Background and Rationale

Approximately 10% of patients report allergies to penicillin (1-3). When these patients require antibiotics, they often receive less effective, more toxic, more broad-spectrum, and more expensive agents than patients without reported penicillin allergies (3). For example, alternative agents to beta-lactam antibiotics include vancomycin and aminoglycosides, which require therapeutic drug monitoring and carry risks of nephrotoxicity and ototoxicity. Clinicians may also prescribe alternative agents such as aztreonam, which is expensive and has less proven clinical efficacy for most types of infections, or fluoroquinolones, which are broad-spectrum and notorious for inciting *C. difficile* infection. Penicillin allergy labels have been associated with increased length of hospital stay, hospitalization costs, antibiotic resistance (e.g., MRSA, *C. difficile*, and VRE infections), and even mortality (2,4). Thus, allergy labeling is a focus area for antimicrobial stewardship programs (ASPs) to prevent resistant infections and improve patient safety.

This newsletter discusses strategies that ASPs can use to maximize both appropriateness of antibiotic therapy and safety for hospitalized patients with reported beta-lactam allergies. Many ASPs start with a focus on detailed allergy history, education, and improved allergy documentation as a means to “de-label” patients who are not truly beta-lactam allergic AND improve the recognition of patients at risk for severe reactions. More advanced ASPs may then move to penicillin skin testing and/or pathways to formal allergy consultation as a way to improve the care for these patients.

Allergy History and Documentation

Most patients that carry the label of a penicillin allergy have negative penicillin skin tests and tolerate oral or intravenous beta-lactam antibiotics without any allergic side effects (1). However, a few patients with reported penicillin allergies are at high risk for severe reactions. Severe, or type I, IgE-mediated allergic reactions include symptoms such as hives, facial swelling, and shortness of breath. These
serious adverse drug events are typically tracked and reported in most hospitals by the Medication Safety or Pharmacy and Therapeutics Committee.

Documenting a careful history of any perceived medication allergies is a crucial first step to treating any patient with antibiotics (2). Unfortunately, medical record documentation is generally not reliable. For example, the medical record may indicate an allergy without characterizing the type of reaction, or, in some cases, the documentation may simply be inaccurate. A patient might report “allergy” to penicillin because of prior gastrointestinal intolerance or even a family history of penicillin allergy. Many busy clinicians do not take the time to take a detailed allergy history or document it clearly. Then, when faced with a decision about prescribing antibiotics, clinicians may review only the medical record without confirming history with the patient. This practice often results in selection of alternative, high risk, antibiotics.

To combat this problem, some ASPs have initiated an ASP-, nurse-, or pharmacy-led allergy assessment protocol to improve the quality of allergy history-taking and documentation. For example, a clinical staff member interviews the patient or family by using a short, pre-made algorithm of questions to determine if a true penicillin allergy exists. If no allergy is present, the patient is “de-labeled,” i.e., the listed allergy is removed from the medical record so that incorrect documentation does not negatively affect antibiotic selection in the future. Likewise, if the interviewer verifies the details of an IgE-mediated penicillin allergy, he or she clearly documents this information in the medical record.

In some scenarios, clinicians can safely give beta-lactam antibiotics such as cephalosporins and carbapenems to hospitalized patients even after confirming a history suggestive of a possible IgE-mediated reaction. If the patient or family can definitively state that the patient has tolerated antibiotic therapy with a cephalosporin or carbapenem in the past, or such tolerance is documented in the medical record, then the patient can receive cephalosporins or carbapenems. There is some association between IgE-mediated allergic reaction to penicillin and related allergy to cephalosporins or carbapenems; however, the risk of cross-reactivity is less than 10% (5). Furthermore, if the prior reaction to penicillin was mild to moderate, such as a delayed-onset rash or pruritis, the clinician can safely challenge with a cephalosporin or carbapenem. If a patient with a documented penicillin allergy tolerates therapy with an alternative beta-lactam agent, the lack of reaction must be documented in the medical record to de-label the patient or clarify the reported allergy.

**Penicillin Skin Testing**

Several studies have demonstrated that a penicillin skin test (PST) is an effective tool to determine the safety of beta-lactam therapy for a patient with a reported penicillin allergy (5). PSTs typically involve two steps: a skin prick test, and then if no reaction is noted, an intradermal test. PSTs performed in this sequence utilizing major and minor determinants of penicillin have negative predictive values of 97-100%: patients with negative PSTs have no higher risk of experiencing an allergic reaction to a beta-lactam antibiotic than a member of the general population. Nonetheless, if concern for possible hypersensitivity reaction persists despite a negative PST, a clinician can provide an oral penicillin
challenge before initiating planned beta-lactam antibiotic therapy (1). After a patient receives penicillin or another beta-lactam antibiotic without an adverse reaction, tolerance of the antibiotic is documented and the conflicting allergy label is removed.

PSTs used for antimicrobial stewardship purposes have been successful in a variety of patient care settings, including the medical wards, intensive care units, and outpatient clinics (1,5). One example study included hospitalized patients with a history of penicillin allergy who were receiving antibiotics other than beta-lactams (6). PSTs were negative for 89% of patients, and 82% changed antibiotics to a regimen containing a beta-lactam. Significant reductions occurred in the use of vancomycin, fluoroquinolones, and clindamycin. PST protocols are feasible in the inpatient setting even for antimicrobial stewardship programs (ASPs) with limited resources. PSTs are simple to perform, and a staff member can interpret the results soon after administering the test (3). In addition to clinicians and stewardship pharmacists, non-specialized pharmacists and other healthcare workers can take patient allergy histories and administer PSTs.

Most studies of PST in the inpatient setting have been small-scale, single-center experiences that examined effects on antibiotic utilization, serious adverse events, and cost. Cost effectiveness varied by study but is not definitively known. There is only one FDA-approved PST (PRE-PEN (TM), ALK), and cost is approximately $130 per patient. Further, PST protocols must have exclusion criteria for some situations where PST may have less sensitivity (e.g., when the patient is receiving anti-histamines or steroids). PSTs should ONLY be used for patients whose prior reaction is consistent with an IgE-mediated allergy (1). Patients with non-IgE mediated reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or serum sickness, are at risk for severe reactions to beta-lactam therapy despite negative PSTs.

Allergy Consultation

Beta-lactam antibiotics are the best treatment options for certain infections, even for patients with severe allergic reactions to beta-lactam antibiotics or positive PSTs. In these situations, clinicians can request allergy consultation to perform desensitization protocols. Desensitization requires significant time, labor, and training, including high-level pharmacy and nursing care (1). Desensitization protocols help ensure that patients receive first-line antibiotic therapy in select situations but do NOT take the place of PSTs in patients with documented penicillin allergy. Desensitization also does not de-label a patient from being penicillin-allergic. If the patient needs the same antibiotic in the future, desensitization must be repeated because drug tolerance is temporary.

Patients labeled as penicillin allergic can also benefit from outpatient referral to an allergist. Skin testing is not always possible during hospitalization due to short duration of hospitalization or lack of an institutional skin-testing protocol. A recent study demonstrated that pharmacist-facilitated referral to allergists increased beta-lactam prescriptions in patients with penicillin allergies. Of the patients referred, 94% had negative PSTs, and 66% were subsequently prescribed a beta-lactam, compared to 26% of patients who were not referred (7).
Conclusion

Patients with penicillin allergy labels are at risk for suboptimal treatment with antibiotics, poorer clinical outcomes, drug-resistant infections, and adverse drug events. ASPs can improve care of these patients with strategies such as allergy assessment and documentation protocols, penicillin skin testing, and/or allergy consultation. DASON can work with your ASP to determine the best strategy and implementation plan for your facility. Implementation of these specific initiatives requires some personnel investment and may require additional resources; however, these practices are associated with important benefits of antibiotic stewardship, including prescription of safer, less expensive, and more effective antibiotics. Thus, beta-lactam allergy de-labeling remains an important target for successful ASPs.

References