Implementation and Impact of a β -Lactam Allergy Assessment Protocol in a Veteran Population

Anna B. Mitchell, PharmD, BCPS; Rachel A. Ness, PharmD, BCPS; Jessica G. Bennett, PharmD; Jarred E. Bowden, PharmD, BCIDP, AAHIVP; Whitney V. Elliott, PharmD, BCPS; Amanda R. Gillion, PharmD, BCPS; and Debendra N. Pattanaik, MD, MBBS

Background: Approximately 10% of the US population reports having a β -lactam allergy, although nearly 90% do not have a true immunoglobulin E (IgE)-mediated reaction. This misconception results in using nonpreferred antibiotics, leading to antimicrobial resistance and treatment failure. To evaluate, clarify, and clear β -lactam allergies, we implemented a pharmacist-driven β -lactam allergy assessment (BLAA) protocol and penicillin allergy clinic (PAC). The purpose of this study was to illustrate the BLAA process, including the pharmacist-run PAC, and assess the impact on allergy clearance.

Methods: Clinical pharmacy specialists (CPS) evaluated hospitalized veterans with β -lactam allergies, using the BLAA protocol. Eligible patients could later be seen in PAC. This was a retrospective observational review of the BLAA protocol to assess recommendations for β -lactam antibiotic use and PAC outcomes.

Results: Between November 2017 and February 2020, 278 patients were evaluated, and 32 were seen in the clinic. The most common allergen was penicillin, and the most reported reaction was a rash (27%) or pruritus and urticaria (18%). Through PAC and the BLAA protocol, 86 patients (31%) were cleared for allergy removal, and 188 (68%) were cleared for alternative β -lactams. The evaluation revealed that 274 patients (99%) were eligible to receive a β -lactam antibiotic, and only 4 patients (1%) were recommended for avoidance of all β -lactams.

Conclusions: These findings highlight the utility of the pharmacist-driven BLAA protocol. We illustrated that most patients with documented β -lactam allergies were eligible for alternative β -lactams. The implementation of the BLAA protocol and pharmacist-run PAC facilitated allergy clearance and has the potential to promote alternative β -lactam use.

Author affiliations can be found at the end of the article.

Correspondence:

Anna Mitchell
(annabirg91@gmail.com)

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Allergies to β -lactam antibiotics are among the most documented drug allergies, and approximately 10% of the US population reports an allergy specifically to penicillin.^{1,2} Many allergic reactions are mediated via the antibody immunoglobulin E (IgE), producing an immediate hypersensitivity response, such as hives or anaphylaxis, which can be life threatening. Reactions also may be mediated by T cells of the immune system, which target various cell lines and can cause a drug reaction with eosinophilia and systemic symptoms or Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).³ Although β -lactam and penicillin allergies are frequently reported, < 5% manifest as either an IgE or T-cell-mediated response.⁴ Furthermore, for the small proportion of patients who once had a true IgE-mediated reaction, including anaphylaxis, 80% experience a decrease in IgE antibodies over time, resulting in a loss of allergic response after about 10 years.² Due to this decline in IgE response and the initial mislabeling of mild non-IgE penicillin reactions, 95% of patients who are labeled as penicillin-

allergic can eventually tolerate a penicillin.²

When a patient's β -lactam allergy is never reevaluated, negative consequences can ensue. This allergy in a patient's medical record can lead to the inappropriate avoidance of the entire β -lactam antibiotic class, which includes all penicillins, cephalosporins, and carbapenems. Withholding these antibiotics in certain situations can lead to negative patient outcomes.⁵⁻⁷ For example, the drugs of choice for the infections syphilis and methicillin-susceptible *Staphylococcus aureus* (*S aureus*) are a penicillin or cephalosporin, and patients labeled as penicillin-allergic are more likely to experience treatment failure from using second-line therapies.⁸ Additionally, receiving non- β -lactam antibiotics puts patients at risk of multidrug-resistant pathogens like methicillin-resistant *S aureus* and vancomycin-resistant *Enterococcus* (VRE) as well as adverse effects, such as *Clostridioides difficile* infection.⁹ Using alternative, and likely broad-spectrum, antibiotics also can be financially detrimental: These medications often are more costly than their β -lactam alternatives, and the inappropriate use of therapies can result in longer hospital courses.⁹⁻¹¹

TABLE 1 β -Lactam Allergy Classifications

Allergy Protocols	Classifications		
	Mild	Moderate	Severe
General reaction description ^a	Maculopapular rash, pruritus without rash Non-IgE-mediated reaction > 5 years ago	Urticaria, pruritic rash IgE-mediated reaction but not anaphylaxis	Anaphylaxis < 5 years ago Positive penicillin skin test < 5 years ago
Immediate recommendation	Alternative β -lactam	Consider alternative β -lactam	Avoid β -lactams (desensitization required)
Penicillin allergy clinic	Amoxicillin oral challenge	Skin test followed by oral challenge	Avoid; could consider skin testing once > 5 years since reaction

Abbreviation: IgE, immune-mediated immunoglobulin.

^aExcludes T-cell reactions (ie, Stevens-Johnson syndrome/toxic epidermal necrolysis; drug reaction with eosinophilia and systemic symptoms).

Penicillin allergies can complicate the antibiotic treatment strategy. The Memphis Veterans Affairs Medical Center (MVAMC) in Tennessee recently examined the negative sequelae of β -lactam allergies and found that more than half the patients received inappropriate antibiotics based on guideline recommendations, allergy history, and culture and sensitivity data.¹² To mitigate the problems for patients with β -lactam allergies, the 2016 guidelines from the Infectious Diseases Society of America (IDSA) on the Implementation of Antimicrobial Stewardship Programs (ASP) recommend that these patients undergo allergy assessment and penicillin skin testing.¹³ In November 2017, MVAMC implemented such a process. The purpose of this study was to describe our pharmacist-run β -lactam allergy assessment (BLAA) protocol and penicillin allergy clinic (PAC) and evaluate their overall outcomes: the proportion of patients who have been cleared to receive an alternative β -lactam antibiotic or who have had their allergy removed altogether.

METHODS

We conducted a retrospective, observational study with approval from the institutional review board at MVAMC. This institution is an academic teaching center with 240 acute care beds and a variety of outpatient clinics available at the main campus, serving veterans in Memphis and the Mid-South area, including west Tennessee, northern Mississippi, and northeastern Arkansas. Patients were consecutively evaluated from November 2017 through February 2020. All MVAMC patients with a documented β -lactam allergy

were eligible for inclusion; there were no exclusion criteria. Electronic health record data were assessed and included basic patient demographics, allergy history, and the outcome of the BLAA and PAC. Descriptive statistics were used for data analysis.

The purpose of the BLAA process is to evaluate, clarify, and potentially clear patients of their β -lactam allergies. Started in November 2017, the process includes appropriate patient screening with documentation of the β -lactam allergy. When patients with a β -lactam allergy are admitted to the hospital, they are interviewed by an inpatient CPS. This pharmacist then enters an assessment into the patient's chart, which includes details of the allergen, reaction, and timing of the event. Based on this information, the CPS provides recommendations: clearance for alternative β -lactams, avoidance of all β -lactams, or removal of the allergy.

In January 2019, the pharmacist-driven penicillin allergy clinic (PAC) was started. Eligible patients receive a skin test to confirm or rule out their allergy after hospital discharge. To facilitate patient identification and screening, the ASP/infectious diseases (ID) clinical pharmacist runs a daily report of hospitalized patients with documented β -lactam allergies. All inpatient CPSs had access to this report and could easily identify and interview patients. Following the interview, the pharmacist enters a note in the patient's chart, using the BLAA template (eFigures 1 and 2 available at doi:10.12788/fp.0172). On completion, a note is viewable in the Notes section adjacent to the patient's allergies. The pharmacist then can enter a PAC consult for eligible patients. Although most patients qualify for PAC,

exclusion criteria include non-IgE-mediated allergies (ie, SJS/TEN), allergies to β -lactams other than penicillins, or recent reactions (ie, within the past 5 years). Each inpatient CPS is trained on this BLAA process, which includes patient screening, chart review, patient interviewing, and the BLAA template and note completion. Pharmacists must demonstrate competency in completing 5 BLAA notes with review from the ASP/ID pharmacist. Once training is completed, this process is integrated into the pharmacist's everyday workflow.

On receipt of the PAC consult, the ASP/ID pharmacist reviews the patient chart to further assess for eligibility and to determine whether oral challenge alone or skin testing followed by the oral challenge is required based on patient risk stratification (Table 1).³ Relative contraindications to PAC include severe or unstable lung disease that requires home oxygen, frequent or recurrent heart

failure exacerbations, or patients with acute or unstable cardiopulmonary, neurologic, or mental health conditions. These scenarios are discussed case by case with the allergy/immunology (A/I) physician.

The ASP/ID pharmacist also reviews the patient's chart for medications that may blunt the histamine response during drug testing. The need to hold these medications before PAC also are individually assessed in conjunction with the A/I physician. The ASP/ID pharmacist and 3 other CPS involved in the creation of the BLAA and PAC have received formal hands-on training on penicillin allergy testing. The PAC process consists of a penicillin skin test, followed by the amoxicillin oral challenge.³ The ASP/ID clinical pharmacist who is trained in penicillin skin testing performs all duties in PAC, with oversight from the A/I attending physician as needed. Currently, the ASP/ID pharmacist runs the PAC once a week with the A/I physician

FIGURE β -Lactam Allergy Evaluations and Outcomes

Abbreviations: BLAA, β -lactam allergy assessment; PAC, penicillin allergy clinic

TABLE 2 Patient Demographics (N = 278)

Characteristics	Results
Age, mean (SD), y	67 (12)
Male, No. (%)	239 (86)
Race, No. (%)	
White	142 (51)
African American	127 (46)
Other	9 (3)

available if needed. Along with documenting an A/I clinic note detailing the events of PAC, the ASP/ID pharmacist also will add an addendum to the original BLAA note. If the allergy is removed through direct testing, it also can be removed from the patient's profile after discussion with the A/I physician. Therefore, the full details necessary to evaluate, clarify, and clear the patient of their β -lactam allergy are in one place.

RESULTS

We evaluated 278 patients, using the BLAA protocol. In this veteran population, patients were generally older males and evenly split between African American and White patients (Table 2). Most patients reported an allergy to penicillin, with a rash being the most common reaction (Table 3).

Of the 278 assessed, 246 patients were evaluated via our BLAA alone and were not seen in PAC. We were able to remove 25% of these patients' allergies by performing a thorough assessment. Of the 184 patients whose allergies could not be removed via the BLAA alone, 147 (80%) were still eligible for PAC but are awaiting scheduling. Patients ineligible for PAC included those with a cephalosporin allergy or a severe and non-IgE-mediated reaction. Other ineligible patients who were not eligible included those with diseases where risk of testing outweighed the benefits.

Of the 32 patients who were seen in PAC, 75% of allergies were removed through direct testing. No differences between race or gender were observed. Of the 8 patients (25%) whose allergies were not removed, 5 had confirmed penicillin allergies with a positive reaction; 4 of these pa-

TABLE 3 Patient Allergens and Reactions (N = 278)

Allergens	Patients, No. (%)
Types	
Penicillin	220 (79)
Cephalosporin	23 (9)
Aminopenicillin $\pm$ β lactamase	23 (9)
Piperacillin $\pm$ tazobactam	9 (3)
Penicillin + cephalosporin	4 (1)
Reactions	
Rash	74 (27)
Pruritus/urticaria	50 (18)
Anaphylaxis	48 (17)
Swelling	26 (9)
Nausea, vomiting, or diarrhea	12 (4)
Shortness of breath or dyspnea	5 (2)
SJS/TEN	4 (2)
Other	22 (8)
Unknown	37 (13)

Abbreviation: SJS/TEN, Stevens-Johnson syndrome toxic epidermal necrolysis.

tients have since tolerated an alternative β -lactam (either a cephalosporin or carbapenem). Three patients had inconclusive tests, most often because their positive control was nonreactive during the percutaneous portion of the skin test; these allergies could neither be confirmed nor removed. Two of these patients have since tolerated alternative β -lactams (both cephalosporins). Although these 8 patients should not be rechallenged with a penicillin antibiotic, they could still be considered for alternative β -lactams, based on the nature and histories of their allergies.

In total, we removed 86 allergies (31% of our patient population) using both BLAA and PAC (Figure). These patients were cleared for all β -lactams. One hundred eighty-eight patients (68%) were cleared to receive an alternative β -lactam based on the nature or history of the allergic reaction. β -lactam avoidance was recommended for only 4 patients (1%), as they had no exposure to any β -lactams, and they had a recent or severe reaction: 2 patients with anaphylaxis in the past 5 years, 1 with SJS/TEN, and 1 with recent convulsions after receiving cefepime. Combining patients whose penicillin allergies were removed with those who had been cleared for alternative β -lactam antibiotics, 99% of patients were cleared for a β -lactam antibiotic.

DISCUSSION

We have implemented a unique and efficient way to evaluate, clarify, and clear β -lactam allergies. Our BLAA protocol allows for a smooth process by distributing the workload of evaluating and clarifying patients' allergies over many inpatient CPS. Furthermore, the BLAA is readily accessible to health care providers (HCPs), allowing for optimal clinical decision making. HCPs can quickly gather further information on the β -lactam allergy, while seeing actionable recommendations, along with documentation of the PAC visit and subsequent events, if the patient has been seen.

This study demonstrated the promotion of alternative β -lactam use for nearly all patients: 99% of our patient population were deemed candidates for a β -lactam type antibiotic. This percentage included patients whose allergies have been fully cleared, both through BLAA alone and in PAC. Also included are patients who have been cleared for an alternative β -lactam and not necessarily a penicillin.

In our PAC, 8 patients were not cleared for penicillins: 5 had penicillin allergies confirmed, and 3 had inconclusive results. Based on the nature of their reactions and previous tolerance of alternative β -lactams, those 5 patients are still eligible for alternative β -lactams. Additionally, the 3 patients with inconclusive results are also eligible for alternative β -lactams for the same reasons. The patients for whom β -lactam antibiotic avoidance was recommended (4 patients, 1%) have not been seen in PAC, as their reactions disqualify them from penicillin skin testing. Two of these patients had anaphylaxis < 5 years ago and will be eligible for PAC if they do not experience anaphylaxis within the 5-year period.

Accounting for those patients who have not been seen in PAC, our results are in concordance with previous studies, which demonstrated that implementation of a similar BLAA process results in clearance of $\geq 90\%$ of penicillin allergies.¹³⁻¹⁷ Other studies have evaluated inpatient implementation of penicillin skin testing or oral challenges; in this study, however, BLAAs were completed while the patient was hospitalized, and patients were seen in PAC after discharge. Completing BLAA during hospitalization not only

allows for faster assessment and facilitates decision making regarding most patients' antibiotic regimens, but also provides a tool that can be used by many pharmacists and HCPs. The addition of our PAC to the BLAA protocol further strengthens the impact on clearance of patients' penicillin allergies.

Limitations

Although our study demonstrates many benefits of implementation of a BLAA protocol and PAC, it has several limitations. This analysis was a retrospective review of the limited number of patients who had assessments completed. Additionally, many patients were waiting to be seen in PAC. This delay is largely due to the length of time to establish our pharmacist-run PAC, the limited number of pharmacists trained and available for skin testing, the time constraints of our staff, and COVID-19 pandemic. Additionally, only pharmacists administer the BLAA questionnaire, but this process could be expanded to other professionals such as nursing staff. Also, this study was not set up as a before-and-after analysis that examined outcomes associated with individual patients. Future directions include assessing the clinical impact of this protocol, such as evaluating provider utilization of β -lactam antibiotics for patients with penicillin allergies and determining associated cost savings.

CONCLUSIONS

This study demonstrated that implementation of a pharmacist-driven BLAA protocol and PAC can effectively remove inaccurate penicillin allergy labels and clear patients for alternative β -lactam antibiotic use. The BLAA process in conjunction with PAC will continue to be used to better evaluate, clarify, and clear patient allergies to optimize their care.

Author affiliations

Anna Mitchell, Jessica Bennett, Jarred Bowden, and Amanda Gillion are all Clinical Pharmacy Specialists in the Department of Pharmacy; and **Debendra Pattanaik** is a Physician in the Department of Allergy/Immunology, all at the Memphis Veterans Affairs Medical Center in Tennessee. **Rachel Ness** is a Clinical Pharmacy Specialist in the Department of Pharmacy at the New Mexico Veterans Affairs Health System in Albuquerque, New Mexico. **Whitney Elliott** is an Inpatient Pharmacy Supervisor in the Department of Pharmacy at the James H. Quillen Veterans Affairs Medical Center in Mountain Home, Tennessee. Debendra Pattanaik is in the Department of Rheumatology at the University of Tennessee Health Science Center in Memphis.

Author disclosures

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eFIGURE 1 β -Lactam Allergy Assessment Evaluation and Questionnaire

What medication are you allergic to?

How long ago did the reaction occur?

Describe the reaction.

Did you have nausea, vomiting, or diarrhea?

Did you get a rash? If yes, describe. Itchy, bumpy, hives? Did your skin peel off (ie, SJS)?

Did you have trouble breathing or feel like your throat was closing?

Did you go to the hospital or have medical treatment for the reaction?

Have you taken any of these medications before?

[Amoxicillin/Augmentin, Cephalexin (Keflex), Ceftriaxone (Rocephin), Cefazolin (Ancef), Cefuroxime (Ceftin), Cefpodoxime (Vantin), Cefdinir (Omnicef), Cefixime (Suprax)]

If deemed appropriate, would you be interested in clearing your allergy in our clinic?

eFIGURE 2

Reminder Dialog Template: BETA LACTAM ALLERGY ASSESSMENT

☒ ALLERGY

Patient with a documented allergy to Beta Lactam Antibiotics

Allergy Details: *

☐ Exposed to and tolerated antibiotic in same class as documented allergy

Antibiotics tolerated and Dates: *

☐ Exposed to and tolerated beta lactam antibiotic in different class from allergy

☐ Severe non-IgE mediated Reaction

☒ Reaction occurred greater than 5 years ago

Recommendations:

☐ Will place routine Beta Lactam Allergy consult for evaluation of outpatient skin testing.

☐ Patient in urgent need of beta lactam antibiotic. Place stat Allergy and Immunology consult for inpatient skin testing or desensitization as needed. Must also page Allergy & Immunology.

☐ Recommend the use of cephalosporins or carbapenem antibiotics if clinically appropriate. Available literature suggests that the risk of an allergic reaction to cephalosporins or carbapenems in a penicillin allergic patient is < 1.5%.

☐ Reaction occurred less than 5 years ago

☐ ADVERSE REACTION:

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