients who had positive PCN skin tests had a vague history of PCN allergy. Our results revealed that 33% of skin test-positive patients, or one in three patients, had a vague history of PCN allergy. Although the range of 0% to 70% is wide, only 7 out of 30 studies showed a proportion less than 18%.

Clearly, differences in patient selection can greatly influence PCN skin test results. It would be expected that a high percentage of positive skin tests would be found if only patients with a convincing history of allergy are skin tested. In fact, studies in which only patients with convincing histories were skin tested consistently have found skin test positive rates greater than 50%.[11–14] Likewise, a high percentage of positive PCN skin tests would be expected if patient selection was limited to persons whose reactions are recent (because PCN-specific antibodies are known to wane over time). Studies with such patient populations also have found skin test positive rates greater than 50%.[15,16]

If physicians choose not to skin test patients with vague histories or if they preferentially skin test those patients with convincing histories, the percentage of skin test-positive patients who have vague histories obviously would be low. Hence, in order to determine the true percentage of skin test-positive patients who have a vague history of PCN allergy, the ideal population for study would be patients with any kind of history of "PCN allergy" who see the allergist for consultation. We cannot be certain that the publications included in our analysis contained such patient populations. Nonetheless, because we excluded studies which selected out patients with particular histories of allergy, and the 30 studies all included subjects with a variety of PCN allergy histories, we believe that the overall patient sample analyzed approximates this ideal population of "all comers" with a history of PCN allergy.

Differences among the studies included ages of patients, type of clinic where skin tests were performed, and length of time between reaction and testing. Also, there were variations in skin testing techniques, in the skin test reagents used, and in the methods of skin test interpretation. Despite these differences, most of the studies showed that a sizeable proportion of patients who had positive skin tests also had a vague history of PCN allergy. One possible explanation for this finding is that patients were unable to recall relevant details about their previous reactions. Another possible explanation may be that positive skin tests demonstrated in these patients simply represent false positive results. Previous studies have shown consistently that patients with a vague history of PCN allergy have higher rates of positive skin tests compared to nonallergic controls.[4,6,7] If false positive results were the sole explanation for our findings, one would not expect to see a difference between these two groups of patients, because theoretically the rate of false positive skin tests should be identical in all patients' skin tests. Another possible explanation for many skin test-positive patients having a vague history is that these cases may represent patients who had an unknown history of allergy, and these unknown histories may have, in fact, been IgE-mediated reactions. However, only 22 out of the 347 patients who had a vague history and were skin test positive had an unknown history. Even if we were to exclude "unknown history" from our definition of vague history, the percentage of vague histories among skin test-positive patients would decrease only slightly, from 33% (347/1063) to 31% (325/1063).

Since lack of accuracy of historical information is inevitable, it would appear that the type of previous reaction should not be a determining factor in whether or not to carry out PCN skin testing. In contrast, in a recent survey of practicing allergists, it was found that the type of PCN allergy history does, in fact, influence their decision regarding when to perform skin testing.[17] In the survey, allergists were asked under which circumstances they would perform PCN skin tests. Patients with five different histories of PCN allergy were presented to them. Of the Fellows of the American Academy of Asthma and Immunology (AAAAI) surveyed, 62% would skin test patients with an unknown distant adult reaction, 60.6% would skin test patients with an unknown childhood reaction, 58.2% would skin test patients with a history of maculopapular rash, 90% would skin test patients with a history of urticaria, and 87.5% would skin test patients with a history of anaphylaxis. Similarly, of the program directors surveyed, 75%, 65%, 56%, 98%, and 97% would perform skin tests in these five respective scenarios. Based on the results of this survey, it is clear that the type of history greatly influences the allergists' approach to the PCN-allergic patient.

In summary, our review of the literature revealed that 33% of patients who have a history of PCN allergy and are PCN skin test positive, have a vague history of PCN allergy. Based on these finding and the above noted survey, it appears that currently many allergists approach PCN skin testing in a manner which may miss a considerable number of patients who have PCN-specific IgE antibodies. We believe that all patients with a history of PCN allergy should be PCN skin tested, regardless of the type of history, if treatment with the antibiotic is being considered.

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