
Female sex as a risk factor for penicillin allergy

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Background: Identification of risk factors is an integral part of a physician's evaluation of a patient.

Objective: To determine whether female sex is an independent risk factor for penicillin allergy.

Methods: Rates of positive penicillin skin test (PST) results, according to sex, were determined in patients with a history of penicillin allergy undergoing penicillin allergy evaluation with major and minor determinants of penicillin between June 1, 2002, and June 30, 2004. Univariate and multivariate logistic regression analyses were used to calculate unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for sex differences in the rates of positive PST results.

Results: Of the 1,921 patients, 1,759 underwent PST and 157 did not; 5 medical records were not available for review. The mean patient age was 60 years. Sixty-four patients (4%) had a positive PST reaction; of these, 53 (83%) were females and 11 (17%) were males (OR, 3.6; 95% CI, 1.9–7.2; $P < .001$). In a multivariate logistic regression analysis adjusted for age, history of multiple drug allergies, and elapsed time from the initial penicillin adverse drug reaction to PST, female sex again had a significant risk of a positive PST reaction (OR, 3.2; 95% CI, 1.6–6.7; $P = .001$).

Conclusion: A greater risk of penicillin allergy exists in association with female sex in patients with a history of penicillin allergy.

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INTRODUCTION

The incidence of self-reported penicillin allergy ranges from 1% to 10%,^{1,2} with the frequency of life-threatening anaphylaxis estimated to be 0.01% to 0.05%.³ The patient's history is a poor predictor of penicillin allergy^{4,5} compared with the penicillin skin test (PST) result. A patient with a negative PST reaction to the major and minor determinants of penicillin and a history of penicillin allergy is at low risk for an immediate-type hypersensitivity reaction to penicillin (1%–3%).^{6–10} Hence, PST with the major and minor determinants of penicillin is a valuable tool in evaluating patients with a history of penicillin allergy.

Identification of risk factors is an integral part of a physician's evaluation of a patient. For example, hypertension and diabetes mellitus are well-known risk factors for coronary atherosclerotic disease (CAD)¹¹ and can help identify patients at greatest risk for CAD. Female sex has been associated with higher rates of adverse drug reactions (ADRs),^{12–15} but the association between female sex and ADRs has not been explored in patients with a history of penicillin allergy. In this study, we show that female sex is an independent risk factor for penicillin allergy.

PATIENTS AND METHODS

Patients

At our institution, patients undergo a preoperative medical examination at the preoperative evaluation (POE) clinic the

day before their elective surgery. We developed a clinical pathway identifying patients with a self-reported penicillin allergy in the POE clinic. These patients are evaluated by an allergist and undergo PST at the POE clinic the same day. These consecutive patients with a history of penicillin allergy seen between June 1, 2002, and June 30, 2004, at the POE clinic for an allergy consultation constitute the patient population.

Study Design

A retrospective study in which medical records were reviewed for basic demographics (age and sex), PST results, other drug allergies, and time from the original penicillin ADR to PST. Two reviewers (M.A.P. and P.J.M.) examined all the patient medical records. At the beginning of the study, the 2 reviewers examined a few medical records together, and later, if questions arose during the medical record review process, the reviewers discussed the question to establish consistency in data collection. For example, if more than 1 PST was performed, we chose the most recent result. All the data were input into a spreadsheet program (Microsoft Excel; Microsoft Corp, Redmond, Washington) and then converted into a JMP file (see the "Statistical Analysis" subsection) for statistical analysis. The Mayo Clinic institutional review board approved the study, and all the participants signed written informed consent forms.

Penicillin Allergy Testing

Penicillin allergy testing was conducted using benzylpenicilloyl polylysine (PrePen; Hollister-Stear; Spokane, Washington), penicillin G potassium (Pfizerpen; Pfizer, New York, New York), amoxicillin, and alkaline hydrolysis mix (penicilloate), as previously reported.¹⁶ The penicilloate was produced by reacting penicillin G with 1N of sodium hydroxide at a pH of 11.5 for 90 minutes, after which the pH was adjusted to 7.4 by the addition of 1N of hydrochloride. The

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penicilloate was lyophilized and stored at 4°C. The penicilloate was diluted with phosphate-buffered saline to 0.01 mol/L and filtered through a 0.22- μ m membrane for sterility weekly to be used for penicillin skin testing. The aqueous penicilloate was stored at 4°C. The benzylpenicilloyl polylysine (PrePen) was used according to the manufacturer's instructions, and the penicillin G potassium was used in a concentration of 6,000 U/mL in phosphate-buffered saline. The amoxicillin was diluted with sterile water to 0.01 mol/L and was filtered through a 0.22- μ m membrane for sterility weekly to be used for PST. Histamine, 0.05 mg/mL, was used as the positive control, and the negative control was phosphate-buffered saline.

Skin prick tests were performed on the volar surface of the forearm with each component of the PST reported previously herein and control reagents. The skin test sites were examined at 15 minutes. A positive PST result was defined as a wheal of 3 $\times$ 3 mm or greater with a surrounding zone of erythema in 1 or more PST components (PrePen, penicillin G, penicilloate, and amoxicillin). Patients with negative or equivocal penicillin prick test results underwent penicillin intradermal testing.

Intradermal skin tests were performed on the volar surface of the forearm. The test reagents were injected intradermally to produce an initial wheal of 2 $\times$ 2 mm. The skin test sites were examined at 15 minutes. A positive intradermal test result was defined as a wheal of 3 $\times$ 3 mm or greater with a surrounding zone of erythema.¹⁷ Patients with a wheal but no flare on PST (prick and intradermal) were considered to be equivocal. Allergy skin testing was performed where resuscitation equipment was available in case of anaphylaxis.

Statistical Analysis

A univariate logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for sex differences in the rates of positive PST results defined at different cutoff values (3 $\times$ 3, 4 $\times$ 4, 5 $\times$ 5, and 6 $\times$ 6-mm wheals and flare). For these analyses, positive PST results (yes = 1 and no = 0) was the dependent variable and sex (male vs female) was the explanatory variable. Patients with an equivocal PST result, a 2 $\times$ 2-mm wheal and flare on PST, or positive cefazolin skin test results but negative PST results were considered to have negative PST results in the statistical analysis. The 3 $\times$ 3-mm wheal and flare on the PST was used for all other estimates of unadjusted and adjusted ORs and 95% CIs. A similar logistic regression analysis was used to calculate the unadjusted ORs and 95% CIs for the sex differences in the rates of reporting a history of multiple drug allergies. A history of multiple drug allergies was defined as 2 or more drug allergies (not including penicillin allergy) in the patient's medical record.

Using the wheal and flare 3 $\times$ 3 mm greater than the negative control to define a positive PST result, the following variables were also evaluated as potential characteristics associated with positive PST results: age, history of multiple drug allergies, and time elapsed from the original penicillin

allergic reaction to PST. After univariate analysis a multivariate logistic regression analysis with positive PST results (3 $\times$ 3-mm wheal and flare) as the dependent variable was then used to estimate adjusted ORs for variables significant univariately at $\alpha = .05$.

A 2-sample *t* test was used to determine whether the mean elapsed time (in years) between the original penicillin allergic reaction and PST was equal in individuals with positive vs negative PST results. Using the χ^2 test we compared the differences in the proportion of males and females who did vs did not undergo PST. A software program (JMP version 6; SAS Institute Inc, Cary, North Carolina) was used to perform the logistic regression analyses. $P \leq .05$ was considered statistically significant.

RESULTS

Between June 1, 2002, and June 30, 2004, 19,429 patients were seen in the POE clinic, of which 1,921 (10%) had a history of penicillin allergy and compose the study population. The overall mean $\pm$ SD age of the study group was 60 $\pm$ 15 years (55 $\pm$ 17 years in the positive PST result cohort; 60 $\pm$ 15 years in the negative PST result cohort). Of the 1,921 patients, 1,759 underwent skin testing for penicillin and 157 did not; 5 medical records were not available for review. Sixty-four of 1,759 patients (4%) (11 males [0.6%] and 53 females [3%]) had a positive skin test reaction to penicillin (major and minor determinants). Of the 1,916 patients whose medical records were reviewed, 1,122 (59%) were female and 794 (41%) were male. Of the 157 patients who did not undergo PST, 95 (61%) were female and 62 (39%) were male (Table 1). Of those with a positive PST reaction (3 $\times$ 3-mm wheal and flare), 53 (83%) were females and 11 (17%) were males, indicating a significant risk of a positive PST result in association with female sex (OR, 3.6; 95% CI, 1.9–7.2; $P < .001$). If the definition of a positive PST result was defined by increasing sizes of the wheal and flare, females still demonstrated an increased risk of penicillin allergy, although the statistical significance is lost at 5 $\times$ 5-mm or greater wheal and flare (Table 2).

Forty of 64 patients (63%) had a positive PST reaction to benzylpenicilloyl polylysine, 20 (31%) had a positive reac-

Table 1. Sex and Penicillin Skin Test Results^a

Penicillin skin test	Participants, No. (%)		
	Male	Female	Total
Positive results	11 (17)	53 (83) ^b	64
Negative results	713 (43)	945 (57)	1,658
Equivocal results	7 (22)	25 (78)	32
Not performed	62 (39)	95 (61)	157
2 $\times$ 2-mm wheal and flare	0	3 (100)	3
Cefazolin skin test positive only; penicillin skin test negative	1 (50)	1 (50)	2

^a Five medical records were not available for review.

^b $P < .001$.

Table 2. Positive Penicillin Skin Test Results Stratified by Wheal and Flare Size

Wheal and flare size, mm	Odds Ratio (95% Confidence Interval)	P value
3 × 3	3.6 (1.9–7.2)	<.001
4 × 4	2.7 (1.3–6.0)	<.01
5 × 5	1.7 (0.8–4.2)	.21
6 × 6	2.2 (0.7–7.7)	.19

tion to penicillin G, 21 (33%) had a positive reaction to penicilloate, and 9 (14%) had a positive reaction to amoxicillin (the total percentage may exceed 100% because some patients had more than 1 positive component of the PST) (Table 3). The mean $\pm$ SD time elapsed from the initial penicillin allergic reaction to PST was 30 ± 16 years (1,630 of 1,916 patients [85%] had information available). Patients with a positive PST result reported a shorter elapsed time between the penicillin ADR and PST vs those with a negative PST result (mean $\pm$ SD: 21 ± 15 vs 31 ± 16 years; $P < .001$, 2-sample *t* test).

Six hundred sixty-two of 1,885 patients (35%) reported a history of multiple drug allergies (information was not available or was missing for 31 patients). Of the 662 patients reporting a history of multiple drug allergies, 483 (73%) were female and 179 (27%) were male. Females were 2.6 times (95% CI, 2.1–3.2 times; $P < .001$) more likely than males to report multiple drug allergies. Twenty-four of 64 patients (38%) with a positive PST result reported multiple drug allergies compared with 578 of 1,672 patients (35%) with a negative PST result ($P = .63$).

Female sex has a greater risk of a positive PST result even when adjusted for time between the initial penicillin allergic reaction and PST (OR, 3.1; 95% CI, 1.6–6.6; $P < .001$). In a multivariate logistic regression analysis adjusted for age, history of multiple drug allergies, and time elapsed from the initial penicillin ADR to PST, female sex again had a significant risk of a positive PST result (OR, 3.2; 95% CI, 1.6–6.7; $P = .001$).

Table 3. Positive Penicillin Skin Test Result Patterns^a

Agent	Male (n = 11 [17%])	Female (n = 53 [83%])	Total (N = 64)
PrePen	6 (9)	34 (53)	40 (63)
Penicillin G	3 (5)	17 (27)	20 (31)
Penicilloate	4 (6)	17 (27)	21 (33)
Amoxicillin	3 (5)	6 (9)	9 (14)
PrePen solely	5 (8)	23 (36)	28 (44)
Penicillin G solely	2 (3)	9 (14)	11 (17)
Penicilloate solely	1 (2)	6 (9)	7 (11)
Amoxicillin solely	0	2 (3)	2 (3)

Abbreviation: PrePen, benzylpenicilloyl polylysine.

^a Data are given as number (percentage [calculated from the 64 total patients with a positive penicillin skin test result]).

DISCUSSION

We describe the first study demonstrating a 3.6-fold greater risk of a positive PST result exists in association with female sex in patients with a reported history of penicillin allergy. The size of the wheal and flare in the PST defining a positive PST result did not affect the increased risk of penicillin allergy in females. However, when a wheal and flare size in the PST greater than 5×5 mm is considered a positive PST reaction, female sex as a risk factor for penicillin allergy is no longer statistically significant. The loss of statistical significance is most likely due to the small sample sizes in the PST positive result cohort as the cutoff size for the wheal and flare considered a positive PST reaction increases.

Sullivan et al¹⁸ showed no effect of sex on PST results when 740 patients with a history of penicillin allergy were evaluated (63.5% males with a positive PST reaction vs 63.3% females). The difference between our studies may be due to the patient populations and different skin testing techniques. Thirty-eight percent of the patients tested by Sullivan and colleague¹⁸ were in the inpatient setting compared with none in the present patient population. Also, their outpatient participants were more likely to have a positive PST result compared with their inpatient counterparts (73.2% vs 57.2%, respectively). In addition, their overall PST positive rate (63.4%) is much higher than that in the literature (7%–20%).^{7–10,15,17,19,20} The present PST positive rate (4%) is much closer to the accepted rates of positive PST results in the literature. The skin testing also differed between the study by Sullivan et al¹⁸ and the present study. In the former study, the penicilloyl-poly-L-lysine (major determinant) was synthesized and standardized in their laboratory and some of the PST was performed with PrePen compared with the present study, which used PrePen only. In addition, in the present study penicilloate was diluted to 10^{-2} M compared with 10^{-3} M. These differences in technique and patient population may explain the different results from the study by Sullivan et al.¹⁸ Furthermore, it is difficult to compare penicillin allergy studies because of the lack of a standardized penicillin test panel and different patient populations.

To explore for any confounding factors that may have affected female sex increased risk of penicillin allergy we used a multivariate logistic regression analysis adjusted for age, history of multiple drug allergies, and time from the initial penicillin ADR to PST. Female sex again demonstrated a statistically significant risk of a positive PST result. Other factors that were unlikely to affect the female sex-increased risk of a positive PST result included general skin test reactivity differences by sex,²¹ age,^{21,22} and atopic history.¹⁷ The present data support that females are at greater risk for penicillin allergy compared with males in patients with a reported history of penicillin allergy.

Females were also 2.6 times more likely than males to report multiple drug allergies in this study population. Female sex has been reported in the literature^{12–14,17,23} as a risk factor for ADRs. In the Boston Collaborative Drug Surveillance

Program²³ the incidence of cutaneous reactions was higher (35%) in females compared with males. Domecq et al,¹³ in a drug surveillance study of 1,920 patients hospitalized, showed that ADRs were significantly higher in females than in males ($P < .0005$). When 5,264 consecutive patients receiving conventional radiocontrast media during computed tomography were reviewed for ADRs to contrast, females were 22 times more likely to develop a severe anaphylactoid reaction to contrast media than males.¹² Hence, the present study is consistent with the reported literature.

The loss of PST positive response with time has been demonstrated in several studies.^{18,24} In the present study, the time elapsed between the initial penicillin allergic reaction and PST was longer in patients with a negative PST result compared with those with a positive PST result. Patients with a distant history of penicillin allergy compared with those with a more recent history are more likely to lose their sensitivity to penicillin with time. Thus, patients with a distant history of penicillin allergic reactions may benefit from PST and evaluation by an allergist.

Strom et al²⁵ reported that there is an association between hypersensitivity after the receipt of sulfonamide antibiotics and a subsequent allergic reaction after the receipt of sulfonamide nonantibiotics, but this association seems to be due to a predisposition to allergic reactions rather than to cross-reactivity with sulfonamide-based drugs. Their work implies that being allergic to one medication predisposes you to having other drug allergic reactions. We show that patients with a history of penicillin allergy and evidence of IgE antibodies to penicillin do not have higher rates of multiple drug allergies compared with patients with a history of penicillin allergy but no evidence of IgE antibodies to penicillin (38% vs 35%). The differences in the outcome between these studies may be due to the differences in the patient population. In the present study, the patient-reported history of penicillin allergy was further confirmed using PST. Participants in the study by Strom et al consisted of those in the source population who contacted their general practitioner about a condition compatible with an allergic reaction within 30 days after receiving a sulfonamide antibiotic, and the reported ADRs to penicillin were not confirmed by PST,²⁵ whereas the present patients had penicillin allergy evaluated and confirmed using PST. Hence, the present result does not support the conclusion of Strom et al²⁵ that a history of drug allergy predisposes to further drug allergic reactions.

Several limitations may have affected these results. A selection bias may have occurred if the 157 patients who did not undergo PST were disproportionately male or female compared with those who did undergo PST. Of the 157 patients who did not undergo PST, 95 (61%) were female and 62 (39%) were male compared with 1,027 female (58%) and 732 male (42%) in patients who did undergo PST ($P \leq 1$, χ^2 test). Thus, it seems unlikely that this selection bias could have affected the results.

An information bias may have been introduced when recording the elapsed time between the initial penicillin allergic

reaction and PST. However, the results showing a longer elapsed time between the initial penicillin allergic reaction and PST and loss of PST positive response with time are consistent with other results in the literature.^{18,24}

This study population consisted of consecutive patients with a reported history of penicillin allergy undergoing pre-anesthesia medical examination at the POE clinic for next-day elective surgery. Furthermore, the present patients were evaluated at an academic tertiary care center. The increased risk of a positive PST result in females compared with males with a history of penicillin allergy may be generalizable only to this patient population. However, this study is consistent with other studies^{12-14,17,23} that have shown that females are at increased risk for drug allergies, which may increase the generalizability to other patient populations.

Finally, other variables that we could not control may have affected the results; however, we attempted to control for many potential confounding factors that the literature or we believed may have affected the analyses and conclusions. Furthermore, the main strength of this study is the large sample size, which makes it a more robust study. In conclusion, a greater risk of penicillin allergy exists in association with female sex in patients with a reported history of penicillin allergy.

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