

Preoperative Evaluation of Patients With History of Allergy to Penicillin: Comparison of 2 Models of Practice

EVANGELO FRIGAS, MD; MIGUEL A. PARK, MD; BRADLY J. NARR, MD; GERALD W. VOLCHECK, MD; DAVID R. DANIELSON, MD; PATRICIA J. MARKUS, RN; KRISTIN E. KLOOS OLSON, RN; DARRELL R. SCHROEDER, MS; AND HIROHITO KITA, MD

OBJECTIVE: To study whether allergy consultation and penicillin allergy skin testing affects the selection of antibacterial prophylaxis perioperatively in surgical patients with history of allergy to penicillin (HOAP).

PATIENTS AND METHODS: From January 1 through June 30, 2004, we compared 2 different models of practice at our institution. At the Preoperative Evaluation Clinic (POEC), all patients with HOAP are evaluated by an allergist and undergo skin testing for allergy to penicillin. At other (non-POEC) preoperative evaluation settings (OPES), patients with HOAP do not undergo allergy consultation and penicillin skin testing before surgery. Of the 4889 patients screened at the POEC during the study period, 412 consecutive patients with HOAP were included in the study. Of the 416 patients screened at OPES, 69 consecutive patients with HOAP were studied. Logistic regression was used to assess whether allergy consultation was associated with the choice of antibiotic for antibacterial prophylaxis perioperatively, after adjusting for age, sex, and type of surgery.

RESULTS: Perioperative cephalosporin use was greater among patients screened at POEC vs those screened at OPES (70% vs 39%, $P<.001$ unadjusted; $P=.04$ adjusted for age, sex, and type of surgery). Vancomycin use was lower for patients screened at POEC vs those screened at OPES (10% vs 28%, $P<.001$ unadjusted; $P=.03$ adjusted).

CONCLUSION: For patients with HOAP, evaluation at the POEC was associated with increased use of cephalosporin and decreased use of vancomycin.

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BPL = benzylpenicilloyl-polylysine; HOAP = history of allergy to penicillin; IRB = Institutional Review Board; MDM = minor determinants mixture; OPES = other (non-Preoperative Evaluation Clinic) preoperative evaluation settings; POABP = perioperative antibacterial prophylaxis; POEC = Preoperative Evaluation Clinic.

For most surgical procedures, an antibiotic is used for perioperative antibacterial prophylaxis (POABP) to decrease the incidence of infection.¹ Although true allergy to penicillin is estimated at approximately 0.01%,^{2,3} the frequency of patient-reported allergy to penicillin is approximately 10%.^{4,5} Because an estimated 40% of patients with allergy to penicillin are also allergic to cephalosporin, physicians frequently avoid prescribing cephalosporin to patients with history of allergy to penicillin (HOAP).³⁻⁸ The clinically relevant allergenic determinants of penicillin have been isolated,⁹⁻¹¹ and the efficacy of allergy skin testing in identifying patients allergic to penicillin has been validated clinically.^{10,12-20} However, skin testing for penicillin allergy remains largely underused because commercial

sources for the necessary reagents are lacking in the United States, and non-β-lactam alternatives for patients with HOAP are readily available.²¹⁻²³ Consequently, vancomycin is often used for POABP in patients with HOAP who undergo surgery.^{1,24}

The Division of Allergic Diseases and Internal Medicine opted to prepare skin test reagents for penicillin in-house, using protocols approved by the Mayo Clinic Institutional Review Board (IRB). Until 1996, the preoperative evaluation of patients for elective surgery took place in a variety of settings at our institution. In 1996, the Department of Anesthesiology streamlined the preoperative screening of many of these patients by establishing the Preoperative Evaluation Clinic (POEC). Elective surgery patients who, for whatever reason, are not screened at POEC are evaluated in other preoperative evaluation settings (OPES) located in different areas of our institution. Since July 2002, the Division of Allergic Diseases, in collaboration with the Departments of Anesthesiology and Surgery, has provided allergy consultation and skin testing to all patients with HOAP at the POEC. At our institution, approximately 50,000 patients have undergone elective surgery in each of the past 5 years. Of these patients, 20% were screened at the POEC and the remainder at OPES. At OPES, allergy consultations and penicillin skin testing are unavailable and the patient's surgical-anesthesia team decides which antibiotic to use for POABP in patients with HOAP. The purpose of the current study was to compare the selection of the antibiotic for POABP in these 2 different models of practice.

PATIENTS AND METHODS

The Mayo Clinic IRB approved this prospective study of patients with HOAP who were scheduled for elective

From the Division of Allergic Diseases (E.F., M.A.P., G.W.V., P.J.M., K.E.K.O., H.K.), Department of Anesthesiology (B.J.N., D.R.D), and Department of Biostatistics (D.R.S.), Mayo Clinic, Rochester, MN.

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Individual reprints of this article are not available. Address correspondence to Evangelo Frigas, MD, Division of Allergic Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (frigas.evangelos@mayo.edu).

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surgery and who consented to be included in the study. The patients with HOAP were identified from patient-completed standard preoperative questionnaires. At the POEC, patients with HOAP were evaluated and skin tested by an allergist and a team of allergy nurses before the decision of which antibiotic to use for POABP was made.

Patients with a history of life-threatening reaction to penicillin or with HOAP that was indicative of non-IgE-mediated reactions, such as exfoliative dermatitis, mucosal lesions, liver or kidney damage, or hemolytic anemia, did not receive a skin test; instead, a non-β-lactam was recommended for POABP. With these exceptions, patients with HOAP who consented to participate in this study underwent skin testing, provided they were not taking antihistamines or other medications that might interfere with the results of this test. We retrieved information on the antibiotic used for POABP and any adverse reactions attributed to it from anesthesia and surgical records. Of the 4889 patients screened at the POEC in the first half of 2004, we studied the first 412 consecutive patients with HOAP. Of the first 416 patients screened in 2004 at OPES, the first 69 consecutive patients with HOAP were included in the study (Table 1).

PREPARATION OF REAGENTS FOR SKIN TESTING

Major Allergenic Determinants of Penicillin G. In accordance with an IRB-approved protocol, we have been custom-making benzylpenicilloyl-polylysine (BPL), the major allergenic determinant of penicillin G, since 2001.²⁵ In the United States, the commercially available preparation of BPL, marketed as Pre-Pen (Hollister-Stier, Spokane, WA), was discontinued in 2003. At our institution, we compound the BPL at the Allergic Diseases Research Laboratory of the Division of Allergic Diseases, as previously reported.^{10,11,15}

Minor Allergenic Determinants of Penicillin G. Unlike Europe,²⁶ the United States has no commercial sources of the minor determinants mixture (MDM) of penicillin G reagents for allergy skin testing. At our institution we have been custom-making reagents for the use of our patients since the mid-1960s in the Allergic Diseases Research

TABLE 1. Allergies to Antibiotics Among Patients Screened at POEC and at OPES^a

Antibiotics implicated in histories	POEC (N=4889)	OPES (N=416)	P value ^b
β-Lactams (penicillin included)	412 (8)	69 (17)	<.001
Penicillin specifically	365 (8)	46 (11)	.009

^a All values are given as number (percentage) of patients. HOAP = history of allergy to penicillin; OPES = other (non-Preoperative Evaluation Clinic) preoperative evaluation settings; POEC = Preoperative Evaluation Clinic.

^b χ² test.

Laboratory of the Division of Allergic Diseases, as previously described.^{10,15} Nuclear magnetic resonance analysis of the composition of our MDM reagent revealed that it contains 60% penicillin G, 30% penicilloate, and 10% penilloate. Before skin testing, the MDM powder is diluted with normal saline to 0.01 mol/L and filtered through a 0.22-μg membrane for sterility. Because the solution of MDM is unstable at room temperature,²⁷ we make it fresh every week and keep it refrigerated at 4°C until it is needed for skin testing.

Penicillin G Solution. The solution of penicillin G for skin testing is prepared weekly at the Food and Drug Allergy Clinic of the Division of Allergic Diseases by an allergy nurse supervised by an allergist. One vial of penicillin G sodium (5,000,000 U/vial) is dissolved in 18.2 mL of sterile water. Phosphate-buffered saline (4.2 mL) is then added to 0.1 mL of the solution. This reagent is kept refrigerated at 4°C until testing.

ALLERGY SKIN TEST PROCEDURE FOR PATIENTS WITH HOAP

At our institution, an allergy nurse performs the skin test in the presence of an allergy consultant. All 3 skin test reagents, MDM (0.01 M), BPL (6×10^{-5} M), and solution of penicillin G (4 mg/mL), are first used for skin prick testing; if results are negative, intradermal testing is performed. At the discretion of the allergist conducting the skin test, the penicillin skin test reagents may be diluted when testing patients with severe HOAP. A solution of histamine (6 mg/mL for prick testing and 0.05 mg/mL for intradermal testing) in phosphate-buffered saline is used as a positive control. For negative controls, we use the diluent and skin testing for dermatographia.

The volar aspect of the patient's forearm is used for skin testing; results are read within 15 minutes of application. A prick or intradermal test that produces a wheal-and-flare reaction with a wheal of 3 × 3 mm or greater is read as positive. Skin tests that elicit wheal without flare are read as equivocal or indeterminate.

STATISTICAL ANALYSES

The age and sex of patients with HOAP who were evaluated at POEC vs OPES were compared using the Wilcoxon rank sum test and χ² test, respectively. Type of surgery was categorized as orthopedic, urologic, neurologic, cardiovascular, or other and compared between groups using the Fisher exact test. We performed χ² and logistic regression analyses to assess whether the evaluation location (POEC vs OPES) was associated with the choice of antibiotic for POABP. Both unadjusted analysis and analyses adjusted for age, sex, and type of surgery were performed. In all cases, 2-tailed P values ≤.05 were used to denote statistical significance.

TABLE 2. Demographics of Patients With History of Antibiotic Allergies^a

Characteristic	History of allergy to β -lactams			HOAP specifically		
	Screened at POEC (n=412)	Screened at OPES (n=69)	P value	Screened at POEC (n=365)	Screened at OPES (n=46)	P value
Age (y)			.08			.01
Mean \pm SD	60 \pm 15	63 \pm 18		60 \pm 15	66 \pm 17	
Median (IQR)	62.5 (51-72)	67 (49-77)		63 (51-72)	68 (53-78)	
Sex			.66			.85
Female	239 (58)	42 (61)		201 (55)	26 (57)	
Male	173 (42)	27 (39)		164 (45)	20 (43)	
Surgery			<.001			<.001
Orthopedic	200 (49)	17 (25)		181 (50)	12 (26)	
Urologic	76 (18)	3 (4)		69 (19)	3 (7)	
Neurologic	45 (11)	1 (1)		43 (12)	0 (0)	
Cardiovascular	2 (<1)	10 (14)		1 (<1)	7 (15)	
Other	89 (22)	38 (55)		71 (19)	24 (52)	

^a All values are given as number (percentage) of patients, unless otherwise indicated. HOAP = history of allergy to penicillin; IQR = interquartile range; OPES = other (non-POEC [Preoperative Evaluation Clinic]) preoperative evaluation settings.

RESULTS

Of the 412 patients from POEC with a history of allergy to β -lactams, 365 patients (89%) had allergy to penicillin specifically, and the remainder had a history of allergy to penicillin and other antibiotics. Of the 69 with HOAP from OPES, 46 patients (67%) had a history of allergy to penicillin specifically and the remainder had a history of allergy to penicillin and to other antibiotics. Demographics of these patients are summarized in Table 2. Patients with HOAP who were screened at the POEC had a sex distribution similar to that of patients evaluated at OPES, but they were somewhat older, with a median age of 68 years (interquartile range, 53-78 years) vs 63 years (interquartile range, 51-72 years) ($P=.01$) (Table 2). Most patients screened at the POEC underwent orthopedic, urologic, or neurologic surgeries, whereas those screened at OPES underwent a greater variety of surgical procedures (Table 2).

Of the patients who reported a history of allergy specifically to penicillin, 254 (70%) of the 365 patients screened at the POEC and 18 (39%) of the 46 patients screened at OPES received cefazolin for POABP ($P<.001$; $P=.04$, adjusted for age, sex, and type of surgery); and 36 patients (10%) at POEC and 13 patients (28%) at OPES received

vancomycin for POABP ($P<.001$, unadjusted; $P=.03$, adjusted for age, sex, and type of surgery) (Table 3). For patients who received neither β -lactam nor vancomycin for POABP, the most commonly used antimicrobial agents were clindamycin, ciprofloxacin, and levofloxacin (Table 3). No immediate or delayed reactions to the penicillin skin tests were noted in any of the patients tested. No life-threatening reactions were linked to the antibiotic used for POABP.

DISCUSSION

In most surgical interventions, POABP is used to decrease the incidence of infection.¹ In the United States, the antibiotic of choice for POABP is cefazolin.²⁴ Because 10% of patients report HOAP,^{4,5} physicians often encounter the dilemma of deciding which antibiotic to use in their care. Some physicians rely on a detailed history to decide which patients with HOAP should receive penicillin or penicillin-related antibiotics.²⁸ However, patients with HOAP often are unable to give a sufficiently detailed history to allow physicians to judge confidently whether their reactions were mediated by IgE.^{6,8} Even experts in this area often find it difficult to distinguish IgE-mediated and non-IgE-

TABLE 3. Antibiotic Administered for POABP in Patients With HOAP, Evaluated at POEC vs OPES^a

Antibiotic given for POABP	History of allergy to β -lactams			HOAP specifically		
	Screened at POEC (n=412)	Screened at OPES (n=69)	P value ^b	Screened at POEC (n=365)	Screened at OPES (n=46)	P value ^b
Cephalosporin	280 (68)	23 (33)	<.001	254 (70)	18 (39)	<.001
Vancomycin	42 (10)	18 (26)		36 (10)	13 (28)	
Other	90 (22)	28 (41)		75 (21)	15 (33)	

^a All values are given as number (percentage) of patients, unless otherwise indicated. HOAP = history of allergy to penicillin; OPES = other (non-POEC [Preoperative Evaluation Clinic]) preoperative evaluation settings; POABP = perioperative antibacterial prophylaxis.

^b χ^2 test.

mediated reactions to antibiotics by history alone.^{8,21,22} However, a detailed history remains the most commonly used approach because skin test reagents for penicillin are not readily available commercially, non-β-lactams are readily available, and the incidence of life-threatening reactions to penicillin is low. Therefore, currently in the United States most physicians who treat patients with HOAP opt for a non-β-lactam antibiotic if they have the slightest suspicion of an allergy to penicillin.^{6,7}

The value of performing skin testing in addition to taking a detailed history has been documented in multiple studies.^{10,13-20,29} These studies have shown that, if skin tests to penicillin produce negative reactions, the risk of a life-threatening reaction from administration of penicillin or cephalosporin is low in patients with and without HOAP.^{15-17,20,29} In our patients with HOAP who had negative results on an allergy skin test to penicillin, we elected not to repeat the skin test, as some authors have suggested, because the risk of resensitization has been reported to be low even after repeated courses of penicillin.³⁰⁻³² In the current study, 8% of patients with HOAP had positive skin test results. In a prior study, our group reported a higher positivity rate, likely because we had included reagents for ampicillin and methicillin in the penicillin skin tests.¹⁵ Other authors have reported higher rates than ours.^{6,33} Variations in the custom-made, nonstandardized compounds used in these studies might account for these differences. In the current study, the skin tests resulted in neither systemic reactions nor other symptoms.

In prior studies by our group^{15,34} and by others,^{29,33,35} an increased frequency of systemic reactions to the skin test itself was noted in approximately 0.1% of patients tested; such reactions were more likely to occur in those with positive results on skin tests. We have had no deaths due to skin testing with the penicillin reagents. Deaths due to penicillin skin testing are extremely rare but have been reported.^{36,37} A recent article suggested that serum-specific IgE to β-lactam be measured in patients with a history of anaphylactic shock to a β-lactam antibiotic and negative results on a skin test to penicillin; however, the sensitivity of this test was reported to be 0% to 20% depending on the initial clinical presentation.³⁸ In our current study, we elected against skin testing in our patients with HOAP and anaphylaxis, instead recommending a non-β-lactam antibiotic.

Benzylpenicilloyl-polylysine, a major penicillin skin test reagent commercially known in the United States as Pre-Pen, has not been commercially available since 2003. Hollister-Stier, the sole producer of Pre-Pen in the United States, was directed by the Food and Drug Administration to cease its production as of the fall of 2003 because of quality concerns. Also not commercially available in the

United States are the skin test reagents of the MDM, fully characterized half a century ago, and reagents needed to perform skin tests for allergy to cephalosporin. At our institution, as in other large medical and research centers, the lack of commercially available skin test reagents has been addressed by compounding them extemporaneously in-house. We have used custom-made MDM reagents since 1969 and custom-made BPL reagents since 2001. Clinical research, conducted in accordance with IRB-approved protocols, is under way to assess their safety, usefulness, and predictive value in our practice. In a prior study, we compared our in-house BPL reagent with the commercially available BPL reagent (Pre-Pen) and found them to be similar.²⁵ Two commercial kits available in Europe to skin test for allergies to penicillin have been shown to have similar potency, sensitivity, and specificity.³⁹

Since 2001, the POEC, in collaboration with the Department of Anesthesiology, has offered patients with HOAP an immediate allergy consultation and penicillin skin testing to help with the selection of the antibiotic to use for POABP in their imminent elective surgery. After the allergy consultation, the allergist shares the assessment of the patient's current status of allergy to penicillin with the patient and his or her surgeon. The allergist also gives the patient a copy of the allergy skin test results for future reference, along with a signed penicillin allergy assessment card that summarizes the allergist's impressions and recommendations. On completion of the evaluation, the allergist updates the patient's allergy module in the electronic medical record. Table 4 summarizes our choice of antibiotic for POABP in the 2 most common clinical scenarios of HOAP (IgE-mediated vs non-IgE mediated), contrasted with the results from penicillin skin testing (positive, negative, indeterminate).

Because cefazolin is currently the antibiotic of choice for POABP in the United States,²⁴ the categories of patients who pose the greatest difficulty in the decision of which antibiotic to use for POABP are those with HOAP that is likely to be mediated by IgE and those with negative or equivocal results of skin tests (Table 4). The incidence of IgE-mediated reaction to cephalosporins in patients with HOAP has not been established. In a prior study at our institution, of 151 patients with HOAP and negative results of penicillin skin test and of 27 patients with HOAP and positive skin test results who received a full course of therapy with cephalosporin, only 2 had a reaction to cephalosporin and both had negative results of penicillin skin tests.¹⁵ Subsequently, others reported that patients with HOAP and negative results of penicillin skin tests can safely receive penicillin^{3,4,29} and are not at increased risk of anaphylaxis when a cephalosporin is given.^{18,40-42} In more recent studies in Europe that used the patient's history in

TABLE 4. Choice of Antibiotic for POABP in the 2 Most Common Clinical Scenarios of HOAP and Penicillin Skin Test Results^{a,b}

Penicillin skin test results	HOAP	
	Likely IgE-mediated	Unlikely IgE-mediated
Negative	Cefazolin (in most cases)	Cefazolin (in most cases)
Positive	Non-β-lactam	Non-β-lactam
Equivocal/indeterminate	Non-β-lactam	Non-β-lactam (in most cases)

^a HOAP = history of allergy to penicillin; POABP = perioperative antibacterial prophylaxis.

^b We do not perform a skin test or recommend a non-β-lactam antibiotic when the patient's HOAP is indicative of exfoliative dermatitis, mucosal lesions, liver or kidney damage, or hemolytic anemia.

conjunction with penicillin skin tests and several cephalosporins (cefuroxime, ceftazidime, ceftriaxone, and cefotaxime), it was found that patients with HOAP and negative or positive results of penicillin skin tests were able to safely receive cefuroxime and ceftriaxone if they had negative results from skin tests of these cephalosporins.⁴³ They were also able to receive meropenem if they had negative results from skin tests of meropenem.⁴⁴ It should be noted that, in the cephalosporin study,⁴³ challenge with cephalosporin was not followed by a therapeutic course and 22 patients declined to be challenged; and that, in the meropenem study, patients did not receive a fully therapeutic dose of meropenem.⁴⁴

Other investigators have advised caution in using cephalosporins among patients with HOAP and with positive or negative results from penicillin skin tests.^{45,46} In a study of cases of fatal anaphylaxis in the United Kingdom from 1992 to 1997, 6 of 12 fatalities occurred in the first course of cephalosporin therapy.⁴⁶ A joint US task force estimated the risk of anaphylaxis to cephalosporin to be less than 1% if the results of skin tests for penicillin are negative.²¹ In the current study, at the completion of the allergy evaluation at POEC, the allergist who conducted the evaluation presented the patient with recommendations for antibiotics to be used for POABP and outlined the risks and benefits of each one. In this study, as in our practice, patients with HOAP always make the final choice as to whether a β-lactam or a non-β-lactam antibiotic is used for their POABP. For this reason, cefazolin was not always chosen in the current study, even when reactions to penicillin were negative (Table 4). On the rare occasion that a patient with HOAP and positive results of skin tests to penicillin needed to receive cefazolin or another cephalosporin for POABP, we recommended skin testing with a solution of the cephalosporin to be used at a concentration of 4 mg/mL, followed by graded administration of the cephalosporin if the skin test reaction was negative or desensitization if it was positive. Graded administration or desensitization are performed under close medical supervision at our institution.

In the current study, we compared a group of patients with HOAP who had allergy consultation and penicillin

skin testing preoperatively with another group of patients with HOAP who had no such consultation or testing. We observed that those who had allergy consultation and skin testing were 3 times less likely to receive vancomycin and 4 times more likely to receive cephalosporin in all types of elective surgery studied (Table 3). This approach should benefit surgical patients with HOAP because the antibiotic of choice for POABP is cefazolin.²⁴ It could also lead to a more judicious use of vancomycin, which is clearly needed given the increasing threat of colonization and infection with vancomycin-resistant enterococci⁴⁷ and the increased prevalence of methicillin-resistant *Staphylococcus aureus* strains with reduced susceptibility to vancomycin.⁴⁸⁻⁵⁰

Poorer survival rates and increased cost of health care have been reported in studies that compared patients with vancomycin-resistant vs vancomycin-susceptible enterococcal infections.^{51,52} In a cost-effectiveness analysis of cardiovascular surgery prophylaxis in patients who were labeled penicillin allergic, the incremental cost of using vancomycin instead of cefazolin was very high.⁵³ A reduction in the use of vancomycin made possible by allergy testing has been reported previously in 2 small studies.^{54,55} The first of these studies had no control group,⁵⁴ whereas the second used historic controls.⁵⁵ Our study confirms that the inclusion of skin testing and an allergy consultation in the preoperative evaluation of patients with HOAP is associated with a decreased use of vancomycin and an increased use of cephalosporin for POABP.

CONCLUSION

In patients with HOAP scheduled to have elective surgery, we compared the selection of antibiotic used for POABP in 2 different models of practice at our institution. We noted a significant increase in the use of cephalosporin and decrease in the use of vancomycin in the model of practice that uses an allergy consultation and skin testing in the selection of the antibiotic compared with the model that does not. This model of practice can be further expanded and validated throughout the United States when reagents

needed for skin tests to determine allergy to penicillin become commercially available. Given the potential benefits to patient care, it is hoped that commercial sources of uniformly produced MDM and BPL skin test reagents soon become available, allowing the expansion of this model of practice to all patients who need it.

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