Original Article

Use of a Penicillin Allergy Screening Algorithm and Penicillin Skin Testing for Transitioning Hospitalized Patients to First-Line Antibiotic Therapy

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What is already known about this topic? The penicillin allergy label has significant public health implications. Different inpatient approaches at academic centers addressing this problem include skin testing by pharmacists or infectious disease providers, and an algorithm to direct cephalosporin challenges.

What does this article add to our knowledge? This article describes an allergy/pharmacist antimicrobial stewardship initiative in which patients were identified for inpatient penicillin skin testing based on high-risk, second-line antibiotic use in a community hospital setting.

How does this study impact current management guidelines? This study provides another approach for penicillin allergy de-labeling, which is in line with multiple national guidelines.

BACKGROUND: Penicillin allergy is the most commonly reported antibiotic allergy. Avoidance of β-lactam antibiotics in hospitalized patients leads to the use of second-line therapies.
OBJECTIVE: The utility of a penicillin allergy history algorithm (PAHA) and subsequent penicillin skin testing (PST) in transitioning hospitalized patients from second- to first-line antibiotic therapy is described.
METHODS: Through an electronic medical record report, pharmacists identified adult inpatients with penicillin allergy receiving moxifloxacin, intravenous vancomycin, aztreonam, daptomycin, or linezolid, in which a β-lactam antibiotic was preferred. The PAHA was administered to identify patients for PST. Skin-test negative patients were transitioned to first-line β-lactam antibiotic therapy.
RESULTS: Fifty patients consented to the study. Historical reactions included hives (16 patients, 32%), angioedema (15, 30%), anaphylaxis (6, 12%), unknown (6, 12%), rash (6, 12%), and dyspnea (1, 2%). Pre-PST antibiotic regimens included vancomycin (82%), aztreonam (22%), moxifloxacin (6%), daptomycin (4%), and/or linezolid (2%). Forty-seven patients (94%) were skin-test negative and were subsequently transitioned to a β-lactam antibiotic. Two patients were skin-test positive and one was histamine nonreactive. No patients experienced an immediate adverse reaction when challenged with a penicillin-based antibiotic. A total of 982 days of second-line antibiotic therapy and at least 23 hospital days to administer the antibiotic were avoided.
CONCLUSIONS: The use of the PAHA and subsequent PST is a safe, effective multidisciplinary intervention that facilitates the transition to β-lactam antibiotics. Our approach is unique in that it prioritizes patients based on the use of second-line antibiotics, and then applies an algorithm to determine eligibility for PST. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Penicillin allergy; Penicillin skin testing; Antimicrobial stewardship*

Penicillin allergy is the most commonly reported drug allergy. Approximately 10% of the United States population reports a penicillin allergy, yet 90% of these patients will tolerate penicillin.[1] The number of inpatients reporting a penicillin allergy is even higher, around 11% to 15%.[1-4] Less than 0.1% of the 25 million patients with a penicillin allergy label undergo skin testing annually.[3]

The penicillin allergy label results in the use of second-line antibiotics. As a whole, these second-line antibiotics have been shown to be less effective against susceptible organisms, and their overuse contributes to antimicrobial resistance, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* (VRE).[4-6] The penicillin allergy label has

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Abbreviations used
AWP- Average wholesale price
C diff- Clostridium difficile
EMR- Electronic medical record
IV- Intravenous
MSSA- Methicillin-susceptible Staphylococcus aureus
PAHA- Penicillin allergy history algorithm
PO- Oral
PST- Penicillin skin testing
VRE- Vancomycin-resistant Enterococcus

also been shown to increase the risk of *Clostridium difficile* (C diff) infection.[3,7]

Patients who do not receive a β-lactam antibiotic when indicated have been shown to have a significantly increased risk of adverse events requiring antibiotic discontinuation and higher rates of hospital readmission regardless of the type of infection.[7] Given the risks associated with the use of second-line antimicrobials in penicillin-allergic patients and their association with multidrug resistant pathogens, current antibiotic stewardship recommendations include penicillin skin testing (PST) in patients with an appropriate history.[8] Costs of second-line antibiotics, including linezolid, daptomycin, and aztreonam, are further reason to avoid their use.

We sought to evaluate the clinical utility and practicality of using the penicillin allergy history algorithm (PAHA) and subsequent PST in patients receiving high-risk antibiotics to transition them to a β-lactam of choice. The PAHA was incorporated as a standardized history-taking tool, given the observed inaccuracies in drug allergy history contained in the electronic medical record (EMR)[9] and the demonstrated inaccuracy of histories obtained between allergists and nonallergists.[10,11] This approach of prioritizing patients for PST based on high-risk antibiotic use has not been extensively studied.

METHODS

Setting and data collection

This was a single-center prospective study conducted at a 528-bed tertiary care medical center from June 2015 through February 2017. At this institution, approximately 15% to 20% of patients report a penicillin allergy on admission. Inpatients ≥18 years of age receiving intravenous (IV) vancomycin, daptomycin, aztreonam, oral (PO) or IV moxifloxacin, and/or PO or IV linezolid were identified via a pharmacy report, generated by the EMR (Hyperspace, Epic Systems Corporation, Verona, WI). The report was screened by an infectious diseases PharmD specialist (M.L.S.) for penicillin-allergic patients for whom a β-lactam antibiotic would be first line based on culture data, or, in the absence of culture data, if more than 7 days of empiric antimicrobial therapy was planned based on documented clinical data. This impression was then discussed with the patient's primary team.

Select patients were identified for further screening using the PAHA (Figure 1). This assessed and categorized allergic reactions based on the Gell and Coombs classification scheme,[1] time elapsed since the reported penicillin reaction, and whether a penicillin antibiotic had been subsequently tolerated. The PAHA defined the management approach depending on the penicillin allergy history. Exclusion criteria included hospitalization in the cardiac, medical, or surgical intensive care unit, inability to provide informed consent, and pregnancy.

Appropriate patients underwent skin prick testing by an allergist (AR) using the major determinant of penicillin, penicilloyl polylysine (Pre-Pen, ALK, Round Rock, Texas), and penicillin G 10,000 U/mL, histamine 6 mg/mL, and a saline negative control. Prick testing was carried out with Quintip skin testing devices (Hollister-Stier, Spokane, Wash) on the volar forearm. A positive test was defined as a wheal 3 mm or more than the negative control in the setting of a reactive positive control. If skin prick testing was negative, then intradermal testing was performed with the same materials except the histamine control of 0.02 mg/mL. Intradermal major determinant and penicillin G were done in duplicate, with a positive test again defined as 3 mm greater than the negative control. A histamine control was placed on patients taking medications with antihistaminic properties, and testing was carried out if this control produced a wheal of 5 mm or greater.

Patients with negative PST were transitioned to a β-lactam antibiotic of choice. Patients transitioning to a cephalosporin or carbapenem antibiotic were challenged with a one-time dose of amoxicillin 500 mg during their hospital stay. This step was omitted for patients who were transitioned to a penicillin-based antibiotic. All patients received a 2-week follow-up phone call to assess the tolerability of their β-lactam antibiotic.

Cost analysis

To estimate the impact of PST on direct antibiotic expenditures, we subtracted the average wholesale price (AWP) per day of antibiotic therapy after PST from the AWP per day of antibiotic therapy before PST. This value was then multiplied by the total duration of antibiotic therapy in days administered after PST.[12] The impact on indirect costs such as pharmacist monitoring time, nursing administration and serum concentration sampling time, and laboratory costs to analyze concentrations was not evaluated. The cost analysis of PST included the costs of penicilloyl polylysine, penicillin G, skin testing supplies, and cost for the penicillin allergy consult by the allergy/immunology physician. Of note, as part of our research protocol, subjects were not billed for physician consultative time, but this figure was included in the cost analysis.

Data collection

Data collected included patient age, gender, race, hospital service, historical reaction to penicillin, type of infection for which β-lactam therapy was preferred, PST result, antibiotic therapy before and after PST, and tolerability of the β-lactam antibiotic as reported on the 2-week follow-up call.

Outcome measures and data analysis

The primary objective was to identify appropriate patients for PST via the PAHA to transition them from second-line antibiotics to a preferred β-lactam antibiotic. Descriptive statistics were used to detail outcomes.

RESULTS

A total of 64 patients were approached for study participation consideration. A total of 9 patients were excluded because of a history suggestive of a severe cutaneous reaction, 5 patients declined PST despite qualifying per the PAHA, and the remaining 50 patients underwent PST. The clinical characteristics of the PST group are described in Table I.

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