

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 2018;6:1349-55)

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

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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

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 1.

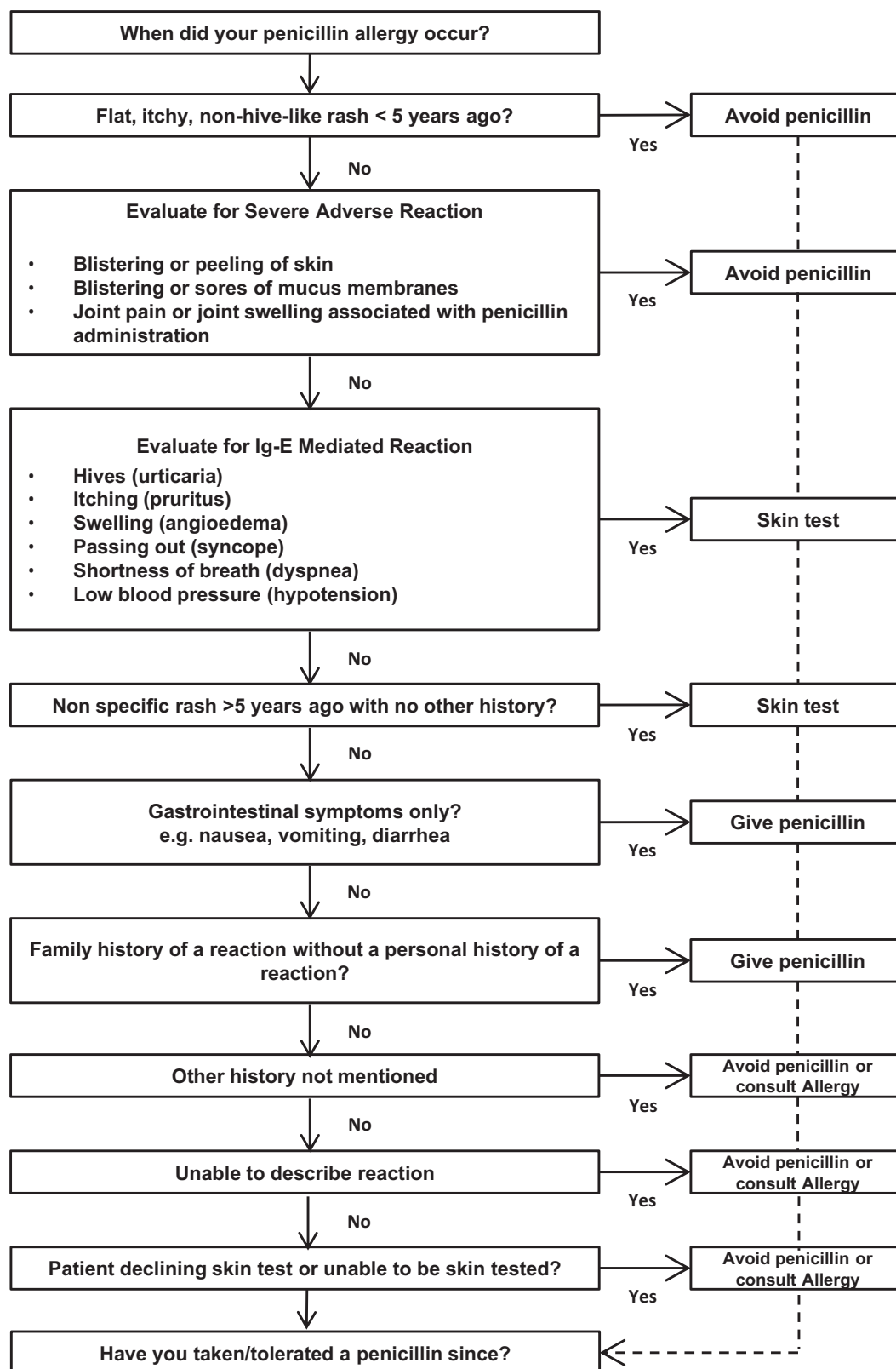


FIGURE 1. The penicillin allergy history algorithm. This instrument was used to obtain history and guide management in enrolled patients.

TABLE I. Clinical characteristics of patients undergoing skin testing

Total number of patients	50
Average age in years ($\pm$ SD)	66 (13)
Female gender, n (%)	27 (54)
Race, n (%)	
Caucasian	42 (84)
Black	3 (6)
Hispanic	5 (10)
Primary service, n (%)	
Internal medicine	40 (80)
General surgery	5 (10)
Vascular surgery	2 (4)
Cardiothoracic surgery	1 (2)
Plastic surgery	1 (2)
Orthopedic surgery	1 (2)

SD, Standard deviation.

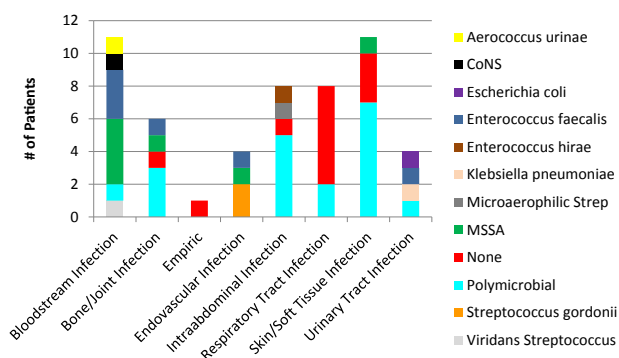
TABLE II. Patient historical reactions to penicillin

Historical reaction	Number (%)
Hives	16 (32)
Angioedema	15 (30)
Unknown	6 (12)
Anaphylaxis	6 (12)
Rash	6 (12)
Shortness of breath	1 (2)

The most common historical reactions included hives, followed by angioedema, unknown, anaphylaxis, rash, and dyspnea (Table II). There were 16 (32%) patients who recalled the exact age when their penicillin reaction occurred, and this average was 14.25 years (range: 3-30). In the remaining 34 (68%) patients, 17 reported that their reaction occurred in adulthood, 14 in childhood, and 3 were unsure.

There were 41 (82%) patients receiving vancomycin, 11 (22%) patients receiving aztreonam, 3 (6%) patients receiving moxifloxacin, 2 (4%) patients receiving daptomycin, and 1 (2%) patient receiving linezolid. There were 8 patients receiving a combination of targeted antibiotics. Infections for which a β -lactam antibiotic was preferred based on the primary team or infectious diseases team impression included infections of the skin/soft tissue, bloodstream, respiratory tract, abdomen, bone/joint, urinary tract, and endovascular system. There was 1 patient receiving empiric treatment. Targeted bacterial species included but are not limited to *Enterococcus* species (20 patients), *Enterobacteriaceae* (21 patients), and susceptible *Staphylococcus* species (15 patients) (Figure 2). Institutional use of the targeted second-line antibiotics for the study period is detailed in Table III.

Of the 50 patients who underwent PST, 47 (94%) were negative. There were 2 (4%) patients who were PST positive (1 patient to PCN G wheal 5, flare 5; the second to PCN G wheal 5, flare 30) in which second-line antibiotic therapy was continued. There was 1 (2%) patient whose intradermal histamine control was nonreactive. Of the PST negative patients, there were 28 (56%) who transitioned to a penicillin-based antibiotic, 13 (26%) to a first- or second-generation cephalosporin, 12 (24%) to a third- or fourth-generation cephalosporin, 2 (4%) to a carbapenem, and 7 (14%) who received a combination of the mentioned antibiotic classes (Figure 3).

**FIGURE 2.** Antibiotic indications and microbiology data for enrolled patients. NOTE: 3 patients had 2 sources of infection. CoNS, Coagulase-negative *Staphylococcus* species; MSSA, methicillin-susceptible *Staphylococcus aureus*.**TABLE III.** Institutional antibiotic use during the study period

Target antibiotic	Average DOT/1000 patient days for study period (SD)
Vancomycin IV (does not include PO)	68.34 (5.96)
Daptomycin	2.36 (1.25)
Aztreonam	2.92 (1.15)
Moxifloxacin (IV and PO)	4.04 (2.16)
Linezolid (IV and PO)	3.59 (1.11)

DOT, Days of therapy; IV, intravenous; PO, oral; SD, standard deviation.

There were no adverse events during PST on any subject or subsequent first challenge. There were 2 patients who developed an adverse reaction to the β -lactam antibiotic, but these were not thought to be IgE mediated. One patient reported developing a mildly pruritic rash on day 4 of amoxicillin/clavulanate. The rash was attributed to the drug, necessitating cessation of therapy. The second patient developed neutropenia within several days of starting ceftriaxone. Therapy was continued for 2 weeks, which then necessitated changing back to second-line antibiotic therapy. All other patients tolerated β -lactam antibiotic therapy.

Direct antibiotic cost savings was calculated to be a total of approximately \$3,500, translating into \$70 per patient. Direct cost savings would have been approximately \$17,000 and \$340 per patient, but the patient with neutropenia with ceftriaxone required resumption of indefinite therapy with daptomycin. We avoided approximately 982 days of second-line antibiotic exposure, based on the planned duration of the inpatient and outpatient β -lactam antibiotic courses (Table IV). Notably, there were 863 days of vancomycin avoided. In addition, a known total of 23 hospital days were avoided based on discussions with the primary team. Per hospital-adjusted expenses per inpatient day for the state of New York,¹³ the cost savings associated with hospital days avoided is approximately \$56,000. The cost associated with PST in this study was estimated to be \$341.40 per patient and \$17,070 for all 50 patients.

DISCUSSION

This study is one of the first to identify patients for PST based on the use of second-line antibiotics including vancomycin, aztreonam, moxifloxacin, linezolid, and daptomycin, and to

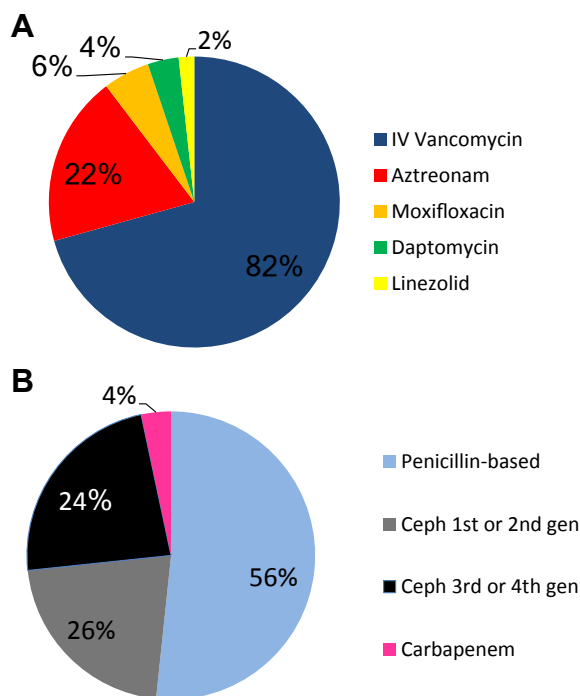


FIGURE 3. A, Antibiotic therapy before PST. B, Antibiotic therapy after PST. NOTE: Percentages exceed 100% because of some subjects receiving more than 1 antibiotic/antibiotic class. IV, Intravenous; PST, penicillin skin testing.

confirm eligibility for PST based on an algorithm. The majority of patients who underwent PST were skin-test negative, which is in line with previous reports.¹⁴⁻¹⁹ In addition, the vast majority of patients (96%) tolerated their β -lactam antibiotic course, which is also in line with previous reports.^{1,19}

In our study, 82% of patients were initially treated with vancomycin, and all were transitioned to a β -lactam antibiotic. Within this group, there were 11 cases of identified methicillin-susceptible *Staphylococcus aureus* (MSSA) infection in our study. This antibiotic optimization has significant clinical implications. There are strong data supporting the superiority of β -lactam antibiotics in the setting of MSSA infections. An increased mortality risk in MSSA bacteremia has been demonstrated for vancomycin as compared with β -lactam antibiotics,²⁰⁻²² and β -lactam antibiotics are superior to vancomycin in preventing relapse or persistence of MSSA bacteremia.²³⁻²⁵ Vancomycin therapy alone has been shown to be a risk factor for relapse and increased adverse effects.²⁴⁻²⁶ Enterococcal infections were the most commonly confirmed infection in our study. It is well accepted that penicillin-based antibiotics are considered first-line therapy against sensitive *Enterococcus* species, per numerous national guidelines.²⁷⁻³⁰ Judicious use of vancomycin in these cases has been advocated to decrease the risk of the development of VRE.²⁷ The transition from IV vancomycin to an oral penicillin-based agent may also facilitate hospital discharge.

There are important safety considerations with the use of second-line antibiotics compared with β -lactam antibiotics. IV vancomycin has a relatively narrow therapeutic index that necessitates the need for therapeutic drug monitoring to minimize the potential for oto- and nephrotoxicity³¹⁻³⁸ and this was the most commonly used antibiotic in our cohort at 82% before

TABLE IV. Days of second-line antibiotics avoided based on clinical indication

Targeted antibiotic	Days of therapy avoided
Aztreonam	66
Daptomycin	40
Moxifloxacin	13
Vancomycin	863
Total	982

PST. In our analysis, 6% of patients were initially treated with a fluoroquinolone and successfully transitioned to a β -lactam antibiotic. The United States Food and Drug Administration has warned against the use of fluoroquinolones for patients with alternative antimicrobial options³⁹ due to neurocognitive and musculoskeletal adverse effects. In addition, fluoroquinolones have demonstrated the strongest association with C diff compared with other classes of antibiotics.⁴⁰ The use of linezolid in our study was low (2%), but this is not considered a preferred or first-line agent particularly for the treatment of prolonged infections (≥ 2 weeks) given the risks of serious hematologic and neurologic toxicities.^{41,42}

In addition to efficacy and safety, cost is an obvious factor for prioritization of patients treated with second-line antibiotics. On the basis of the duration of antibiotics administered after PST, we avoided 863 days of vancomycin therapy in our cohort of patients, which has significant cost implications. An indirect cost analysis accounting for pharmacist monitoring time, nursing administration and serum concentration sampling time, and laboratory costs to analyze vancomycin concentrations would likely reveal significantly higher antibiotic-related cost savings per patient than our conservative calculation of \$70 per patient. This relatively low direct cost savings is also impacted by the fact that many patients in our cohort were transitioned from vancomycin (AWP approximately \$5.00-30.00/day) to either ampicillin or ampicillin/sulbactam (AWP approximately \$30.00-95.00/day). These figures are estimates, and although AWP is a standardized metric to compare medication prices nationally, it may fluctuate based on the source, and generally overestimates drug cost.⁴³ Although our study was not designed to evaluate indirect cost savings, 863 avoided days of vancomycin in a cohort of 50 patients is a substantial finding that likely assisted in minimizing adverse drug reactions as well as health care resources required. Furthermore, the transition away from vancomycin has significant implications for combatting antimicrobial resistance.

In our study, aztreonam was discontinued in 22% of patients, daptomycin was discontinued in 4% of patients, and linezolid in 2% of patients. These 3 antimicrobials carry a significant cost burden when compared with β -lactam antibiotics, ranging from 6- to 10-fold higher than first-line therapies.⁹ For example, the direct cost of daptomycin is \$500-1000 per day, depending on patient weight and indication, whereas amoxicillin at a dose of 500 mg three times daily has a direct cost of as little as \$1.00 per day.⁹ The use of second-line antibiotics can also contribute to extended and more costly hospital stays, particularly in patients whose discharge plans include a skilled nursing facility. These facilities may refuse admission to patients receiving cost-prohibitive and/or IV antibiotics. Although length of hospital stay was not a targeted endpoint in our study, it was communicated that PST facilitated discharge in 4 patients totaling 23

hospital days avoided given an easy transition to an oral β -lactam antibiotic. It is quite possible that additional hospital days were avoided by transitioning to an oral β -lactam antibiotic. The 23 hospital days avoided equates to a cost savings of \$56,000. These figures compare favorably with an estimated total of \$17,070 total cost for PST. In some cases, the initial point of care costs associated with PST itself could be greater than initial direct antibiotic cost savings, though this does not account for future savings in hospital length of stay, cost of hospital stay, cost avoidance of future antibiotics, or avoidance of adverse reactions to second-line antibiotics in patients who no longer have a penicillin allergy label.

There have been excellent recent studies detailing approaches to penicillin allergy in the inpatient setting that involve algorithms in the categorization and management of patients with penicillin allergy at major academic institutions.^{44,45} As compared with the Blumenthal et al algorithm, our PAHA was similarly developed for nonallergist inpatient providers to accurately categorize penicillin reactions, but focuses on further evaluation and potential elimination of the penicillin allergy through PST. Our approach differs from the approach detailed by Chen et al. in which specific antibiotics were targeted. This targeting of specific antibiotics may be a high yield strategy for health systems in which PST by pharmacists is not permissible by law and/or health systems with more limited resources. This triaging of patients based on their second-line antibiotic use is a strategy to reduce antibiotic-associated risk and cost with available allergy/immunology resources, and may be more applicable in nonacademic hospitals.

The collaboration of pharmacists and physicians is an important element of our study design. In New York State, pharmacists were prohibited from skin testing at the time of study design and enrollment, unlike the approach detailed by Chen et al⁴⁵ and others.¹⁷ However, our approach makes use of a hospital-based infectious disease PharmD screening patients for possible PST. Studies of physicians have detailed that many are unaware of the existence of PST,⁴⁶⁻⁴⁹ and the presence of an infectious disease PharmD advocating for PST to achieve optimal second-line therapy was an effective strategy in our design. Allergy/immunology physicians have particular expertise and training in penicillin allergy history and management and our particular institutional design kept this aspect of antimicrobial stewardship in the allergy/immunology purview, although our approach could be expanded to other specialties with appropriate drug allergy training, as there is precedent for this.⁵⁰

Although the algorithm we employed was not applied to every patient screened for inclusion into our study, it was applied to all patients consented in the study to confirm eligibility for PST. The simplicity of the algorithm raises the possibility of involving multiple members of the health care team, including medical and pharmacy students, advanced practice providers (ie, nurse practitioners, physician assistants), nurses, physicians, and pharmacists. This is an area of planned further study. A recent analysis in our institution has illustrated the overall incomplete documentation and characterization of penicillin allergy in inpatient EMR with the penicillin allergy label, spanning nurses, advanced practice providers, and physicians.⁴⁶ Use of this PAHA would be an opportunity for standardization of history taking among all inpatient health care providers with a tool developed by an allergist. If this approach proves fruitful in further study, it would be prime to incorporate into the EMR to standardize history documentation across all inpatient health care professionals.

There are limitations to our approach. Although we screened patients based on second-line antibiotic use, we prioritized patients to consent based on the documented EMR history, which limits our analysis of the effectiveness and generalizability of the PAHA, and slants the historical reactions of our patient cohort toward that of an IgE-mediated allergy. In addition, the average number of patients screened for study enrollment per day were not formally tracked. However, we do not believe that this weakens our conclusions because cost savings and improved clinical outcomes with penicillin allergy de-labeling have previously been documented.^{3,51} We also acknowledge that the algorithm is conservative in that it avoids skin testing patients with a delayed rash within 5 years of the evaluation, and this could be amended in future studies, as patients with an itchy rash may have experienced an IgE-mediated reaction and could have been candidates for PST. Enrollment in the study was slower than expected, and this is partially attributable to the pilot nature of the study and that the availability of allergy/immunology consultation for PST was variable. A previous initiative at our institution addressing aztreonam overuse significantly diminished aztreonam orders in penicillin-allergic patients,⁵² and this likely contributed to fewer eligible patients for the study overall. Lastly, the generalizability of our approach is limited to hospitals where allergy/immunology consultants who perform PST are available.

In conclusion, our multidisciplinary approach that stratifies patients for PST based on second-line antibiotic use and confirms suitability for PST with the PAHA is a practical approach that is potentially applicable in both the academic and nonacademic setting. The collaboration with an ID PharmD and allergy/immunology physician with the primary hospital teams is shown to transition patients to more effective, less toxic, and potentially less expensive β -lactam antibiotics. Our approach is unique and effective in this era where antimicrobial stewardship is paramount.

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