Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy

Miguel Park, MD; Patricia Markus, RN; Damir Matesic, MD; and James T. C. Li, MD

Background: We developed a clinical pathway to optimize the use of antimicrobials by decreasing vancomycin use in preoperative patients with a history of penicillin allergy.

Objective: To decrease the use of vancomycin in surgical patients with a self-reported penicillin allergy.

Methods: In June 2002, same-day allergy consultation and penicillin skin testing were made available for preoperative patients with self-reported penicillin allergy at the preoperative evaluation (POE) clinic. We reviewed the penicillin allergy skin test results, recommendations, and β-lactam antibiotic administration outcomes from July 1, 2002, to September 16, 2003.

Results: A total of 1,204 of 11,819 patients were evaluated for β-lactam allergy at the POE clinic. Of these, 1,120 were approved by the institutional review board for inclusion in the study and 9 were excluded from the study. Of the remaining 1,111 patients, 1,030 (93%) underwent skin testing for penicillin allergy. Forty-three (4%) had a positive skin test result to penicillin. A total of 947 (85%) of the 1,111 patients with a history of β-lactam allergy were advised to use a β-lactam antibiotic, and 164 (15%) were advised to avoid β-lactams. A total of 955 patients (86%) actually received preoperative antibiotics. Of these 955 patients, 716 (75%) received cefazolin, and only 149 (16%) received vancomycin compared with 30% historical controls ($P < .01$). Among the patients with a negative penicillin skin test result who received a cephalosporin, 5 (0.7%) of 675 experienced an adverse drug reaction to a cephalosporin.

Conclusions: Establishment of a clinical pathway in a preoperative clinic that includes allergy consultation and penicillin skin testing reduced vancomycin use to only 16% in surgical patients with a history of β-lactam allergy.

Ann Allergy Asthma Immunol. 2006;97:681–687.

INTRODUCTION

Patients undergoing surgical procedures use prophylactic antimicrobial agents to reduce the incidence of postoperative surgical site infection. In many of the surgical specialties, cefazolin is the preferred prophylactic antimicrobial agent.[1] In vitro tests have shown moderate cross-reactivity between cephalosporin and penicillins,[2–4] which may be due to the shared β-lactam ring and similar side chains.[3] Pumphrey and Davis,[5] in a study of fatal anaphylaxis in the United Kingdom from 1992 to 1997, revealed that 6 of 12 fatalities were from the first course of a cephalosporin. Three of the 6 were known to be allergic to amoxicillin and 1 to penicillin. Hence, some caution is still advised if a cephalosporin is to be given in patients with a history of penicillin allergy. Drug allergy practice guidelines recommend that when a non–β-lactam antibiotic substitute is not available for patients needing a cephalosporin, patients with a history of an immediate-type hypersensitivity to penicillin should undergo penicillin skin testing.[2] However, allergy evaluation with penicillin skin testing is not always accessible. Thus, patients with a history of penicillin allergy often receive prophylactic vancomycin before surgery.

Division of Allergic Diseases, Mayo Clinic, Rochester, Minnesota.
Received for publication December 15, 2005.
Accepted for publication in revised form June 28, 2006.

Although vancomycin is a valuable alternative for penicillin allergic patients, with the emergence of vancomycin-resistant enterococci and recent reports of *Staphylococcus aureus* strains with reduced susceptibility to vancomycin,[6] the reduction and judicious use of vancomycin have been recommended.[7] Importantly, vancomycin-resistant enterococci infections have been associated with a decreased survival rate and higher health care costs compared with those with vancomycin-susceptible enterococci.[8,9]

Li et al[10] have shown that prophylactic vancomycin use in patients with a history of penicillin allergy undergoing elective orthopedic surgery can be reduced by a targeted allergy consultation and penicillin allergy skin testing. Our institution developed a similar clinical pathway in a preoperative evaluation (POE) clinic. The purpose of the clinical pathway was to reduce the prophylactic use of vancomycin in elective surgical patients with a self-reported penicillin allergy using same-day penicillin skin testing and allergy consultation.

PATIENTS AND METHODS

Study Patients

In June 2001, our institution established a POE clinic. At the POE clinic, patients undergo a preoperative medical examination before nonemergency surgery. In 2002, we developed a clinical pathway for patients with self-reported penicillin allergy. Patients with a history of penicillin allergy were referred by the surgeons for on-site, same-day allergy con-

sultation and penicillin skin testing before surgery. The institutional review board approved the study, and all patients signed a written informed consent.

Allergy Consultation

The consultation and penicillin allergy skin test appointments were scheduled to accommodate patients undergoing surgery the next day. Penicillin allergy skin tests were administered by an allergy nurse, followed by evaluation and management by an allergist. To accommodate same-day consultation, the medical history was obtained and the medical records were reviewed before the allergy skin tests were performed. The allergy nurse or allergist notified the surgical services regarding the recommendation for antimicrobial prophylaxis.

Penicillin Allergy Testing

Penicillin allergy testing was conducted with benzylpenicilloyl polylysine (PrePen), penicillin G potassium (Pfizerpen), and penicilloate, as previously reported.[11,12] The penicilloate was produced by reacting penicillin G with 1N sodium hydroxide at a pH of 11.5 for 90 minutes, after which the pH was adjusted to 7.4 by addition of 1N hydrochloride. The 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-μm membrane for sterility weekly to be used for penicillin skin testing. The aqueous penicilloate was stored at 4°C. We are currently in the process of developing a penilloate reagent. The benzylpenicilloyl polylysine 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. Histamine at 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 penicillin and control reagents. The skin test sites were examined at 15 minutes. A positive test result was defined as a wheal of 3 $\times$ 3 mm or greater with a surrounding zone of erythema.[2] Patients with negative prick test results to penicillin underwent 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.

Patients with a wheal but without a flare on the penicillin skin test (skin prick and intradermal) were considered to be equivocal. Allergy skin testing was performed where resuscitation equipment is available in case of anaphylaxis.

Study Design

We reviewed the penicillin allergy testing, consultation, and antibiotic administration outcomes of all patients enrolled from July 1, 2002, to September 16, 2003. The medical records of all patients were reviewed for basic demographics, prophylactic antibiotic administration, and the presence or absence of a recorded hypersensitivity to cefazolin and other β-lactam antimicrobial agents when administered to the patient. Using the χ^2 test, we compared the differences in the proportion of study patients and historical controls receiving vancomycin for surgical prophylaxis. $P \leq .05$ was considered statistically significant.

RESULTS

POE Clinic and Demographics

From July 1, 2002, through September 16, 2003, 11,819 patients were seen for their preoperative medical examination at the POE clinic, and 1,204 (10%) were evaluated for penicillin or cephalosporin allergy. Of these, 1,120 patients consented to participate in the study. Medical records for review were available in 1,115 patients (654 women and 461 men), but an allergist did not evaluate 2 patients and 2 additional patients did not have a history of a β-lactam antibiotic allergy. These 4 patients were excluded from our study. Hence, 1,111 patients constitute our study population. The mean $\pm$ SD age was 60 $\pm$ 15 years (range, 14–94 years). The top 3 surgical specialties seen in the POE clinic were orthopedics (28%), urology (22%), and neurosurgery (15%). A total of 1,072 (96%) of 1,111 patients reported a history of a penicillin allergy only, and 39 (4%) of 1,111 patients had a history of a cephalosporin allergy with and without a history of a penicillin allergy. Fifteen (38%) of 39 patients had a history of both penicillin and cephalosporin allergy, whereas 24 (62%) had only a history of cephalosporin allergy.

Penicillin Skin Test Results and Allergist Recommendations

Of the 1,111 patients, 1,030 (93%) underwent penicillin skin testing, whereas 81 (7%) did not. Forty-three (4%) of 1,030 patients had a positive penicillin skin test result, 973 patients (94%) had a negative penicillin skin test result, and 14 patients (1%) had an equivocal skin test result. Among the 81 patients who did not undergo penicillin skin testing, 62 (77%) were advised to avoid β-lactam antimicrobial agents. A total of 947 (85%) of 1,111 patients with a history of β-lactam allergy were advised by the allergist to use β-lactams such as cefazolin, and 164 (15%) were advised to avoid β-lactam antimicrobial agents.

In patients with a sole history of penicillin allergy, 999 (93%) of 1,072 patients underwent penicillin skin testing and 73 (7%) did not. As summarized in Figure 1, positive skin test results were found in 43 patients (4%). Forty of these patients were advised to avoid β-lactams, and 3 were permitted to use β-lactam antibiotics, taking into account the type of reaction they experienced and whether they tolerated a repeated exposure to another β-lactam antibiotic in the past. In 10 patients (1%) with equivocal skin test results, 7 were advised to avoid β-lactams and 3 were permitted to use β-lactams. Finally, of 946 nonreactors (95%), 905 were advised to use β-lactam antibiotics, whereas the rest of them were advised to avoid them. Of 73 patients not undergoing penicillin skin testing for various reasons, 54 were advised to avoid β-lactam and the rest were permitted to receive them preoperatively. In a subgroup of patients with a history of cephalo-

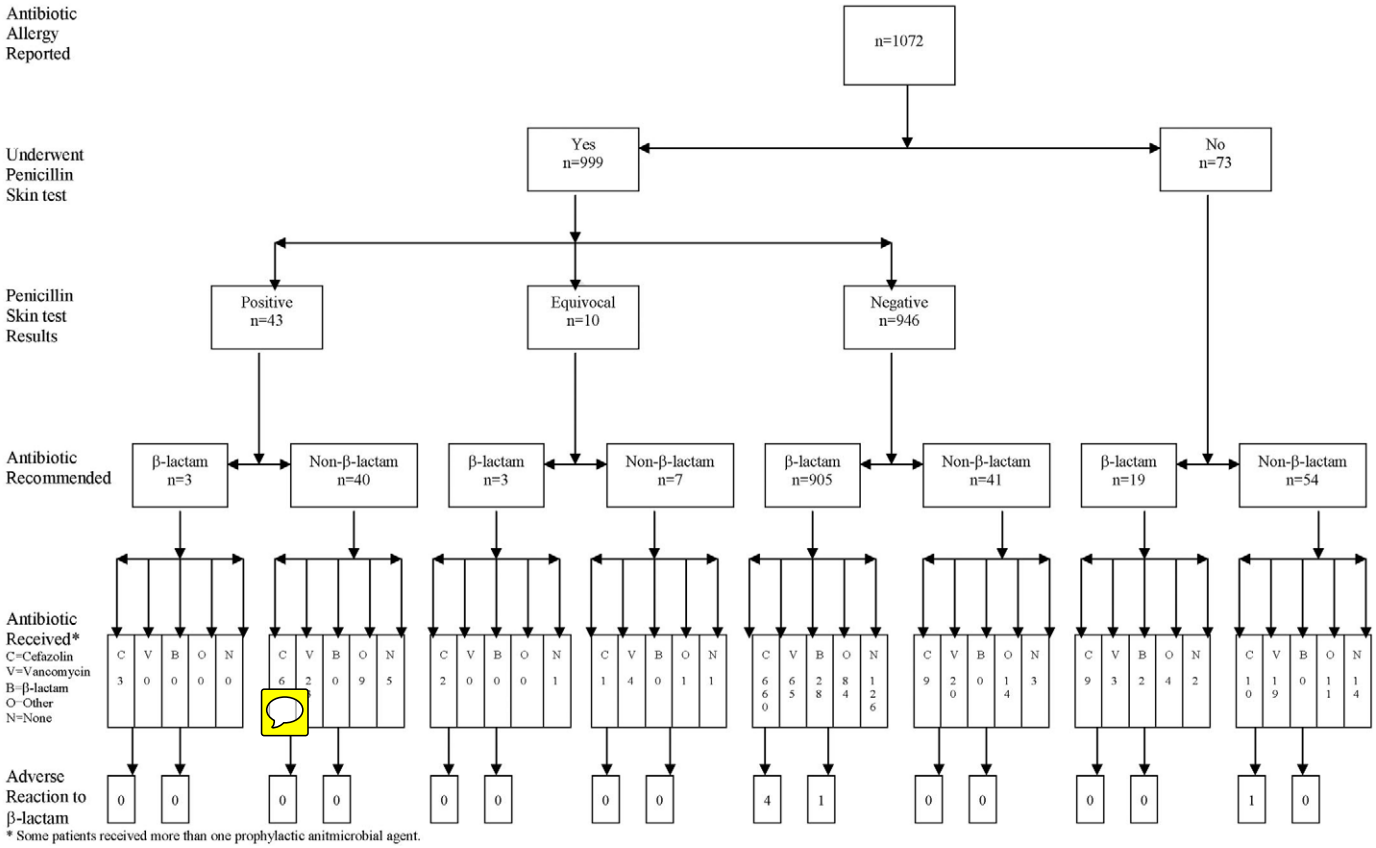

Figure 1. Clinical outcomes in 1,072 patients with a history of penicillin allergy.

sporin allergy, with and without a history of a penicillin allergy, 31 (79%) of 39 patients underwent penicillin skin testing and 8 (21%) did not (Fig 2). Twenty-seven (87%) had a negative penicillin skin test result, and 4 (13%) had an equivocal penicillin skin test result. Ten of 27 patients with a negative penicillin skin test result were advised to avoid cephalosporin antimicrobial agents, and all 4 patients with an equivocal penicillin skin test result were also advised to avoid β-lactam antimicrobial agents. All 8 patients who did not undergo penicillin skin testing were advised to avoid β-lactam antimicrobial agents.

The top 4 reasons for not performing a penicillin skin test were a negative histamine control in 25 (30%), history of anaphylaxis to a cephalosporin or penicillin in 11 (13%), tolerance of cefazolin in the past in 9 (11%), or patient refusal in 8 (10%). The remaining reasons for not performing a penicillin skin test were previous reaction to a cephalosporin, current rash, non–IgE-mediated adverse drug reaction, history consistent with an adverse effect, dermatographism, and unknown.

Pattern of Antibiotic Administration

Nine hundred fifty-five patients (86%) received preoperative antimicrobial prophylaxis. Eight hundred ninety-nine (94%) of the 955 patients who received preoperative antimicrobial prophylaxis had a penicillin skin test. Of these 955 patients, 716 (75%) received cefazolin, 60 (6%) clindamycin, 33 (3%) ciprofloxacin, and 25 (3%) levofloxacin (Table 1). Some patients received more than 1 antibiotic prophylaxis.

Among patients who were permitted to use β-lactam antimicrobial agents, 688 (73%) of 947 patients were given cefazolin, 69 (7%) vancomycin, 88 (9%) other antibiotics such as clindamycin and ciprofloxacin, 30 (3%) other β-lactam antimicrobial agents, and 131 (14%) no antibiotics. The total percentages exceed 100%, because some patients were given more than 1 antibiotic. Of those who were advised to avoid β-lactams, 80 (49%) of 164 patients were given vancomycin, 28 (17%) cefazolin, 39 (24%) other antibiotics, 1 (0.6%) other β-lactam antimicrobial agent (ampicillin), and 25 (15%) no antibiotics.

Figure 1 shows the clinical outcomes of 1,072 patients with a sole history of penicillin allergy in whom a prophylactic antimicrobial agent was administered. Of note, only 149 patients (16%) received vancomycin compared with 38 (30%) of 127 previously published historical controls[10] ($P < .01$). In patients with a history of a cephalosporin allergy with and without a history of penicillin allergy who underwent

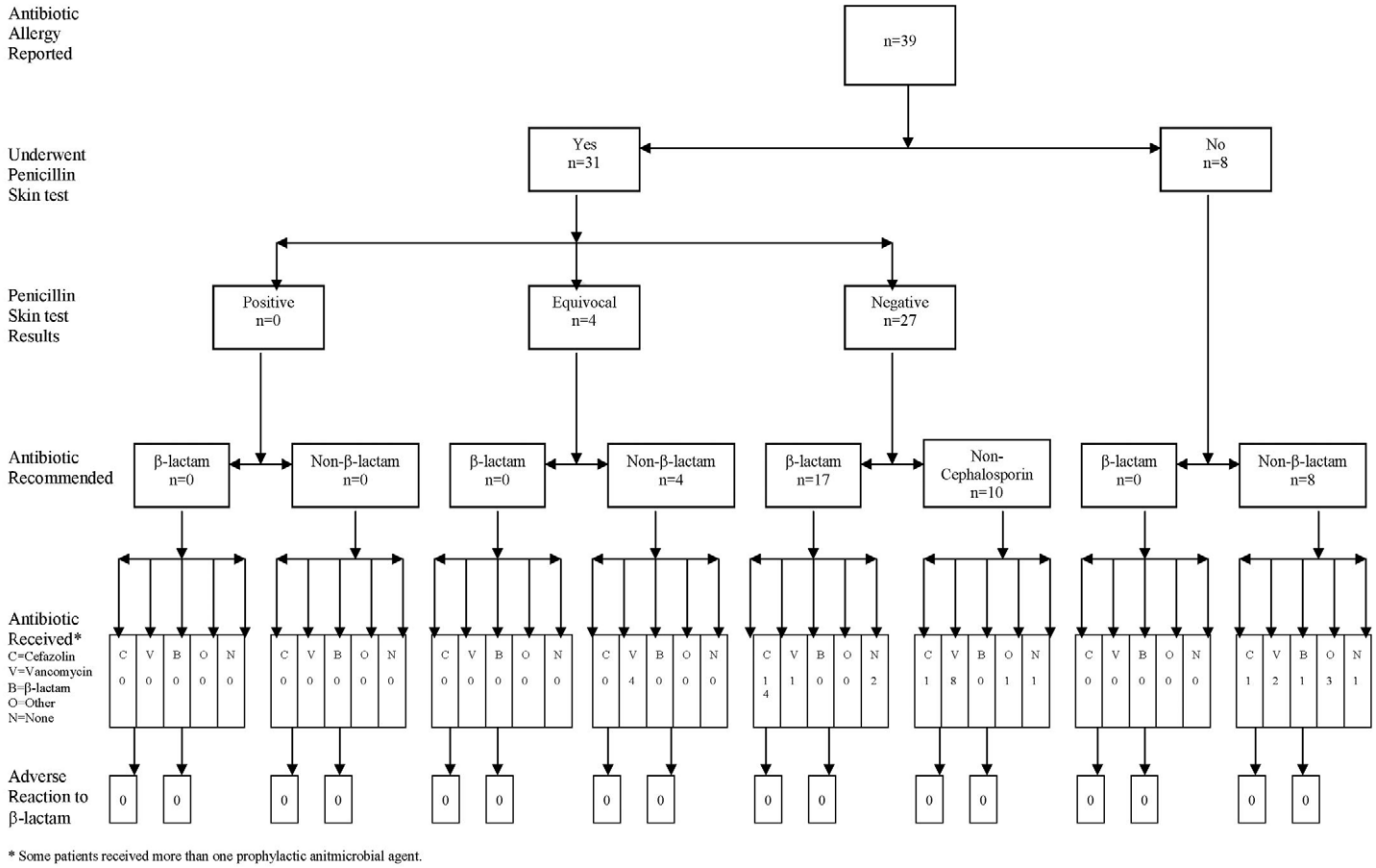

Figure 2. Clinical outcomes in 39 patients with a history of cephalosporin with and without penicillin allergy.

Table 1. Antibiotics Administered Perioperatively

Antibiotic administered	No. (%) of patients (N = 955)*
Cefazolin	716 (75)
Vancomycin	149 (16)
Clindamycin	60 (6)
Ciprofloxacin	33 (3)
Levofloxacin	25 (3)
Ampicillin	22 (2)
Gentamycin	5 (0.5)
Cephalexin	4 (0.4)
Ceftriaxone	3 (0.3)
Metronidazole	2 (0.2)
Dicloxacillin	1 (0.1)
Gatifloxacin	1 (0.1)
Linezolid	1 (0.1)
Piperacillin/tazobactam	1 (0.1)

* Some patients received more than 1 antibiotic.

penicillin skin testing and were advised to avoid β-lactam antimicrobial agents, 12 (39%) of 31 were given vancomycin, 1 (3%) cefazolin, 1 (3%) other antibiotics, and 1 (3%) no antibiotics. Of those who were permitted to use β-lactam antimicrobial agents, 14 (45%) were given cefazolin, 1 (3%) vancomycin, and 2 (6%) no antibiotics. Among the 8 patients who did not undergo penicillin skin testing and were advised to avoid β-lactam antimicrobial agents, 3 (38%) of 8 were given other antibiotics, 2 (25%) received vancomycin, 1 (13%) cefazolin, 1 (13%) other β-lactam antimicrobial agent, and 1 (13%) no antibiotics.

Adverse Reactions

Review of the medical records revealed that 5 (0.7%) of 675 patients with a negative penicillin skin test result who received a cephalosporin developed a probable adverse reaction to a cephalosporin. Four were to cefazolin and 1 to ceftriaxone. Of the 4 patients who had an adverse reaction to cefazolin, 1 patient had an episode of hypotension, 2 other patients developed pruritus, and 1 patient reported throat swelling and difficulty breathing without objective evidence when examined by the physician. The patient who received ceftriaxone developed serum sickness–like symptoms. All patients recovered without further sequela, and no further cephalosporins were given. Twenty (25%) of 81 who did not undergo penicillin skin testing received cefazolin, and 1 (5%) of 20 developed hypotension that responded to a fluid bolus. This one patient reported urticaria with penicillin in the past. The patient did not undergo penicillin skin testing because of

a negative histamine control from taking cetirizine and was advised to avoid β-lactams after the evaluation by the allergist. No patients with an equivocal penicillin skin test result who received a cephalosporin had an adverse drug reaction.

Among the 43 patients with a positive penicillin skin test result, 40 (93%) were advised to avoid β-lactams and 3 (7%) were permitted to use cefazolin. These 3 patients had received cefazolin in the past without an adverse drug reaction. Nine (21%) of 43 patients with a positive penicillin skin test result received cefazolin, and no adverse drug reactions were noted.

DISCUSSION

To our knowledge, this is the largest series of patients demonstrating the utility of penicillin allergy testing and allergy consultation in reducing vancomycin use in patients with a history of penicillin allergy. In our study of 1,111 patients, vancomycin use was reduced to 16% compared with 30% among historical controls ($P < .01$) previously reported by Li et al[10] at our institution. Furthermore, by including a broad range of surgical specialties, our study confirmed the wide applicability of penicillin allergy testing and allergy consultation in reducing vancomycin use in patients with a history of penicillin allergy. We have previously reported our experience with routine preoperative penicillin skin testing in 60 elective orthopedic surgery patients reporting allergy to penicillin or cephalosporins, where we found a significant reduction in vancomycin use.[10] In another study, Harris et al[13] were able to modify antibiotic use in 95% of patients with a history of penicillin allergy by penicillin skin testing in a small group of hospitalized (28 patients) and perioperative patients (16 patients). Our study, along with those mentioned herein,[10,13] clearly demonstrates the utility of penicillin skin testing in the reduction of vancomycin use in surgical patients with a history of penicillin allergy.

Ninety-four percent of our patients had a negative penicillin skin test result, which is consistent with other reports in the literature.[14–16] Most patients who are not penicillin allergic by penicillin skin testing can safely receive penicillin[14,17–19] and are not at an increased risk of an immediate-type hypersensitivity reaction when a cephalosporin is given.[4,20–23] Daulat et al[24] reviewed the medical records of 606 selected patients with a reported history of penicillin allergy who had received a cephalosporin. Penicillin skin tests were not performed in most of these patients. They reported that only 1 (0.17%) of 606 patients experienced an adverse reaction (worsening of patient's eczema). In a retrospective medical record review that assessed the risk of intraoperative allergic reactions to cephalosporins in patients with a reported history of penicillin allergy (413 patients), only 1 of 300 patients given preoperative cephalosporin had a probable allergic reaction to the cephalosporin.[25] In the study, patients with a questionable penicillin allergy (not defined in the text) or who had an allergy to an unknown medication were not considered "truly" allergic to penicillin. Patients with a history of anaphylaxis to penicillin may have been excluded from the study or given a noncephalosporin antimicrobial agent. Solensky et al[26] showed that 347 (33%) of 1,063 patients with a history of penicillin allergy and positive penicillin skin test results had a "vague" history of prior reaction to penicillin. A "vague" history was defined as one unlikely to be IgE mediated (such as maculopapular rash, gastrointestinal symptoms, or an unknown reaction). The authors conclude that patients with a vague history should still undergo penicillin skin testing, because a large number of penicillin allergic patients (those with evidence of IgE to penicillin on penicillin skin test) would be missed. Thus, the patient's history may not be the most prudent method for assessing the risks of administering cephalosporins in patients with a history of penicillin allergy.

Among patients with a history of penicillin allergy confirmed with a positive penicillin skin test result, an adverse reaction rate of 4.4% (6 of 135) has been reported in the literature.[27] Similarly, in a study by Romano et al,[28] patients with a history of penicillin allergy, a positive penicillin skin test result, but a negative skin test result to cefuroxime, ceftazidime, ceftriaxone, and cefotaxime were able to tolerate cefuroxime and ceftriaxone when challenged by these cephalosporins. However, the challenges were not followed by a full therapeutic course, and 22 patients declined to be challenged. When patients with a history of penicillin allergy and a negative penicillin skin test result are given a cephalosporin, only 2 (0.6%) of 351 patients had an adverse reaction.[27] In our study, only 5 patients (0.8%) who received a cephalosporin after a negative penicillin skin test result developed an adverse drug reaction, a reaction rate remarkably similar to other reports.[27] This is the largest series of patients with a history of penicillin allergy and a negative penicillin skin test result who have been challenged with cephalosporins. Thus, adverse drug reactions to cephalosporins are rare in patients with a reported history of penicillin allergy but a negative penicillin skin test result.

These studies suggest a low risk of a hypersensitivity reaction in patients with a history of penicillin allergy. However, caution is advised. Pumphrey et al,[5] in a study of fatal anaphylaxis in the United Kingdom from 1992 to 1997, revealed that 6 of 12 fatalities were from the first course of a cephalosporin. Three of the 6 were known to be allergic to amoxicillin and 1 to penicillin. Hence, some caution is still advised if a cephalosporin is to be given in patients with a history of penicillin allergy.

The Joint Task Force on Practice Parameters[2] recommends that if a non–β-lactam antimicrobial agent substitute is not available for patients needing a cephalosporin, patients with a history of an immediate-type hypersensitivity reaction to penicillin should undergo penicillin skin tests. If penicillin skin test results are negative, cephalosporin can be administered with a less than 1% risk of immediate adverse reaction. However, if penicillin skin test results are positive, then the patient should either avoid β-lactam antimicrobials or be considered for cephalosporin desensitization. Patients with a history of penicillin allergy who subsequently have tolerated a cephalosporin agent do not need to undergo penicillin skin

testing before readministration of the same cephalosporin drug.

Essential to the success of this clinical pathway is the logistics involved in a timely allergy evaluation and identification of the patients. Most surgical patients in our institution undergo a preoperative medical evaluation. These patients are evaluated by a physician and also are met by a business representative to answer any questions regarding insurance coverage and costs. Patients with a history of penicillin and/or cephalosporin allergy are identified by medical records or by the physician performing the preoperative evaluation and referred to an on-site allergist. A rotating allergist and nurse specialist who administer the penicillin skin test spend a half-day each day 5 days a week evaluating these patients. The allergist evaluates these referred patients, and a recommendation is provided on the same day they are referred. The allergy nurse or allergist notifies the surgical services regarding the recommendation for antimicrobial prophylaxis. Interestingly, 29 (18%) of 164 patients who were advised to avoid β-lactam antibiotics by the allergist received cefazolin and/or other β-lactam antimicrobial agent. Among these, 1 patient who received cefazolin developed hypotension and responded to a fluid bolus. The patient recovered without sequela. In an ongoing attempt at quality improvement and patient safety, all patients are now given a card with the allergist's recommendations to be given to the admitting nurse in addition to calling the surgical service. In addition, allergists amend the patient's drug allergy status in the electronic medical record after the evaluation and recommendations, making the new changes available to the surgical service. Currently, our institution will implement a clinical pathway in which the pharmacist will not be able to dispense a β-lactam antimicrobial agent without first contacting the prescribing physician if penicillin allergy is listed in the electronic medical record. This model of a fully integrated practice has resulted in a safe reduction of vancomycin use. However, the cost-effectiveness and ongoing quality improvement and patient safety evaluations of our clinical pathway will need further follow-up in the future.

Recently, at the 16th National Forum on Quality Improvement in Health Care, 6 interventions in health care that have been proven to prevent avoidable deaths have been recommended (www.ihi.org). One of these 6 changes suggested the prevention of adverse drug events. By reducing the unnecessary use of vancomycin and identifying those patients at risk of an immediate-type hypersensitivity reaction among patients with a history of penicillin allergy, our clinical pathway provides an effective and safe system to fulfill this requirement.

Our study has several limitations. It was conducted at an outpatient academic tertiary center and in the same building, which facilitated a timely evaluation by an allergist. Cardiovascular, thoracic, and pediatric surgical patients were not evaluated in the POE clinic and, consequently, not included in our study. Nevertheless, this is the largest series of this kind, representing a broad number of surgical specialties that demonstrate the benefits of penicillin allergy testing and allergy consultation in reduction of vancomycin use in surgical patients with a history of penicillin allergy.

Currently, the major determinant (benzylpenicilloyl) for penicillin skin testing is no longer commercially available. Only some of the major medical centers are able to produce their own major and minor determinants. However, the major determinant will be available in the near future through AllerQuest. Therefore, the implementation of this clinical pathway is currently limited to the major medical centers. We hope that the results of our study, clearly showing the benefits of preoperative penicillin allergy testing, will encourage manufacturers to resume production of penicillin skin test reagents and encourage commercial production of the minor determinants.

REFERENCES

1. Osmon DR. Antimicrobial prophylaxis in adults. *Mayo Clin Proc*. 2000;75:98–109.
2. Disease management of drug hypersensitivity: a practice approach. *Ann Allergy Asthma Immunol.* 1999;83:665–677.
3. Blanca M, Fernandez J, Miranada A, et al. Cross-reactivity between penicillin and cephalosporins: clinical and immunological studies. *J Allergy Clin Immunol*. 1989;83:381–385.
4. Anne S, Reisman RE. Risk of administering cephalosporin antibodies to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol*. 1995;74:167–170.
5. Pumphrey RS, Davis S. Under-reporting of antibiotic anaphylaxis may put patients at risk. *Lancet*. 1999;353:1157–1158.
6. Hiramatsu K, Aritaka N, Hanaki H, et al. Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. *Lancet*. 1997;350: 1670–1673.
7. Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *Am J Infect Control.* 1995;23:87–94.
8. Stosor V, Peterson LR, Postelnick M, Noskin GA. *Enterococcus faecium* bacteremia: does vancomycin resistance make a difference? *Arch Intern Med*. 1998;158:522–527.
9. Pelz RK, Lipsett PA, Swoboda SM, et al. Vancomycin-sensitive and vancomycin-resistant enterococcal infections in the ICU: attributable costs and outcomes. *Intensive Care Med*. 2002;28: 692–697.
10. Li J, Markus P, Osmon D, et al. Reduction of vancomycin use in orthopedic patients with a history of antibiotic allergy. *Mayo Clin Proc*. 2000;75:902–906.
11. Voss HE, Redmond AP, Levine BB. Clinical detection of the potential allergic reactor to penicillin by immunologic tests. *JAMA*. 1966;196:679.
12. Solley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: clinical experience with a battery of skin-test reagents. *J Allergy Clin Immunol*. 1982;69:238–244.
13. Harris AD, Sauberman L, Kabbash L, Greineder DK, Samore MH. Penicillin skin testing: a way to optimize antibiotic utilization. *Am J Med*. 1999;107:166–168.
14. Salkind A, Cuddy P, Foxworth J. Is this patient allergic to penicillin? an evidence-based analysis of the likelihood of penicillin allergy. *JAMA*. 2001;285:2498–2505.
15. Gadde J, Spence M, Wheeler B, Adkinson NF Jr. Clinical

experience with penicillin skin testing in a large inner-city STD clinic. *JAMA*. 1993;270:2456–2463.
16. Mendelson LM, Ressler C, Rosen JP, et al. Routine elective penicillin allergy skin testing in children and adolescents: study of sensitization. *J Allergy Clin Immunol*. 1984;73:76–81.
17. Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med*. 1987;107:204–214.
18. Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy*. 1988;18: 515–540.
19. Solensky R, Earl H, Gruchalla R. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med*. 2002; 162:822–826.
20. Shepherd GM, Burton DA. Administration of cephalosporin antibiotics to patients with a history of penicillin allergy [abstract]. *J Allergy Clin Immunol.* 1993;91:262.
21. Greenberger PA. 1070 Penicillin major and minor determinants have high negative predictive value when cephalosporins are administered to penicillin-allergic patients. *J Allergy Clin Immunol.* 2003;111(2, pt 2):S335.
22. Macy E, Burchette RJ. Oral antibiotic adverse reactions after penicillin skin testing: multi-year follow-up. *Allergy*. 2002;57: 1151–1158.
23. Novalbos A, Sastre J, Cuesta J, et al. Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. *Clin Exp Allergy*. 2001;31:438–443.
24. Daulat S, Solensky R, Earl HS, Casey W, Gruchalla RS. Safety of cephalosporin administration to patients with histories of penicillin allergy. *J Allergy Clin Immunol*. 2004;113: 1220–1222.
25. Goodman EJ, Morgan MJ, Johnson PA, et al. Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic reaction. *J Clin Anesth*. 2001;13:561–564.
26. Solensky R, Earl HS, Gruchalla RS. Penicillin allergy: prevalence of vague history in skin test-positive patients. *Ann Allergy Asthma Immunol*. 2000;85:195–199.
27. Kelkar PS, Li J. Cephalosporin allergy. *N Engl J Med*. 2001; 345:804–809.
28. Romano A, Gueant-Rodriguez RM, Viola M, Pettinato R, Gueant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med*. 2004;141:16–22.

Requests for reprints should be addressed to:
Miguel Park, MD
Division of Allergic Diseases
Mayo Clinic
100 First Ave SW
Rochester, MN 55905
E-mail: park.miguel@mayo.edu