

A practical guide for pharmacists to successfully implement penicillin allergy skin testing

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Purpose. The purpose of this article is to offer practical guidance for pharmacists to successfully implement penicillin allergy skin testing (PAST).

Summary. Less than 10% of patients labeled as having a penicillin allergy are confirmed as present upon skin testing. This labeling results in use of alternative antibiotics and thus unwanted adverse consequences including potentiated antimicrobial resistance, increased costs, and worse clinical outcomes. Stewardship guidelines recommend PAST to enhance use of first-line agents; however, this was a weak recommendation with low-quality evidence. Recent efforts and subsequent research since publication of guidelines have demonstrated beneficial effects from increasing use of PAST among stewardship programs to improve outcomes. A number of different models exist demonstrating successful implementation of PAST at various healthcare facilities. There are important logistical factors to consider during implementation of PAST such as target population, optimal preparation, leadership structure, resource availability, and state regulations. Pharmacists as leaders of antimicrobial stewardship teams and experts in drug allergies are a natural fit to help implement PAST in healthcare settings to improve overall outcomes. This article offers guidance to institutions considering implementation of PAST.

Conclusion. PAST is rapidly becoming an effective, long-term antimicrobial stewardship tool to optimize antimicrobial prescribing in both the inpatient and outpatient settings. Pharmacists have demonstrated significant benefit as providers of PAST services in a variety of healthcare settings with a number of different healthcare professionals.

Keywords: allergy, antimicrobial stewardship, penicillin, pharmacist, skin testing

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A penicillin allergy label is expected in the medical record of approximately 30 million patients in the United States alone.^{1,2} However, the true allergy rate is far lower, as less than 10% of penicillin “allergic” patients test positive when undergoing allergy skin testing.³ Labeling of penicillin allergy varies quite substantially among institutions and healthcare settings.^{2,4} The unintended consequences of a penicillin allergy label are well documented. Hospitalized patients with documentation of a penicillin allergy are more likely to receive second-line or broad-spectrum

antimicrobial therapy that is often more costly, more toxic, and results in worse clinical outcomes and increased bacterial resistance.^{1,5,6,7} Outpatients with a penicillin allergy are also likely to receive more antibiotics and use more healthcare resources, compared to those without a documented allergy.⁸

Inappropriate or suboptimal antibiotic prescribing in patients with a penicillin allergy is a target initiative for antimicrobial stewardship programs (ASPs).^{5,9} Allergy reconciliation and education of providers on risks of antibiotic cross-reactivity are possible

interventions to curb inappropriate prescribing. However, in some cases, the need for alternative intervention may be indicated, including penicillin allergy skin testing (PAST). The use of PAST has been described for over 50 years, primarily in specialized allergy clinics for outpatient assessment of targeted patients.¹⁰ Recently published antimicrobial stewardship guidelines from the Infectious Diseases Society of America (IDSA) recommend PAST in select patients for improved prescribing.⁹ Several studies have demonstrated the utility of PAST as an ASP tool to optimize antimicrobial selection, minimize unnecessary antibiotic exposure, and improve patient outcomes.^{11–13}

PAST has been implemented with success using varied processes and personnel, including allergists, nurses, infectious diseases (ID) fellows, and pharmacists, in both inpatient and outpatient settings.^{12–14} Questions remain about the appropriate placement of PAST in a management algorithm among patients with a documented penicillin allergy requiring antibiotics. This article provides guidance to institutions considering PAST implementation and offers criteria for appropriate use at the patient level. Institutional examples below will also discuss resource considerations, legal restrictions, and program sustainability concerns. A full description of the allergy testing process is described elsewhere.¹²

Questions to consider prior to initiating PAST

Question 1. Why is PAST worth the effort? There are many clinical indications where β -lactam therapy is clinically superior or preferred. Some examples include surgical prophylaxis, infections due to methicillin-susceptible *Staphylococcus aureus* (MSSA), severe infectious due to *Pseudomonas aeruginosa*, *Helicobacter pylori* infections, and several sexually transmitted infections, most notably syphilis.¹⁵ When preferred β -lactams cannot be used, treatment options are often limited to broader spectrum or second-line antimicrobials such as carbapenems, vancomycin, fluoroquinolones, or aztreonam.^{7,8} This increased

KEY POINTS

- Data documenting effectiveness of penicillin allergy skin testing (PAST) on clinical outcomes as an antimicrobial stewardship tool continues to surface in the literature.
- Assessment of many logistical factors is required in order to efficiently implement PAST within an individual patient care setting.
- Pharmacists are well suited to be integrally involved in the planning and implementation of PAST due to their training in drug allergy management, availability within health systems including rural areas, and established leadership in directing antimicrobial stewardship initiatives.

use of broad-spectrum antimicrobials contributes to increasing antimicrobial resistance, costs, and toxicity.

The longitudinal financial implications of being labeled with a penicillin allergy have been well-demonstrated with noted increases in hospital length of stay and increased prevalence of *Clostridium difficile*, methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistance *Enterococcus* (VRE) infections.¹⁶ Removing the allergy via PAST can benefit the patient for the acute episode and also for potential subsequent infections. In addition to benefiting patients on an individual level, reduced use of broad-spectrum antimicrobials helps patients on a societal level due to its implications in reducing the growth of antimicrobial resistance.

Question 2. Who should be tested? Detailed screening evaluation of any patient with a listed allergy to penicillin is a valuable antimicrobial stewardship initiative, regardless of institutional availability of PAST. An in-depth patient interview to ascertain their

allergy history should be undertaken, understanding that most self-reported penicillin allergies are inaccurate, even if documented in the medical record. Information such as type of reaction, timing of reaction, any history of rechallenge, and specific names of β -lactam agents received should be attempted during the interview. Additionally, emerging data suggests that oral amoxicillin challenge in low risk patients with nonimmediate reactions to penicillins may be a safe and effective modality to exclude allergy.¹⁷ Further research is required to best delineate patients who would benefit from this strategy. The key point is that PAST is an important component of an overall antibiotic allergy assessment program after good initial screening. Comprehensive screening can eliminate the need for PAST in a number of patients due to demonstration of inappropriate labeling. Consultation should be for a penicillin allergy evaluation, not specifically for PAST.

PAST is indicated for patients with documented or suspected clinical penicillin hypersensitivity. However, many patients report an “unknown” reaction to penicillin and thus may require PAST to rule out severe hypersensitivity. Most patients “lose” the allergy over time with only about 20% of patients retaining the allergy 10 years after the initial reaction, including patients reporting anaphylaxis.¹⁸

When PAST programs are initiated, determination by the individual facility should be made on the targeted population for testing. While many patients will have documented penicillin allergies, testing of all individuals is not feasible for most facilities. Specific criteria, for example, could include patients who are actively receiving non- β -lactam antibiotics, receiving higher cost agents, or receiving known inferior therapy. It could also be restricted to specific services or wards such as those patients alerted to ASP, infectious diseases consult service, or patients scheduled for surgery.

Several problems exist when identifying a drug allergy. First, defining the difference between an adverse drug

reaction and a true allergy can be confusing, especially for a patient. Another issue in identifying drug allergies is assigning causality. Many times, patients receive multiple drugs simultaneously, particularly in the hospital setting. If a patient were to develop hives after initiating therapy, antimicrobials are often an easy option to point blame. Often patients are not re-challenged on suspected medications and then carry the suspected allergy indefinitely regardless of when the initial allergy occurred.

Along the same lines of identifying the culprit in a suspected drug allergy is the lack of reliable diagnostic procedures and in vitro assays to detect true allergy. In vitro assays carry a high specificity, but a low sensitivity specific to penicillin. This means a negative in vitro test will not adequately exclude a penicillin allergy. Using an immediate hypersensitivity skin test to detect IgE-mediated penicillin allergies is the preferred method.³

While it is simple to perform a detailed medication history, we frequently encounter penicillin “allergic” patients who have received penicillin-based antibiotics after documentation of their “allergy.” This would eliminate the need for PAST for that particular patient. This was demonstrated recently with aztreonam when investigators

showed that often the subject’s penicillin allergy was erroneous, thus leading to discontinuation of aztreonam therapy.¹⁹ Furthermore, allergy records are often not updated to reflect uneventful administration of penicillin in patients with previously documented allergies.²⁰

Any patient with a history of desquamating cutaneous reactions such as drug rash with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), and Stevens-Johnson Syndrome (SJS) would not be a candidate for PAST. Also, any patient who reports a history suggestive of hepatitis, interstitial nephritis, idiopathic thrombocytopenic purpura, serum sickness, or hemolytic anemia (i.e., non-immunoglobulin E [IgE-mediated] hypersensitivities) would be ineligible. A summary of contraindications to PAST can be found in Table 1. Each institution’s criteria for exclusion of patients will likely vary based on local clinical expertise and experience of practitioners providing PAST as well as other local factors. Some potential other exclusion criteria include:

1. History of anaphylaxis to β -lactam agents within the last 5–10 years.
2. Skin condition that could interfere with accurate reading of PAST result.

3. Resources unavailable to treat anaphylaxis if it occurs.
4. Patients who are immunocompromised (e.g., patients with HIV/AIDS with absolute CD4 count less than or equal to 200 cells/mm³, neutropenia [absolute neutrophil count (ANC) < 500 cells/mm³], receiving immunosuppressant medications other than corticosteroids).

If a decision is made to skin test, patients should be assessed for any concomitant medications which may affect the results, such as antihistamines. Because histamine serves as the positive control in the initial step of the skin test, receipt of medications with antihistamine properties (e.g., corticosteroids, histamine-2 receptor antagonists, antiemetics [phenothiazines]) may increase the risk of a negative histamine result. We recommend holding histamine-1 receptor antagonists for ideally 48–72 hours prior to PAST (less time may be necessary for short-acting antihistamines, such as diphenhydramine) with consideration for holding other medications with antihistamine activity to minimize potential for false histamine-negative controls during testing.

Question 3. What are potential pitfalls after a negative penicillin

Table 1. Gell-Coombs Drug Allergy Classifications with Examples^a

Gell-Coombs Classification	Immune Cause	Typical Manifestations	Examples of Associated Agents
Type I (Immediate) ^b	IgE	Anaphylaxis, laryngeal edema, urticaria, hives	β -lactams
Type II (Cytotoxic)	IgG, IgM	Cytopenia	Penicillin, heparin, quinidine
Type III (Immune Complex)	IgG, IgM	Serum sickness	Thymoglobulin, penicillin, phenytoin
Type IV (Delayed)	T-Lymphocytes	Contact dermatitis	Latex, sulfa, penicillin
SJS and TEN (miscellaneous)	T Cells	Erythema with necrosis and detachment	Sulfonamides, cephalosporins, anticonvulsants, NSAIDs
DRESS syndrome (miscellaneous)	Eosinophils	Cutaneous eruptions, multi-organ failure	Anticonvulsants, sulfonamides

^aSolensky R, Khan DA, Bernstein IL et al. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol.* 2010; 105:273e1–78. SJS = Stevens-Johnson Syndrome; TEN = toxic epidermal necrolysis; NSAID = nonsteroidal anti-inflammatory drug; DRESS = drug rash with eosinophilia and systemic symptoms.

^bCandidate for penicillin allergy skin testing.

skin test? Patients are often relieved to learn their PAST result is negative. However, in order for their penicillin allergy to be successfully removed from the medical record, a process known as “de-labeling,” certain tasks should be performed to prevent the patient from mistakenly being “re-labeled” as penicillin allergic in the future.

First, the medical record at the testing institution should immediately document the lack of penicillin allergy. Staff at each institution should determine which documentation method is best for their facility, potentially consulting risk management for further advice. Some centers may require informed consent while others use PAST as part of standard care. One option includes removing the penicillin allergy completely with a note documenting the negative PAST result with or without details of penicillin-based antibiotic administered. An example of how this is documented in the electronic health record (EHR) is given in Figures 1 and 2. A second option would be to enter a “place holder” in the record with details of the negative PAST. The ultimate goal is to document the PAST appropriately to prevent relabeling the patient as penicillin allergic. Some EHRs have the potential to provide

notification that the patient has received PAST and had a negative result when there is an attempt to relabel the penicillin allergy (Figure 3).

Second, the patient and family members should be educated that any providers and pharmacies involved in prescribing and dispensing antibiotics to the patient should be informed of their negative PAST result. Any primary care providers, specialists, and dentists should also be informed. Incorporating a notification process in which the patient's various providers and pharmacy are contacted directly by a PAST staff member regarding the patient's test helps to ensure the results are appropriately received by all necessary parties. Giving the patient a pocket card with the details of the PAST result is another way to promote dissemination.

Third, patients will often present to different healthcare facilities where allergy records may differ. Again, the patient will have to educate their providers of the negative PAST result. Developing a citywide databank for all negative PAST patients to be shared with the antimicrobial stewardship pharmacists and physicians to prevent “re-labeling” is a potential solution, although patient privacy concerns will

need to be addressed before this can be implemented.

Fourth, some patients may still be skeptical of the negative skin test results. Administering the oral challenge of amoxicillin (250 mg × 1 dose) may help place their minds at ease. Alternatively, administering the penicillin agent in the hospital (i.e., piperacillin-tazobactam) after the negative skin test where the patient is being monitored closely is an appropriate option.

Lastly, in rare circumstances, patients may experience a delayed reaction to penicillin which could be different from the initial reaction reported by the patient. Therefore, patients should be counseled on this potential reaction and seek medical attention if it occurs.

Question 4. How will the components of PAST be prepared and stored? *PAST Kit Preparation.*

Developing a process for preparing and storing PAST supplies is essential to providing an effective PAST service in any setting. The materials required to perform a PAST are located in Table 2. They are classified as PAST reagents, medications for acute reactions, and miscellaneous supplies.

If conducted in a facility with a sterile compounding laboratory, the PAST

Figure 1. Example of penicillin allergy test in electronic health record. PHASST= Palmetto Health Antimicrobial Stewardship and Support Team.

TEST, TEST (MRN: A00000017) - Add Allergy/Adverse Effect

Type: Allergy This is the explanation for Allergy.

*Substance: ve PCN Allergy Skin Test ☒ Free text No Allergy checking is available for free text substances.

Reaction(s): Add Free Text

*Severity: <not entered> Info source: <not entered> Comments:

At: <not entered> Onset: <not entered>

Recorded on behalf of: *Category: Drug Allergy Status: Active Reason:

Comments: Patient had a negative penicillin allergy skin test on 9/25/2017. Allergy profile updated. Please refer to PHASST note for further details or page 352-1322 for questions.

OK Cancel

Figure 2. Example of penicillin allergy skin test documentation in electronic health record.

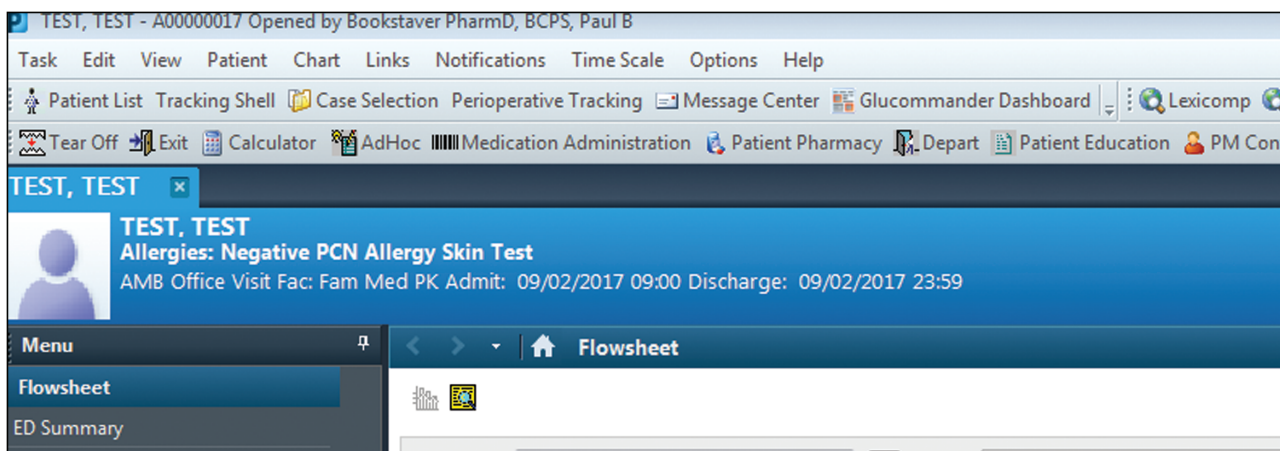
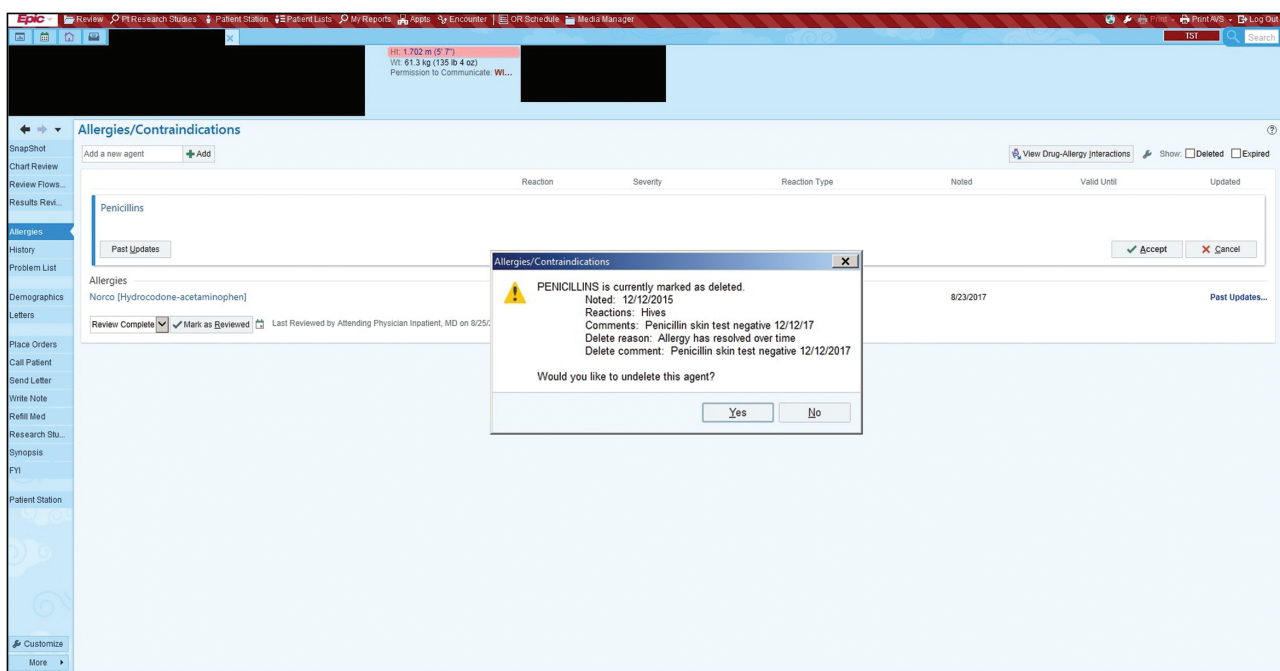


Figure 3. Example alert notification of attempt to relabel penicillin allergy after penicillin allergy skin testing completed.



reagents can be prepared by a pharmacy technician or pharmacist in a sterile environment and dispensed to whom-ever is designated to perform the PAST. If a sterile compounding laboratory is not available, the PAST reagents can be prepared in the patient room, or in another designated location, using aseptic technique. Once prepared, it is imperative the syringes are labeled properly to minimize the risk of confusing one reagent from another during the testing

process. Depending on the institution's policy, the PAST reagents typically have a 24-hour expiration date at room temperature once compounded. Table 3 contains an example of PAST reagent compounding and batching instructions with expiration dating. ASP staff at each institution should decide which best fits their practice site.

The medications for acute reaction can be compiled in a kit with the necessary syringes and needles to administer

the medications. Alternatively, these medications can be stored in an automated dispensing cabinet, or in a crash cart located near the patient room. A protocol for administering these medications has been previously described.¹²

Question 5. Who will take ownership of the program? When initiating PAST at an institution, there are many tasks that need to be completed prior to the skin testing. Healthcare systems differ in the number of committees

Table 2. PAST Kit Contents

Category	Agents
PAST reagents ^a	• Benzylpenicilloyl polylysine 6 × 10⁻⁵ mEq (0.25 mL) ampule • Penicillin G 10,000 IU/mL • 0.9% sodium chloride injection, preservative-free • Histamine base 1 mg/mL (5 mL)
Medications for acute reactions	• Diphenhydramine 25 mg i.v./oral • Methylprednisolone 125 mg i.v. • Epinephrine (1:1,000) 0.5mg/0.5 mL
Miscellaneous supplies	• Epicutaneous allergy skin testing devices (i.e., 22–28-gauge needle or puncture stick) • Skin test ruler • Timer • Gauze • Alcohol swabs • Skin marker

^aPAST = penicillin allergy skin test. See Table 3 for compounding details.

required (e.g., medication executive committee, formulary subcommittee) for review and approval prior to formulary addition. Because this is more of a process than a pure drug formulary decision, more stakeholders are likely to be involved in the decision. Adding the penicillin skin testing reagents to formulary, developing system protocols to guide the process, developing orders sets with all components required, and ensuring all laws are followed is much easier to accomplish with a single person tasked with leading the duty. As questions come up with testing and new information becomes available, there should be an identified expert at the institution.

Question 6. Who needs to be trained? There are many different models for staffing PAST, which are discussed in detail below. It is important to decide who will be performing the PAST on patients prior to developing a protocol at your institution, as the identification of patients and steps of the process are dependent on this decision. Initial free on-site training from the manufacturer of benzylpenicilloyl polylysine skin test antigen (Pre-Pen, AllerQuest, Plainville, CT) is available for centers ready to begin PAST in order to train multiple personnel at one time.

Question 7. What approach is best for structuring the testing process? This is probably the most

common question the authors receive from pharmacists attempting to begin PAST at their facilities. There are a number of successful models for PAST that have been published.^{12,13} Pharmacists, physicians, ID fellows, nurses, allergists, or a mix of any of the above have demonstrated successful programs. Most published literature represents an inpatient model, but PAST also has value as an outpatient practice, such as in pre-operative evaluation for surgical prophylaxis. State laws vary across the country, which may make certain models more feasible than others. Each facility should perform an “inventory” of resources available for the PAST process and decide which model works best for them. This is generally the rate limiting step in the process.

The remainder of this article discusses the healthcare professionals who may be involved in various PAST models, including the advantages and disadvantages of the models to help guide decision making, as well as considerations for providing outpatient PAST and adhering to state regulations.

Staff involved in PAST models

Pharmacists. One of the biggest challenges in implementing a PAST program remains securing sufficient personnel to operate the service. Board-certified allergists are the traditional providers who assess the need for,

perform, and interpret PAST for individual patients. Yet given the shortage of practicing allergists in many inpatient healthcare institutions, some centers have implemented pharmacist-led PAST services. Studies have demonstrated the success of having a pharmacist who has completed appropriate training to assess, perform, interpret, and counsel regarding PAST.^{21,22}

Pharmacists are well-positioned to offer PAST services given their existing duties as part of the healthcare team and expertise and training with drug allergy issues. Identification of patients with penicillin allergy who are eligible for a PAST consultation can be performed by a pharmacist at the point of order or prescription verification.²³ Some centers have even implemented specific criteria for pharmacists to review, such as ordering of aztreonam or other high-cost alternative agents, to help prioritize PAST consultations.^{24,25} Pharmacists are also trained to conduct patient allergy and medication histories, ensuring accuracy of an initial assessment for PAST as many patients will not require testing once a thorough history is performed. In previous reports, 2–12% of patients evaluated by a pharmacist had a penicillin allergy ruled out after the initial patient interview without further need for PAST. The absence of allergy was typically determined by confirming prior tolerance to penicillin via patient report and pharmacy records.^{21,22} Another essential component of PAST consultation is patient and provider education regarding the results and implications of PAST, especially when recommending de-labeling of a penicillin allergy. Pharmacists routinely counsel patients on adverse drug reactions and communicate with outside partners to update allergy histories. Pharmacists are also skilled in optimizing antimicrobial use and can make patient-specific recommendations (e.g., antimicrobial de-escalation, dosing, monitoring, drug interaction management) to the primary provider(s) after PAST results are available.

Select pharmacists frequently serve as core members of institutional ASPs. The goals of ASPs are inherently aligned

Table 3. Sample Instructions for Compounding, Batching, and Expiration Dating for PAST Reagents^a

PAST Reagent	Example Compounding and Batching Instructions	Expiration Dating ^b
1. Benzylpenicilloyl polylysine 6×10 ⁻⁵ mEq/0.25 mL (Pre-Pen)	- Break 1 ampule and draw up the entire contents (approximately 0.2 mL) into a 1-mL syringe using a filter needle. - Remove filter needle from the leur-lock syringe and discard. - Insert a 1-mL leur-lock syringe with needle attached into the 1 mL leur-lock syringe with filtered benzylpenicilloyl polylysine and draw up 0.05 mL. Remove needle and place a cap on the end of the syringe (Label “scratch test”). - Insert an intradermal syringe into the 1-mL leur-lock syringe and transfer the remaining filtered contents into the intradermal syringe (Label “intra-dermal test”). NOTE: The final product volume should be approximately 0.2 mL of benzylpenicilloyl polylysine in an intradermal syringe. DO NOT break more than 1 ampule of benzylpenicilloyl polylysine, even if the final volume is < 0.2 mL.	Refrigerated: Ampule: Date on Ampule Syringe: 24 hours Room Temperature: 24 hours (both)
2. Penicillin G 10,000 units/mL	- Start with a 5,000,000-unit vial (as powder for injection) and dilute down to 1,000,000 units/mL - Place 1 mL (1,000,000 units) into a 10-mL empty vial - Add 9 mL of 0.9% sodium chloride, preservative free, to create a concentration of 100,000 units/mL (Label Solution A) - Remove 3 mL of Solution A and place in an empty 30-mL vial. - Add 27 mL of 0.9% sodium chloride, preservative free, to the 30-mL vial to create a concentration of 10,000 units/mL (Label Solution B). - Remove 0.5 mL of Solution B and place in an empty 5-mL vial - Repeat the above process up to 60 times. - Freeze penicillin G 10,000 units/mL vials until ready to perform PAST. - When ready to perform the PAST, unthaw vial and draw up 0.05 mL into a leur-lock syringe without a needle attached (Label “scratch test”), and draw up 0.2 mL into an intradermal syringe (Label “intra-dermal test”).	Frozen: Vial: 28 days Refrigerated: Syringe: 24 hours Vial: 24 hours Room Temperature: 24 hours (Both)
3. 0.9% sodium chloride injection, preservative free	- Draw up 0.05 mL into a leur-lock syringe, without a needle (Label “scratch test”). - Draw up 0.2 mL into an intradermal syringe (Label “intra-dermal test”).	Refrigerated: 24 hours Room Temperature: 24 hours
4. Histamine base 1 mg/mL (Histatrol)	- Twist off the dropper applicator and place on an alcohol swab in the hood. - Draw up 0.05 mL in a leur-lock syringe (Label “scratch test”). - Remove the needle from the leur-lock syringe and discard, and place a cap on the end of the syringe.	Refrigerated: Vial: 28 days or Syringe: 24 hours Room Temperature: 24 hours (both)

^aPAST = penicillin allergy skin test.^bFrozen = -15°C to -50°C; Refrigerated = 2°C to 8°C; Room temperature = 20°C to 25°C.

with those of PAST programs; both aim to optimize antimicrobial use and minimize their unintended consequences.⁹ Antimicrobial stewardship pharmacists are often tasked with the daily operations of ASPs, including preauthorization and prospective audit and feedback, providing a natural opportunity to identify patients eligible for PAST and serve as specialists for general pharmacists regarding more difficult cases of penicillin allergy.²⁶ Given their extensive interaction with population-level data, antimicrobial stewardship

pharmacists also have unique expertise with tools and outcome measures which are relevant for PAST programs. Clinical decision support systems are increasingly being leveraged to assist PAST programs with aspects such as identifying eligible patients and educating providers, especially in smaller institutions with limited personnel.^{22,27} ASPs often have access to build such systems or have existing relationships with information technology and clinical informatics personnel to help design the process. Following successful

implementation, demonstration of a PAST program's impact should require tracking of specific outcome measures like antimicrobial use (broad vs. narrow spectrum), antimicrobial resistance, and adverse drug reactions (e.g. associated with β-lactams vs. non-β-lactams). Many ASPs already follow or have the capacity to follow these measures directly. Thus, antimicrobial stewardship pharmacists are particularly well-positioned to lead PAST programs from development to implementation and, ultimately, assessment.

Despite the inherent advantages to pharmacist-led PAST programs, specific challenges persist regarding issues such as training, scope of practice, billing, and personnel resources. There is currently a lack of initial training and continuing education programs to ensure competency of pharmacists providing PAST services. Published reports, such as Leis et al.,¹¹ typically describe a locally developed training program provided by an allergist. Such training may be difficult to offer in smaller institutions without access to such expertise. In addition, pharmacy practice laws and business models vary by locale. The authors are currently unaware of any examples of pharmacists billing for services rendered during a PAST consultation. In one pharmacist-led model published in 2004, pharmacists attempted to charge \$60 per hour for the PAST service; this billing effort was ultimately unsuccessful.²¹ PAST may serve as a prime case for professional pharmacy organizations and associated allies to help advocate for novel pharmacist billing mechanisms. This latter point is especially pertinent since, as with any healthcare providers performing PAST, there is a high opportunity cost for a pharmacist to spend 1–2 hours of uninterrupted time performing a PAST on an individual patient. This may lead to personnel shortage issues within the pharmacy or may limit the hours PAST consultations are available (e.g., business hours only). Training interested pharmacy residents may offer an additional solution for PAST administration. These considerations must be weighed before implementing a new pharmacist-led PAST program.

Pharmacist with ID physicians. Integration of PAST into ID practice and training provides a unique model to optimize antibiotic utilization in the hospital, as responsibilities for antimicrobial stewardship and hospital infection control are growing areas for ID-trained physicians.²⁸ An academic hospital with an ID fellowship training program is a promising setting for integrating PAST into ID practice by engaging ID medical fellows in antimicrobial stewardship and training them in a novel procedure. A PAST service

incorporating ID fellowship trainees not only offers personnel to administer PAST in settings without access to an allergist, but also provides a valuable learning experience to the trainees. ID physicians are frequently consulted to evaluate patients reporting a penicillin allergy and play an important role in the antibiotic selection and management of these patients. One major advantage of this model is that ID providers are often the first ones to recognize the need for testing and can quickly perform the test and act on the results. Additionally, by providing this training to ID medical fellows, these physicians are well-positioned upon graduation to implement PAST in their future practices expanding overall access to testing. In institutions with allergy and immunology training programs, those fellows may provide an additional resource for PAST services.

A PAST model managed by ID fellows has been in place at the University of Maryland Medical Center since 2014. A formal penicillin allergy consult service was established as an antimicrobial stewardship initiative, where ID fellows, under ID attending physician supervision, perform detailed drug allergy histories and determine the appropriateness for PAST. Patients who are eligible and consent for PAST have skin tests performed by the ID fellow with ID attending physician supervision. Responsibility for covering the penicillin allergy consult pager rotates monthly to the medical fellow covering the internal medicine ID/HIV service, where the fellow's schedule is more flexible as their primary role is teaching. The model has proven successful; in the first 11 months of the program, 76 patients underwent PAST, with 96% of the valid tests being negative, and 84% with a negative test having antibiotics changed based on the results of the test.¹³ The penicillin allergy consult service works closely with the antimicrobial stewardship pharmacists who frequently refer patients for evaluation for testing and provide training for the ID fellows in PAST and subsequent antibiotic changes. Clinical pharmacists rounding with patient care teams frequently make referrals to the penicillin allergy team as well.

A similar model of antimicrobial stewardship-initiated PAST is in place at Vidant Medical Center, a tertiary care hospital in North Carolina, where patients with β -lactam allergies are identified through antimicrobial stewardship reviews with PAST performed, as appropriate, by ID fellows. This program demonstrated an estimated annual cost savings of \$82,000 in patients who received PAST-guided antibiotic changes.²⁹

Pharmacist with nurses. Often community-based non-academic medical centers lack access to inpatient allergists and may also have limited access to ID consultants or trainees. In these cases, pharmacist- and nursing-driven PAST may be especially beneficial. One example of a successful pharmacist-nursing model is a 714-bed community based regional referral health system in Savannah, Georgia. PAST was added to the health system formulary following antimicrobial subcommittee and pharmacy and therapeutics committee review. Being a non-teaching hospital without medical residents, ID fellows, or a dedicated allergy service, it was decided the best way to structure the team was with an antimicrobial stewardship pharmacist to guide PAST and a nurse to administer the test via a protocol with 3 phases: puncture, intradermal, and oral challenge (optional phase). Prescribing of PAST is currently restricted to ID physicians or recommendations from the antimicrobial stewardship pharmacist during day shift hours, including weekends. The antimicrobial stewardship pharmacist evaluates all patients prescribed PAST for exclusions for use and any medications that would interfere with conducting the test (e.g., antihistamines). The product is then profiled and prepared by the antimicrobial stewardship pharmacist, who coordinates a time to administer the test with the nurse. The protocol was developed and modified to fit the institution for nurse utilization during administration. It includes specific documentation of the results and interpretation of the test. The nurse interprets the test and the antimicrobial stewardship pharmacist confirms the interpretation. The antimicrobial stewardship pharmacist is then

responsible for updating patient allergies, documenting the procedure via progress note, and contacting the prescribing physician for changes in antimicrobial therapy. The patient is also counseled and provided a handout on test results by the antimicrobial stewardship pharmacist, especially for a negative test, to say that they are no longer allergic to penicillin and to inform all providers.¹²

Pharmacist with allergist. The collaboration between a pharmacist and allergist was one of the first multidisciplinary approaches described for PAST.^{14,21,22,23,24,30,31} Although various inpatient and outpatient strategies have been successfully implemented, overall outcomes have been similar among models that include an allergist.

One such model includes a PAST service administered and interpreted by pharmacists, but supervised and directed by allergists.^{21,22} Chen et al.²² described a pharmacist-allergist team approach to PAST which used a computerized algorithm for the selection and prioritization of hospitalized subjects who may clinically benefit from testing. When indicated, a trained pharmacist was authorized to screen patients, order the necessary supplies, and administer the test. Atypical penicillin allergy histories were discussed and reviewed with the allergist on call. Of the 223 skin-test-negative patients, plus an additional 5 patients with prior penicillin tolerance, a total of 1152 days of alternative antibiotic therapy was avoided throughout the study period.

Pharmacist identification of penicillin allergic patients with subsequent allergy-applied skin testing is another collaborative approach reported in the medical literature.^{14,23,24,30,31} Ramsey et al.¹⁴ detailed the use of a penicillin allergy history algorithm and subsequent skin testing in hospitalized patients receiving second-line antibiotic therapy. Pharmacists utilized the algorithm to identify appropriate candidates and scheduled an allergy consultation for skin testing. Of the 47 skin-test-negative patients transitioned to a β -lactam antibiotic post-testing, 982 days of second-line antibiotic therapy and at least 23 hospital days were

avoided. Similarly, Park et al.²³ conducted an observational study evaluating the impact of a pharmacist-allergist collaborative on antibiotic exposure in penicillin allergic patients in the outpatient setting. Pharmacists identified, educated, and referred appropriate clinic patients to an allergist for outpatient skin testing. Of the 503 patients enrolled in this study, 71 (14%) pursued testing. In the cohort of patients requiring antibiotics during the study period, significantly more β -lactam antibiotics were prescribed in patients evaluated by an allergist than in those who were not (66% vs. 26%) ($p < 0.0001$).

A collaborative effort between pharmacists and allergists for PAST is an effective multidisciplinary intervention that has shown to reduce second-line antibiotic exposure. The utilization of this approach optimizes the identification of appropriate candidates based on the allergy history, including atypical reactions, as well as post-testing antibiotic selection.

Outpatient PAST

While pharmacist involvement with PAST services has primarily been focused in acute settings where the results will immediately impact (usually parenteral) antibiotic therapy, it is important to remember that allergy skin tests for a variety of potential allergens are commonly performed in allergists' outpatient clinics. Such testing, even in patients with a history of severe reactions to the potential allergen, does not usually require inpatient admission, or intensive care unit monitoring, although access to those services should be readily available. PAST is very safe if scratch testing is performed before intradermal testing.³² Thus, PAST is a reasonable procedure in the outpatient or inpatient setting. In the clinic setting, PAST can be done not only to determine immediate appropriate antimicrobials, but also proactively in patients labeled with a penicillin allergy before antibiotics are needed.³³ Macy et al.³⁴ prospectively performed PAST in patients with a history of penicillin allergy who were not currently receiving antibiotics and was able to remove that label from patients' electronic medical

record. This same group of investigators recently examined health care utilization of patients who had received PAST matched with controls and found after 4 years that PAST patients had fewer clinic visits, emergency department visits, and hospital admissions.³⁵ Given the limited resources most pharmacy and ID departments have, routine testing without an allergist component may not be feasible. However, targeted use of an allergy assessment program that includes PAST may be possible in many health systems. Of particular value may be performing PAST on patients undergoing major surgery to help select appropriate prophylaxis. For example, in patients about to undergo elective total knee or hip arthroplasty, setting up a time (often in conjunction with pre-operative assessment or education appointments) for assessment and possible PAST by pharmacists performed in a clinic may be feasible and result in more appropriate surgical antimicrobial prophylaxis. For outpatient PAST performed by pharmacists, logistics and billing of the program are often the biggest hurdles to a successful service. Securing appropriate clinic space (or perhaps space in an infusion center) is often the first step to outpatient PAST. Scheduling of patient and pharmacist can also be a challenge. Finally, the financials of the program need to be taken into account. Currently there are up to 9 Current Procedural Terminology (CPT) codes that can be applied to 1 test, with an additional CPT code for oral challenge.³⁶ Depending on the setting and healthcare personnel involved, an outpatient office visit can also be billed. Results of a systematic review indicated an outpatient prescription cost savings of \$14–\$193/patient in patients with self-reported penicillin allergy if not penicillin allergic.³⁷ Although the health system may find a financial disincentive to the program from loss of pharmacists' time and the supplies needed for PAST, as the article mentioned above demonstrates, this may be more than offset by decreased health-care utilization. Also of importance is ensuring continuity of the results of the allergy assessment in all the patient records.

Table 4. 2017 Results of State Boards of Pharmacy Inquiries Concerning PAST^a

State	PAST Allowed?	Comments by BOP Contact
Alaska	No information	
Alabama	No information	
Arizona	Maybe	No current regulations. CPA are allowed; pharmacist administered and interpreted labs may be allowed if the CPA protocol is very detailed. PAST may be allowed if approved
Arkansas	No information	
California	Yes	
Colorado	Yes	Colorado Law 6.00.10 defining pharmaceutical care states pharmacists and physicians can create agreements and write protocols dictating the pharmacist's scope. The protocols and limits of the pharmacist are up to the parties entering into the agreement.
Connecticut	No	
Delaware	No	There are no CPAs between pharmacists and physicians for drug therapy management.
Florida	Maybe	CPA Protocols are reviewed on a case by case basis
Georgia	Maybe	CPA Protocols are reviewed on a case by case basis
Hawaii	No information	
Idaho	No information	
Illinois	No information	
Indiana	Maybe	CPA Protocols are reviewed on a case by case basis
Iowa	Yes	
Kansas	Yes	
Kentucky	No information	
Louisiana	No information	
Maine	No	
Maryland	Yes	
Massachusetts	No information	
Michigan	Yes	
Minnesota	Yes	Allowed as long as test is in accordance with CLIA rules or is waived
Mississippi	No information	
Missouri	No information	
Montana	No information	
Nebraska	Yes	CPA required
Nevada	No	
New Hampshire	Maybe	CPA Protocols are reviewed on a case by case basis
New Jersey	Yes	
New Mexico	No	
New York	No	
North Carolina	Yes	
North Dakota	No information	

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Table 4. 2017 Results of State Boards of Pharmacy Inquiries Concerning PAST^{a,b}

State	PAST Allowed?	Comments by BOP Contact
Ohio	No	Allergy testing is diagnostic in nature and does not fall under the management/administration of medication
Oklahoma	Yes	CPA required
Oregon	Yes	
Pennsylvania	No	
Rhode Island	No information	
South Carolina	Yes	CPA required. Inpatient PAST pilot approved by BOP
South Dakota	No information	
Tennessee	Yes	
Texas	Yes	Allowed if hospital approved
Utah	Yes	
Vermont	Maybe	Pilot inpatient project for PAST has been approved
Virginia	No information	
Washington	Yes	
West Virginia	Maybe	Pilot inpatient project for PAST has been approved
Wisconsin	Maybe	
Wyoming	Yes	

^aBOP = Board of Pharmacy; PAST = penicillin allergy skin test; CPA = Collaborative Practice Agreement; CLIA = Clinical Laboratory Improvement Amendments; No information = no response to multiple email and phone inquiries.

^bInformation from 2017. Pharmacists should contact their State Boards of Pharmacy for the latest status of penicillin skin testing in their state.

State board of pharmacy regulations and PAST

The practice of pharmacy has evolved significantly in the last 50 years in many areas. However, changes in pharmacy practice in the United States have not been uniform, owing to several factors. One of these factors is that rules governing pharmacy practice are determined at the state, rather than federal level. Thus, the rules determining what activities a pharmacist may perform within the scope of their practice may vary significantly from state to state. All 50 boards of pharmacy in the United States were contacted and asked whether PAST completed by a pharmacist would be consistent with that state's rules governing pharmacists' scope of practice. The results are displayed in Table 4. It should be noted that some boards of pharmacy did not respond. If a pharmacist in a state where Board of Pharmacy

rules prohibit administration of PAST by pharmacists, this does not mean that a collaborative team conducting PAST cannot be formed. For example, a certain state board may suggest that administration of PAST is beyond that state's rules concerning scope of practice for pharmacists. However, that board may allow a nurse to administer the PAST and have a pharmacist interpret the results. Pharmacists are encouraged to work with their state board of pharmacy to determine a plan that would allow an allergy assessment program including PAST and still be in compliance with scope of practice rules.

Conclusion

PAST is rapidly becoming an effective, long-term antimicrobial stewardship tool to optimize antimicrobial prescribing in both the inpatient and outpatient settings. Pharmacists have demonstrated

significant benefit as providers of PAST services in a variety of healthcare settings with a number of different healthcare professionals. Further implementation of allergy assessment and PAST by pharmacists nationally and internationally will help make the vast majority of penicillins allergies a thing of the "past".

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References

- Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. *Curr Allergy Asthma Rep.* 2014; 14:476.
- Shah NS, Ridgway JP, Pettit N et al. Documenting penicillin allergy: the impact of inconsistency. *PLoS One.* 2016; 11:e0150514.
- Solensky R, Khan DA, Bernstein IL et al. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol.* 2010; 105:259–73.
- Bourke J, Pavlos R, James I, Phillips E. Improving the effectiveness of penicillin allergy de-labeling. *J Allergy Clin Immunol Pract.* 2015; 3:365–34.e1.
- Trubiano JA, Chen C, Cheng AC et al. Antimicrobial allergy “labels” drive inappropriate antimicrobial prescribing: lessons for stewardship. *J Antimicrob Chemother.* 2016; 71:1715–22.
- Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. *Pharmacotherapy.* 2011; 31:742–7.
- Al-Hasan MN, Acker EC, Kohn JE et al. Impact of penicillin allergy on empirical carbapenem use in gram-negative bloodstream infections: an antimicrobial stewardship opportunity. *Pharmacotherapy.* 2018; 38:42–50.
- Su T, Broekhuizen BDL, Verheij TJM, Rockmann H. The impact of penicillin allergy labels on antibiotic and health care use in primary care: a retrospective cohort study. *Clin Transl Allergy.* 2017; 7:18.
- Barlam TF, Cosgrove SE, Abbo LM et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis.* 2016; 62(10):e51–77.
- Perlman F. Value of skin testing for penicillin allergy. *JAMA* 1965; 192:64–5.
- Leis JA, Palmay L, Ho G et al. Point-of-care β -lactam allergy skin testing by antimicrobial stewardship programs: A pragmatic multicenter prospective evaluation. *Clin Infect Dis.* 2017; 65:1059–65.
- Jones BM, Bland CM. Penicillin skin testing as an antimicrobial stewardship initiative. *Am J Health-Syst Pharm.* 2017; 74:232–7.
- Heil EL, Bork JT, Schmalzle SA et al. Implementation of an infectious disease fellow-managed penicillin allergy skin testing service. *Open Forum Infect Dis.* 2016; 3:ofw155.
- Ramsey A, Staicu ML. Use of a penicillin allergy screening algorithm and penicillin skin testing for transitioning hospitalized patients to first-line antibiotic therapy. *J Allergy Clin Immunol Pract.* 2018; 6:1349–55.
- Blumenthal KG, Parker RA, Shenoy ES, Walensky RP. Improving clinical outcomes in patients with methicillin-sensitive staphylococcus aureus bacteremia and reported penicillin allergy. *Clin Infect Dis.* 2015; 61:741–9.
- Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: a cohort study. *J Allergy Clin Immunol.* 2014; 133:790–6.
- Confino-Cohen R, Rosman Y, Meir-Shafir K et al. Oral challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. *J Allergy Clin Immunol Pract.* 2017; 5:669–75.
- Solensky R, Earl HS, Gruchalla RS. Clinical approach to penicillin-allergic patients: a survey. *Ann Allergy Asthma Immunol.* 2000; 84:329–33.
- Estep PM, Ferreira JA, Dupree LH et al. Impact of an antimicrobial stewardship initiative to evaluate β -lactam allergy in patients ordered aztreonam. *Am J Health-Syst Pharm.* 2016; 73(5 suppl 1):S8–13.
- Oliver WD, Heil EL, Thom KA et al. Allergy profile should be updated after uneventful administration of a penicillin or penicillin-related antibiotic to a patient with penicillin allergy. *J Allergy Clin Immunol Pract.* 2017; 5:184–6.
- Wall GC, Peters L, Leaders CB, Wille JA. Pharmacist-managed service providing penicillin allergy skin tests. *Am J Health-Syst Pharm.* 2004; 61:1271–5.
- Chen JR, Tarver SA, Alvarez KS et al. A proactive approach to penicillin allergy testing in hospitalized patients. *J Allergy Clin Immunol Pract.* 2017; 5:686–93.
- Park MA, McClimon BJ, Ferguson B et al. Collaboration between allergists and pharmacists increases β -lactam antibiotic prescriptions in patients with a history of penicillin allergy. *Int Arch Allergy Immunol.* 2011; 154:57–62.
- King EA, Challa S, Curtin P, Bielory L. Penicillin skin testing in hospitalized patients with β -lactam allergies: effect on antibiotic selection and cost. *Ann Allergy Asthma Immunol.* 2016; 117:67–71.
- Staicu ML, Brundige ML, Ramsey A et al. Implementation of a penicillin allergy screening tool to optimize aztreonam use. *Am J Health-Syst Pharm.* 2016; 73(5):298–306.
- Staicu ML, Plakosh M, Ramsey A. Prospective evaluation of electronic medical record penicillin allergy documentation at a tertiary community teaching hospital. *Ann Allergy Asthma Immunol.* 2017; 119:94–5.
- Caplinger C, Smith G, Remington R, Madaras-Kelly K. Evaluation of a computerized decision support intervention to decrease use of anti-pseudomonal carbapenems in penicillin allergic patients. *Antibiotics (Basel);* 2016; 5 pii: E7.
- Chandrasekar P, Havlicek D, Johnson LB. Infectious diseases subspecialty: declining demand challenges and opportunities. *Clin Infect Dis.* 2014; 59:1593–8.
- Rimawi RH, Cook PP, Gooch M et al. The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. *J Hosp Med.* 2013; 8:341–5.
- Forrest DM, Schellenberg RR, Thien VV et al. Introduction of a practice guideline for penicillin skin testing improves the appropriateness of antibiotic therapy. *Clin Infect Dis.* 2001; 32:1685–90.
- Harris AD, Sauberman L, Kabbash L et al. Penicillin skin testing: a way to optimize antibiotic utilization. *Am J Med.* 1999; 107:166–8.
- Gadde J, Spence M, Wheeler B, Adkinson NF Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA.* 1993; 270:2456–63.
- Mirakian R, Leech SC, Krishna MT et al.; Standards of Care Committee of the British Society for Allergy and Clinical Immunology. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy.* 2015; 45:300–27.
- Macy E, Roppe LB, Schatz M. Routine penicillin skin testing in hospitalized patients with a history of penicillin allergy. *Perm J.* 2004; 8:20–4.
- Macy E, Shu YH. The effect of penicillin allergy testing on future health care utilization: a matched cohort study. *J Allergy Clin Immunol Pract.* 2017; 5:705–10.
- American Academy of Allergy, Asthma & Immunology. Coding for penicillin testing. <https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Management/finances-coding/Coding-for-Penicillin-Testing.pdf> (accessed 2018 Dec 18).
- Mattingly TJ 2nd, Fulton A, Lumish RA et al. The cost of self-reported penicillin allergy: a systematic review. *J Allergy Clin Immunol Pract.* 2018; 6:1649–54.e4.