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Collaboration between Allergists and Pharmacists Increases β-Lactam Antibiotic Prescriptions in Patients with a History of Penicillin Allergy

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Key Words
Allergist · Pharmacist · Penicillin allergy · β-Lactam antibiotic · Penicillin · Antibiotics

Abstract
Background: Over 90% of patients with a history of penicillin allergy have negative penicillin skin tests. Pharmacists are trained to identify and resolve medication-related problems. We hypothesized that collaboration between allergists and pharmacists to identify and evaluate patients with a history of penicillin allergy would increase β-lactam antibiotic prescription. ***Methods:*** We conducted a prospective observational study in which patients with a history of penicillin allergy were identified and educated at the pharmacy about penicillin allergy and offered an allergist consultation with a penicillin skin test. All patients were followed up to determine which antibiotics were subsequently prescribed. ***Results:*** A total of 503 patients were enrolled, and 71 (14%) were evaluated by an allergist. Sixty-seven of these 71 patients (94%) had a negative penicillin skin test. Twenty-nine patients evaluated by an allergist and 205 patients not evaluated were prescribed antibiotics. Patients prescribed antibiotics and evaluated by an allergist were compared to those not evaluated by an allergist, with the following results: 19 of 29 patients (66%) were prescribed a β-lactam antibiotic compared to 54 of 205 (26%; $p < 0.0001$); 8 of 29 patients (28%) were prescribed penicillin compared to 7 of 205 (3%; $p < 0.0001$); 15 of 29 patients (52%) were prescribed a cephalosporin compared to 48 of 205 (23%; $p < 0.01$), and 10 of 29 patients (34%) were prescribed a non-β-lactam antibiotic compared with 177 of 205 (86%; $p < 0.0001$). ***Conclusion:*** A collaborative effort between allergists and pharmacists can increase β-lactam antibiotic prescriptions and decrease non-β-lactam prescriptions in patients with a history of penicillin allergy.

Introduction

β-Lactam antimicrobial agents are still the treatment of choice for many infections [1]. However, many patients are not prescribed penicillins due to a previous history of adverse reaction to penicillins [2]. Over 80% of patients with a self-reported history of penicillin allergy do not have evidence of IgE antibodies to penicillin on skin testing [3, 4]. Moreover, several studies have shown the utility and safety [5, 6] of penicillin skin testing among penicillin-allergic patients in optimizing antibiotic use and in subsequent hospital visits [7–10]. The adverse reaction

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rate in patients who receive penicillin is 1–3% in patients with a history of penicillin allergy and a negative penicillin skin test to both the major and minor determinant [11, 12]. Thus, many patients with a personal history of penicillin allergy are unnecessarily denied the benefits of penicillin and are given broader-spectrum antimicrobial agents. The emergence of more antibiotic-resistant bacteria, such as vancomycin-resistant enterococci, and recommendations for the judicious use of vancomycin [13, 14] further demonstrate the need to use first-line antibiotics whenever possible. Unnecessary use of broad-spectrum antibiotics has a financial impact as well. The mean antibiotic costs for penicillin-allergic patients are 63% higher than for patients who are not allergic to penicillin [15]. Therefore, appropriate identification, evaluation and treatment of patients with a reported history of penicillin allergy have become essential.

At the 16th National Forum on Quality Improvement in Health Care, 6 interventions in health care that have been proven to prevent avoidable deaths were recommended (www.ihi.org), including *the prevention of adverse drug events*. Pharmacists are trained to prevent, identify and resolve medication-related problems. The role of the pharmacist is foremost to ensure that patients receive medication that is safe and effective. Concerns regarding medication safety and the amount of direct patient contact make the pharmacist an ideal ally with the allergist in the identification of patients with a history of penicillin allergy and in the prevention of medication errors. At our institution, no formal relationship between the Pharmacy and the Division of Allergic Diseases existed before our study for the purpose of identifying and decreasing adverse drug reactions and medication errors. We show that a collaborative effort between the allergist and the pharmacist with the goal of identifying and evaluating patients with a history of penicillin allergy can optimize antibiotic prescription among patients with a history of penicillin allergy in the outpatient setting.

Methods

Study Population

A clinical pathway was developed in which the pharmacist identified patients with a history of penicillin allergy at the time of service in the pharmacy while filling a prescription for any medication. The patient received brief education about penicillin allergy and a penicillin allergy pamphlet from the pharmacist. The patient was offered referral to the Division of Allergic Diseases. The Division of Allergic Diseases was contacted by either the pharmacy or the patient in order to set up an appointment for penicillin skin testing and evaluation by an allergist. Payment was required for the evaluation for penicillin allergy in the Division of Allergic Diseases.

Patients seen at our institution's outpatient pharmacies from October 2006 to November 2007 who had an allergy to penicillin documented in the electronic medical record were recruited to participate in the study.

Study Design

We conducted a prospective observational study in which patients were reviewed for basic demographics (age and sex), penicillin skin test results, type of adverse drug reaction to penicillin in the past and antibiotics used/prescribed (by chart review/electronic medical record) after the patient was educated by the pharmacist. The patients were followed for 6 months to 1 year. All patients with a history of penicillin allergy who were seen and educated about penicillin allergy by the pharmacist were enrolled in the study and entered into a database (described further below). The antibiotics were categorized as penicillins, cephalosporins, β-lactam antibiotics and non-β-lactam antibiotics. The type of adverse drug reactions to penicillin were categorized as rash to penicillin, itchiness, hives/angioedema, anaphylaxis, shortness of breath, unknown reaction and nonspecific adverse drug reactions (such as 'local inflammation', syncope, nausea, vomiting). Two reviewers were employed to review the patients' charts. Before the charts were reviewed, the two reviewers examined a few charts together in order to establish consistency. If any questions arose during the review process, the reviewers discussed the question to establish consistency in data collection. All the data were input into a spreadsheet program (Microsoft Excel; Microsoft Corp, Redmond, Wash., USA) and converted into a JMP file (see Statistical Analysis below) for statistical analysis. The Institutional Review Board approved the study and all participants signed a written informed consent form.

Penicillin Skin Testing

Penicillin allergy skin testing was conducted using benzylpenicilloyl polylysine, penicillin G potassium (Pfizerpen®, Pfizer, New York, N.Y., USA) and penicilloate, as previously reported [16]. The penicilloate was produced by reacting penicillin G with 1 N NaOH at a pH of 11.5 for 90 min, after which the pH was adjusted to 7.4 by addition of 1 N HCl. The penicilloate was diluted with phosphate-buffered saline to 0.01 mol/l and filtered through a 0.22-μm membrane for sterility. Penicillin G potassium was used at a concentration of 6,000 U/ml in phosphate-buffered saline. A skin prick test with 6 mg/ml histamine or 0.1 mg/ml histamine administered intradermally 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 of the penicillin and control reagents. The skin test sites were examined after 15 min. A positive test result was defined as a wheal of 3 × 3 mm or greater with a surrounding zone of erythema [3]. Patients with negative prick test results to penicillin underwent intradermal testing.

Intradermal skin tests were also performed on the volar surface of the forearm. The test reagents were injected intradermally to produce an initial wheal of 2 × 2 mm. The skin test sites were examined after 15 min. A positive intradermal test was defined as a wheal of 3 × 3 mm or greater with a surrounding zone of erythema [3].

Patients with a wheal but without a flare on the penicillin skin test (skin prick and intradermal) were considered to be equivocal.

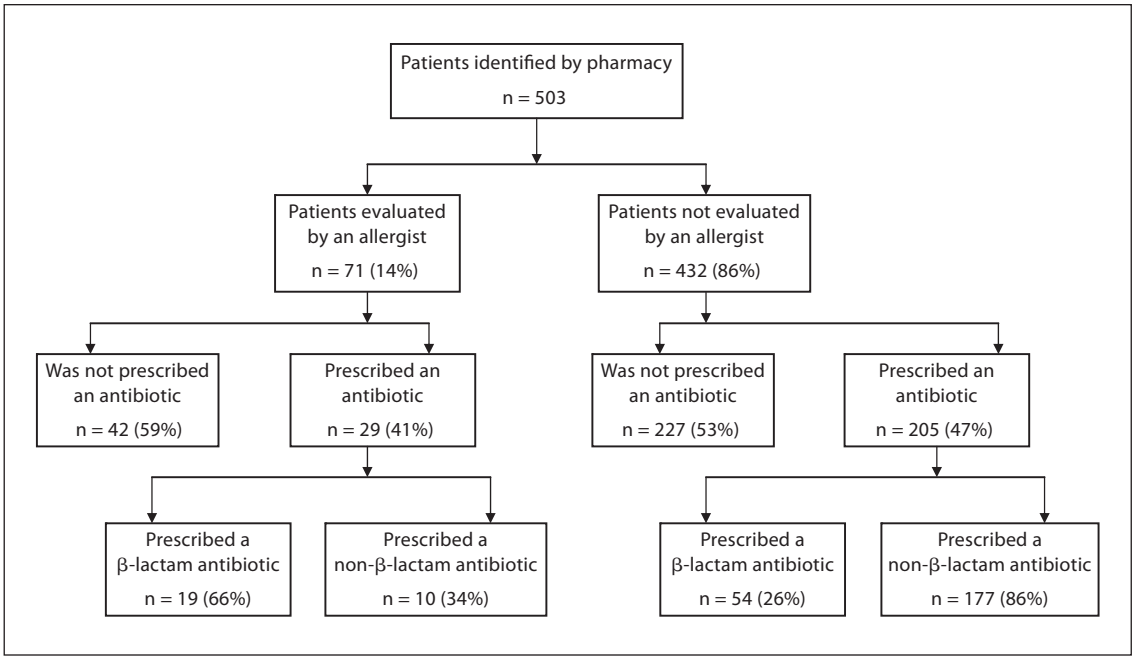

Fig. 1. Enrollment and outcomes. Some patients were prescribed more than 1 antibiotic, and thus the total number of antibiotics prescribed may not equal the number of patients who were prescribed an antibiotic.

Allergy skin testing was performed in a place where resuscitation equipment was available in case of anaphylaxis.

Statistical Analysis

All demographic data are represented as means ± standard deviation for age and gender with absolute numbers and percentages. The type of antibiotic used (penicillins, cephalosporins, β-lactam antimicrobials and non-β-lactam antimicrobials) and types of adverse drug reactions are represented as absolute numbers and percentages. β-Lactam antimicrobials were defined as penicillins and cephalosporins. No patients were given carbapenems.

Using the χ^2 test, we compared the differences in the proportion of penicillin-allergic patients who were evaluated by an allergist versus penicillin-allergic patients who were not evaluated by an allergist with regards to the antibiotic prescribed, i.e. β-lactam antimicrobial, penicillin, non-β-lactam microbial and/or cephalosporins. For example, in patients who received a β-lactam antimicrobial, those who were evaluated by an allergist were compared to those who where not evaluated by an allergist. The χ^2 test was also used to compare the differences in the proportion of types of adverse drug reactions to penicillin in the past among patients with a history of penicillin allergy who were evaluated by an allergist compared to those who were not evaluated by an allergist. A two-sided t test was employed to evaluate the difference between the mean age of those patients who were evaluated for penicillin allergy compared to those who did not undergo penicillin allergy evaluation. A software program (JMP version 7.0, SAS Institute Inc., Cary, N.C., USA) was used to perform the statistical analyses. A p value ≤ 0.05 was considered statistically significant.

Results

Demographics

A total of 503 study subjects were enrolled, and 71 of these 503 patients (14%) were evaluated by an allergist for penicillin allergy. Among the patients who were evaluated for penicillin allergy by an allergist, 52 (73%) were evaluated within 1 month after identification and teaching by the pharmacist and 19 (27%) were evaluated after 1 month (fig. 1).

The mean age of the study population was 51 ± 20 years. The mean age of the patients evaluated by an allergist for penicillin allergy was 58 ± 19 years, compared to 50 ± 20 years in the group who were not evaluated by an allergist (p = 0.002). Of the 503 enrolled subjects, 288 (57%) were female and 215 (43%) were male. No gender differences between the patients who were evaluated for penicillin allergy and those who were not evaluated were noted.

Types of Adverse Drug Reactions to Penicillin in the Past

Among the 503 patients, 118 (23%) had a history of rash to penicillin, 38 (8%) itchiness, 201 (40%) hives, 13 (3%) anaphylaxis, 16 (3%) shortness of breath, 105 (21%)

Table 1. Antibiotic prescriptions

Antibiotics prescribed	Evaluated by an allergist (n = 29)	Not evaluated by an allergist (n = 205)	p value
β-Lactams	19 (66)	54 (26)	<0.0001
Penicillins	8 (28)	7 (3)	<0.0001
Cephalosporins	15 (52)	48 (23)	0.001
Non-β-lactams	10 (34)	177 (86)	<0.0001

Values in parentheses represent percentages. Some patients were prescribed more than 1 antibiotic, and thus the total number of antibiotics prescribed may not equal the number of patients who were prescribed an antibiotic.

unknown reaction and 84 (17%) nonspecific adverse drug reactions to penicillin. Some patients described more than one type of adverse drug reaction to penicillin; thus, the total number of adverse reactions exceeds the number of patients. Patients who were evaluated for penicillin allergy were more likely to list itchiness and nonspecific adverse drug reactions to penicillin as the adverse reaction to penicillin than those who were not evaluated [13 of 71 (18%) vs. 25 of 432 (6%), respectively (p = 0.0002); 22 of 71 (31%) vs. 62 of 432 (14%), respectively (p = 0.0005)].

Penicillin Skin Test Results

Seventy of the 71 patients (99%) who were evaluated by an allergist also underwent penicillin skin testing. Of the 71 patients, 67 (96%) had a negative penicillin skin test, 2 patients (3%) had a positive penicillin skin test (intradermal skin test to amoxicillin, intradermal skin test to penicillin G), 1 patient (1%) had an equivocal penicillin skin test and 1 patient (1%) had no skin test.

Antibiotic Prescription Pattern

Antibiotics were prescribed for 29 patients evaluated by an allergist and 205 patients not evaluated by an allergist. Among the patients who were prescribed an antibiotic, 19 of 29 (66%) were prescribed a β-lactam antimicrobial after the penicillin allergy consultation compared to 54 of the 205 (26%; p < 0.0001) among the patients who did not undergo penicillin allergy evaluation. Eight of 29 patients (28%) were prescribed penicillins after the penicillin allergy consultation compared to 7 of 205 (3%; p < 0.0001) among the patients who did not undergo penicillin allergy evaluation. Fifteen of 29 patients (52%) were prescribed cephalosporins after the penicillin allergy consultation compared to 48 of 205 (23%; p = 0.001) among the patients who did not undergo penicillin allergy evaluation. Only 1 patient with a history of penicillin allergy evaluated by an allergist, with a negative penicillin skin test and prescribed a β-lactam antimicrobial agent, had an adverse drug reaction (nonspecific rash) to penicillin. Ten of 29 patients (34%) were prescribed a non-β-lactam antimicrobial after the penicillin allergy consultation compared to 177 of 205 (86%; p < 0.0001) among the patients who did not undergo penicillin allergy evaluation (table 1). Some patients were prescribed more than one antibiotic, including β-lactam antimicrobials and/or non-β-lactam antimicrobials, and thus the total number of antibiotics prescribed may not be equal to the number of patients who were prescribed an antibiotic.

Discussion

To our knowledge, this is the first successful collaboration between allergists and pharmacists using penicillin skin testing which has resulted in increased prescription of β-lactam antibiotics with a corresponding decrease in non-β-lactam prescriptions in patients with a history of penicillin allergy in the outpatient clinical setting. In this study, 66% of the patients with a history of penicillin allergy, identified by the pharmacist and evaluated by an allergist, were prescribed a β-lactam antibiotic compared to 26% of patients who were not evaluated by an allergist (p < 0.0001). Over a quarter of the patients who were educated by the pharmacist and offered penicillin allergy evaluation by an allergist were seen more than 1 month after identification by the pharmacist. The education about penicillin allergy by the pharmacist had a long-standing effect on the patient's behavior which translated to the patient being seen more than 1 month after being educated by the pharmacist. Hence, this study demonstrates that a collaborative effort between pharmacists and allergists at a large multispecialty clinic can change antibiotic prescribing patterns in patients with a history of penicillin allergy even though the prescribing physicians were not specifically informed verbally or in writing about the results of the penicillin allergy evaluation.

Our observation that 96% of patients with a history of penicillin reaction had negative penicillin skin tests is similar to previous studies [8, 11, 12]. Patients with a history of penicillin reaction and negative penicillin skin testing are unlikely to experience immediate-type adverse drug reactions when challenged with penicillin. Adverse reaction rates in this population have been found

to range from 1 to 3% [11, 12]. The vast majority of patients with a history of penicillin allergy with negative penicillin skin testing can tolerate penicillin upon rechallenge. Thus, a referral to an allergist with subsequent penicillin skin testing can modify the medication prescribed in patients with a history of penicillin allergy.

Several studies have demonstrated that penicillin allergy evaluation using penicillin skin testing can be a useful strategy to change antibiotic use in patients with a history of penicillin allergy. Arroliga et al. [17] conducted a prospective observational study in which 100 patients with a history of penicillin allergy admitted to an intensive care unit were evaluated by penicillin skin testing. All patients were receiving prophylactic antibiotics, and 96 patients underwent penicillin skin testing. Thirty-eight patients were changed to a β-lactam antibiotic. Harris et al. [7] showed that penicillin skin testing in the hospital was able to modify antibiotic use in 82% of enrolled patients, and the use of vancomycin was decreased. Perencevich et al. [10] conducted a retrospective study in which they followed 38 patients with a history of penicillin allergy but negative penicillin skin tests. There were 35 admissions, 70% of the patients required a β-lactam antibiotic and all patients received a β-lactam. However, no control population was used [10]. Studies have demonstrated decreased vancomycin usage and increased β-lactam usage when patients with a history of penicillin allergy undergo penicillin skin tests in inpatient or perioperative settings [8, 9, 17]. Del Real et al. [18] demonstrated increased penicillin usage and decreased vancomycin and fluoroquinolone usage after penicillin skin testing in a combined outpatient and inpatient study. At our institution, we have shown in several studies that patients with a history of penicillin allergy who are undergoing a preanesthetic medical examination for an elective surgical procedure and who had undergone a penicillin skin test and allergy evaluation were prescribed less vancomycin than those who were not evaluated by an allergist [8, 9, 19]. Hence, these studies in combination with the present study demonstrate the utility of penicillin skin testing and evaluation by an allergist in modifying the antibiotic used in patients with a history of penicillin allergy. Moreover, our study confirms the value of collaboration between allergists and pharmacists in identifying, educating and evaluating patients with a history of penicillin allergy and modifying antibiotic prescriptions.

There are several limitations to our study. The study was conducted in a tertiary care center with fully integrated electronic medical records. This may limit the generalizability of the study. In addition, a selection bias may have occurred. Patients with a more severe adverse drug reaction to penicillin in the past may not have been willing to undergo penicillin skin testing. However, when we compared the reaction to penicillin in the past in patients who were evaluated by an allergist versus those patients who were not evaluated by an allergist, only itchiness and nonspecific adverse drug reactions were shown to be statistically different. Moreover, anaphylaxis and shortness of breath were not statistically different. This makes it less likely that the reaction to penicillin in the past consistently influenced whether the patients consented to penicillin skin testing and allergist evaluation.

In conclusion, our study demonstrates that initiating a collaborative effort between pharmacists and allergists can modify and optimize antibiotic prescription in patients with a history of penicillin allergy. Once benzylpenicilloyl is commercially available again, further evaluation of patients with a history of penicillin allergy by allergists and collaboration between pharmacists and allergists can result in improved patient safety and optimize antibiotic prescriptions.

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