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BRIEF REPORTS

The Impact of Penicillin Skin Testing on Clinical Practice and Antimicrobial Stewardship

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BACKGROUND: Penicillin skin testing (PST) is a simple and reliable way of diagnosing penicillin allergy. After being off the market for 4 years, penicilloyl-polylysine was reintroduced in 2009 as PRE-PEN. We describe the negative predictive value (NPV) of PST and the impact on antibiotic selection in a sample of hospitalized patients with a reported history of penicillin allergy.

METHODS: We introduced a quality improvement process at our 861-bed tertiary care hospital that used PST to guide antibiotic usage in patients with a history consistent with an immunoglobulin E (IgE)-mediated reaction to penicillin. Subjects with a negative PST were then transitioned to a β-lactam agent for the remainder of their therapy. NPV of skin testing was established at 24-hour follow-up. We are reporting the result of 146 patients tested between March 2012 and July 2012.

RESULTS: A total of 146 patients with a history of penicillin allergy and negative PST were treated with β-lactam antibiotics. Of these, only 1 subject experienced an allergic reaction to the PST. The remaining 145 patients tolerated a full course of β-lactam therapy without an allergic response, giving the PST a 100% NPV. We estimated that PST-guided antibiotic alteration for these patients resulted in an estimated annual savings of $82,000.

CONCLUSION: Patients with a history of penicillin allergy who have a negative PST result are at a low risk of developing an immediate-type hypersensitivity reaction to β-lactam antibiotics. The increased use of PST may help improve antibiotic stewardship in the hospital setting. *Journal of Hospital Medicine* 2013;8:341–345. © 2013 Society of Hospital Medicine

Self-reported penicillin allergy is common and frequently limits the available antimicrobial agents to choose from. This often results in the use of more expensive, potentially more toxic, and possibly less efficacious agents.[1,2]

For over 30 years, penicilloyl-polylysine (PPL) penicillin skin testing (PST) was widely used to diagnose penicillin allergy with a negative predictive value (NPV) of about 97% to 99%.[3] After being off the market for 5 years, PPL PST was reapproved in 2009 as PRE-PEN.[4] However, many clinicians still fail to utilize PST despite its simplicity and substantial clinical impact. The main purpose of this study was to describe the predictive value of PST and impact on antibiotic selection in a sample of hospitalized patients with a reported history of penicillin allergy.

METHODS

In 2010, PST was introduced as a quality-improvement measure after approval and support from the chief of professional services and the medical staff executive committee at Vidant Medical Center, an 861-bed tertiary care and teaching hospital. Our antimicrobial stewardship program is regularly contacted for approval of alternative therapies in penicillin allergic patients. The PST quality-improvement intervention was implemented to avoid resorting to less appropriate therapies in these situations. Following approval by the University and Medical Center Institutional Review Board, we designed a 4-month study to assess the impact of this ongoing quality improvement measure from March 2012 to July 2012.

Hospitalized patients of all ages with reported penicillin allergies were obtained from our antimicrobial stewardship database. Their charts were reviewed for demographics, antibiotic use, clinical infection, and allergic description. Deciding whether to alter antibiotic therapy to a β-lactam regimen was based on microbiologic results, laboratory values, clinical infection, and history of immunoglobulin E (IgE)-mediated reactions, as defined by the updated drug allergy practice parameters.[5] IgE-mediated reactions included: (1) immediate urticaria, laryngeal edema, or hypotension; (2) anemia; and (3) fever, arthralgias, lymphadenopathy, and an urticarial rash after 7 to 21 days.[5–7] We defined anaphylaxis as the development of angioedema or hemodynamic instability within 1 hour of penicillin administration. A true negative reaction was a lack of an IgE-mediated reaction to all the drug challenges.

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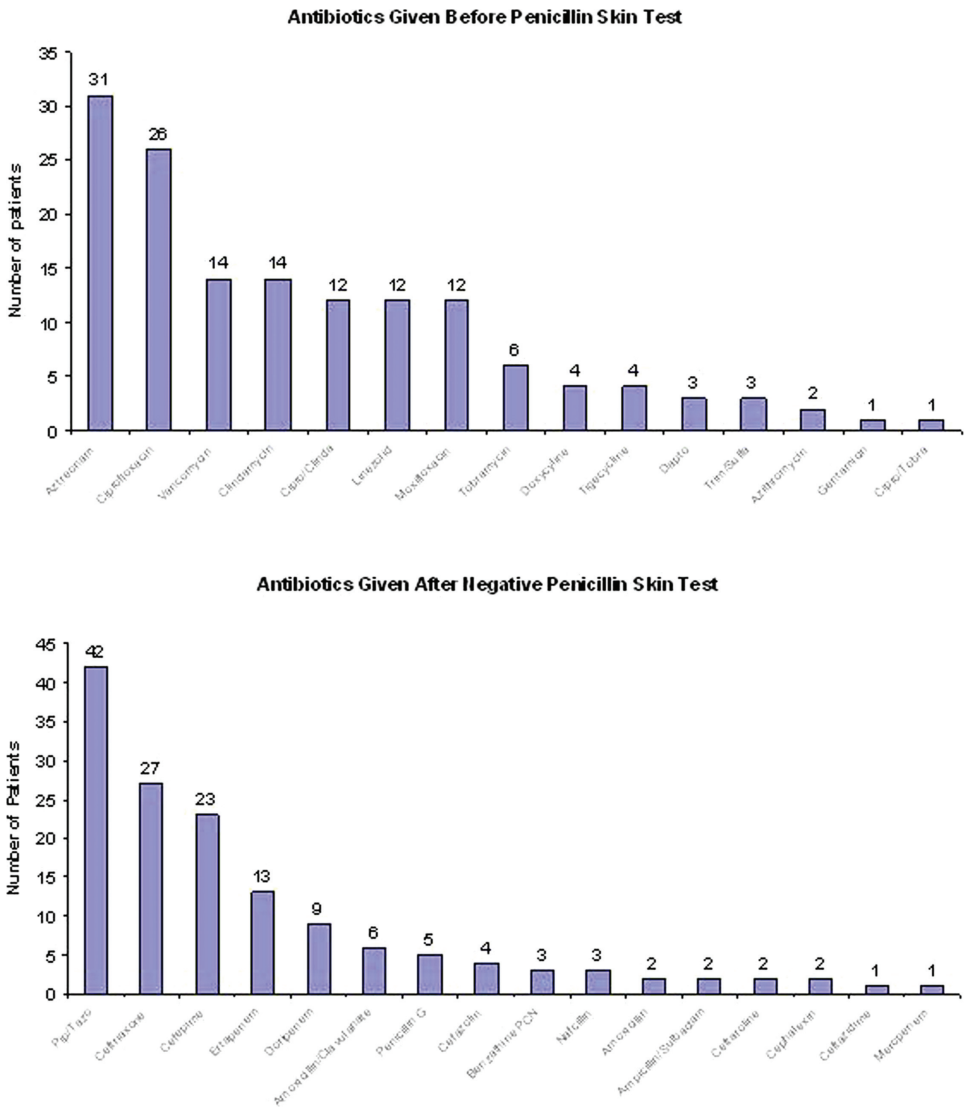

FIG. 1. Antibiotics used prior to penicillin skin testing and β-lactams transitioned to after a negative penicillin skin test. The upper graph illustrates the antibiotics used prior to penicillin skin testing in 146 patients over the 5-month study period. The lower graph illustrates the β-lactam antibiotics used after a negative penicillin skin test in the same patients. Abbreviations: Cipro, ciprofloxacin; Clinda, clindamycin; Dapto, daptomycin; Pip/Tazo, piperacillin-tazobactam; Tobra, tobramycin; Trim/Sulfa, trimethoprim-sulfamethoxazole.

Patients in the medical, surgical, labor, and delivery wards; intensive care units; and emergency department underwent testing. The β-lactam agent used after a negative PST was recorded, and the patients were followed for 24 hours after transitioning their therapy to a β-lactam regimen. Excluded subjects included those with (1) non–IgE-mediated reactions, (2) skin conditions that can give false positive results, (3) medications that may interfere with anaphylactic therapy, (4) history of severe exfoliative reactions to β-lactams, (5) anaphylaxis less than 4 weeks prior, (6) allergies to antibiotics other than penicillin, and (7) uncertain allergy history.

PST Reagents/Procedure

Our benzylpenicilloyl major determinant molecule, commercially produced as PPL, was purchased as a PRE-PEN from ALK-Abello, Round Rock, Texas. Penicillin G potassium, purchased from Pfizer, New York, New York, is the only commercially available minor determinant and can improve identification of

TABLE 1. Prevalence of Reported Antimicrobial Drug Allergy in 4031 Charts Reviewed Over a 5-Month Period

Antibiotic	No. of Patients Reporting An Allergy	% Per Total Charts Reviewed
Penicillin	428	10.6
Sulfonamide	271	6.7
Quinolone	108	2.7
Cephalosporin	81	2.0
Macrolide	65	1.6
Vancomycin	39	0.9
Tetracycline	20	0.5
Clindamycin	18	0.4
Metronidazole	9	0.2
Linezolid	2	0.05

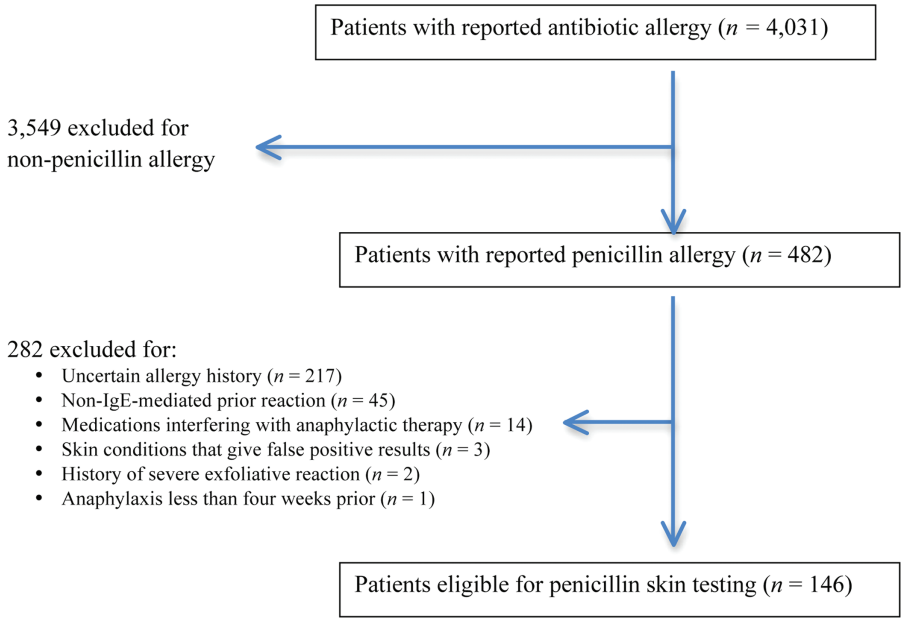

FIG. 2. Study design with inclusion and exclusion criteria. Abbreviations: IgE, immunoglobulin E.

penicillin allergy by up to 97%.[2] The PST panel also included histamine (positive control) and normal saline (negative control).

Skin Testing Procedure

An infectious diseases fellow (R.H.R. or B.K.) was supervised in preparing for potential anaphylaxis, applying the reagents and interpreting the results based on drug allergy practice parameters.[5] The preliminary epicutaneous prick/puncture test was performed with a lancet in subjects without prior anaphylaxis using full-strength PPL and penicillin G potassium reagents. If there was no response within 15 minutes, which we defined as a lack of wheal formation $\geq$3 mm or greater than that of the negative control, 0.02 to 0.03 mL of each reagent was injected intradermally using a tuberculin syringe and examined for 15 minutes.[5] If there was no response, patients were then challenged with either a single oral dose of penicillin V potassium 250 mg or whichever oral penicillin agent they previously reported an allergy to. If no reaction was appreciated within 2 hours, their therapy was changed to a β-lactam agent including penicillins, cephalosporins, and carbapenems for the remaining duration of therapy (Figure 1) An estimate of NPV was obtained after 24 hours follow-up.

Statistical Analysis

We designed a study to estimate whether the reapproved PST achieves an NPV of at least 95%.[3] We hypothesized that clinicians will be willing to utilize PST even if it has an NPV of slightly less than 98% compared to the current standard of treating patients without PST.[7] Assuming an equivalence margin of 3%, we estimated a sample size of 146 to achieve at least 82% power to test a hypothesis of NPV $\leq$95% using a 1-sided Z test with a type-I error rate of 5%.[8] Once the sample size of 146 subjects was reached, we stopped recruiting patients.

Sample characteristics of the subjects who underwent testing were summarized using descriptive statistics. Sample proportions were calculated to summarize categorical variables. Mean and standard deviation were calculated to summarize continuous variables. Cost analysis of antibiotic therapy was estimated from the Vidant Medical Center antibiotic pharmaceutical acquisition costs. Estimated cost of peripherally inserted central catheter (PICC) placement and removal as well as laboratory testing costs were obtained from our institution's medical billing department. Marketing costs of pharmacist drug calibration and nursing assessments with dressing changes were obtained from hospital-affiliated outpatient antibiotic infusion companies.

RESULTS

A total of 4031 allergy histories were reviewed during the 5-month study period to achieve the sample size of 146 patients (Table 1). Of those, 3885 were excluded (Figure 2). Common infections included pneumonias (26%) and urinary tract infections (20%) (Table 2) Only 1 subject had a positive reaction with hives, edema, and itching approximately 6 minutes after the agents were injected intradermally. The remaining 145 (99%) had negative reactions to the PST and oral challenge and were then successfully transitioned to a β-lactam agent without any reaction at 24 hours, giving an NPV of 100%. Ten subjects were switched from intravenous to oral β-lactam agents (Figure 1). Avoidance of PICC placement

TABLE 2. Information Gathered During the Penicillin Skin Test Study

Categories	No. of Patients (%)
Time since last reported penicillin use	
1 month–1 year	6 (4)
2–5 years	39 (27)
6–10 years	23 (16)
>10 years	78 (53)
Reported IgE-mediated reactions	
Bronchospasm	23 (16)
Urticarial rash	100 (68)
Edema	32 (22)
Anaphylaxis	21 (14)
Age on admission, y	
20–50	28 (19)
51–60	29 (20)
61–70	41 (28)
71–80	24 (16)
>80	24 (16)
Gender	
Male	55 (40)
Female	88 (60)
Race	
White	82 (56)
Black	61 (42)
Hispanic	3 (2)
Infections being treated	
Bacteremia	7 (4.8)
Catheter-related bloodstream infection	2 (1.4)
Empyema	1 (0.7)
Epidural abscess	2 (1.4)
Infective endocarditis	4 (2.7)
Intra-abdominal infection	24 (16.4)
Meningitis	1 (0.7)
Neutropenic fever	1 (0.7)
Osteomyelitis	6 (4.1)
Pericardial effusion	1 (0.7)
Prosthetic joint infection	5 (3.4)
Pneumonia	40 (27.4)
Skin and soft-tissue infection	20 (13.7)
Syphilis	3 (2.1)
Urinary tract infection	29 (19.7)

NOTE: **Abbreviations:** IgE, Immunoglobulin E.

($1,200) and removal ($65), dressing changes, weekly drug-level testing, laboratory technician, and pharmaceutical drug calibration costs allowed for a healthcare reduction of $5,233 ($520/patient) based on the 146 patients studied. The total cost of therapy would have been $113,991 if the PST had not been performed. However, the cost of altered therapy following a negative PST was $81,180, a difference of $32,811 ($225/per patient) in a 5-month period. The total estimated annual difference, including antibiotic alteration and associated drug-costs, would be $82,000.

DISCUSSION

PST is the most rapid, sensitive, and cost-effective modality for evaluating patients with immediate allergic reactions to penicillin. Over 90% of individuals with a true history of penicillin allergy have confirmed sensitivity with a PST, implying most patients who are skin tested negative are truly not allergic.[7,9–12] Our study shows that the reapproved PST with the PPL and penicillin G determinants continues to have a high NPV. A patient with a negative PST result is generally at a low risk of developing an immediate-type hypersensitivity reaction to penicillin.[2,11] PST frequently allowed for less expensive agents that would have been avoided due to a reported allergy. The estimated annual savings of $82,000 dollars from antibiotic alteration with successful transition to a β-lactam agent after a negative PST illustrates its value, supports its validity, and makes this study novel.

Many β-lactamase inhibitors (ie, piperacillin-tazobactam), fourth generation cephalosporins (ie, cefepime), and carbapenems still remain costly. Despite this, we were still able to achieve a significant reduction in overall cost. In addition to financial benefits, PST allowed for the use of more appropriate agents with less potential adverse effects. Narrow-spectrum, non–β-lactam agents were sometimes altered to a broader-spectrum β-lactam agent. We also frequently tailored 2 agents to just 1 broad-spectrum β-lactam. This led to more patients being given broad-spectrum agents after the PST (72 vs 89 patients). However, we were able to avoid using second-line agents, such as aztreonam, vancomycin, linezolid, daptomycin, and tobramycin, in many patients with infections that are often best treated with penicillin-based antibiotics (ie, syphilis, group B *Streptococcus* infections). With increasing incidence and recovery of multidrug-resistant bacteria, PST may also allow use of potentially more effective antimicrobial agents.

A possible limitation is that our prevalence of a true penicillin allergy was <1%, whereas Bousquet et al. illustrate a higher prevalence of about 20%.[7] Although our prevalence may not be generalizable, Bousquet's study only assessed patients with allergies <5 years prior.

The introduction of PST into clinical practice will allow trained healthcare providers to prescribe cheaper, more appropriate, less toxic antimicrobial agents. The overall benefit of reintroducing penicillin agents when needed in the future is far more cost-effective than what is described here. PST should become a standard of care when prescribing antibiotics to patients with a history of penicillin allergy. Medical providers should be aware of its utility, acquire training, and incorporate it into their practice.

Disclosures: Paul P. Cook, MD, has potential conflicts of interest with Gilead (investigator), Pfizer (investigator), Merck (investigator and speakers' bureau), and Forest (speakers' bureau). Neither he nor any of the other authors has received any sources of funding for this article. For the remaining authors, no conflicts were declared. The corresponding author, Ramzy Rimawi, MD, had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

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