Antibiotic stewardship support through penicillin allergy testing: A POCKET GUIDE

Second Edition

PRE-PEN®
(benzylpenicilloyl polylysine injection USP)
Skin Test Antigen
Support optimal antibiotic use

Antibiotic resistance is a clinical and public health crisis. The misuse of antibiotics is a primary driver of this issue and antibiotic stewardship programs are challenged to change clinical practice patterns in response to this growing problem.

This guide provides a practical overview of implementing penicillin allergy skin testing as a key component of stewardship efforts.

Penicillin allergy skin testing is a novel approach to address the misuse of antibiotics and supports optimal antibiotic utilization.¹

Evaluation and diagnosis of penicillin allergy is recommended in the CDC’s “US Antibiotic Awareness Week” program², IDSA Stewardship Guidelines³, SHEA Guidelines and is endorsed by the AAAAI.⁴
The use of antibiotics is the single most important factor leading to **antibiotic resistance** around the world.

Antibiotics are among the most commonly prescribed drugs used in human medicine.  

The number of antibiotic-resistant bacteria continues to increase every year.  

The number of antibiotics in the approval pipeline continues to decrease each year.
23,000 deaths in the US each year are caused by drug-resistant bacteria.\textsuperscript{5}

\textbf{Up to 50\%} of all antibiotics prescribed are not needed or are not optimally effective as prescribed.\textsuperscript{6}

\textbf{23,000 deaths}
Know the facts

Penicillin allergy is the most commonly reported drug allergy.\(^7\)

**Penicillin Allergy**

**Ten percent** of the patients in the US report penicillin allergy.\(^7\)

**9 out of 10** reporting penicillin allergy are not truly allergic when assessed by skin testing.\(^7\)
AN UNVERIFIED PENICILLIN ALLERGY IS A SIGNIFICANT PUBLIC HEALTH PROBLEM.¹

False reporting of penicillin allergy may lead to broad spectrum antibiotics use which is linked to increased antibiotic resistance, cost and toxicity.¹
Know the facts

True hypersensitivity to penicillin decreases over time.\(^8\)

- More than half of skin test positive patients lose sensitivity by 5 years.\(^8\)
- 80% of skin test positive patients lose sensitivity by 10 years.\(^8\)

The AAAAI encourages more widespread use of penicillin allergy skin testing.\(^4\)
Unverified penicillin allergy in hospitalized patients is associated with longer hospital stays and increased rates of serious drug resistant infections.\textsuperscript{9}

In the largest study of penicillin allergy testing in hospitalized patients, penicillin skin testing prevented over \textbf{500} inpatient days and more than \textbf{600} outpatient days on alternative agents.\textsuperscript{8}

Incorrect penicillin allergies therefore constitute a major barrier to antimicrobial stewardship, with significant clinical and economic implications, including increased antimicrobial resistance, overall care costs, and length of stay and, ultimately, increased mortality.\textsuperscript{1}
Support core elements

Actions to Support Optimal Antibiotic Use

- Reporting
- Tracking
- Accountability
- Drug Expertise
- Action

Optimal Antibiotic Use
Specific interventions like a penicillin allergy assessment protocol and benefits from skin testing, are critical to stewardship program success & continued funding and support.\textsuperscript{11,12}
Incorporate penicillin allergy testing into your facility

1. Acquire P&T approval to add required supplies to formulary

2. Establish a penicillin allergy skin testing protocol
   - Include patient criteria to qualify for testing
     - Any patient with a history of a reaction to a penicillin antibiotic that has been IgE mediated or a patient who is currently denied access to beta-lactam antibiotics out of concern for such reactions may qualify for testing
     - Patients with a history of severe skin reactions, such as Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis should not undergo penicillin allergy skin testing since such testing may reactivate their disease
• Identify your Penicillin Testing Champions to administer the test
  — Typically 5-7 individuals, which may include a variety of providers:
    - Fellows
    - Medical Assistants
    - Medical Residents
    - Nurse Practitioners
    - Pharmacist*
      *Check with state board
    - Physicians
    - Physician’s Assistants
    - Registered Nurses
  — Additional points to consider:
    - Individual’s scope of practice
    - Individual’s availability to administer 1-hour test
    - Individual’s willingness to educate others
  — Proceed to page 13 to learn more about the recommended training process
Incorporate penicillin allergy testing into your facility (Cont.)

3. Develop order set for all departments
   - Testing is recommended for but not limited to:
     - Allergy & Immunology
     - Critical Care
     - Emergency Department
     - Family Medicine
     - Infectious Disease
     - Internal Medicine
     - Long-term care
     - Oncology
     - Otolaryngology
     - Perioperative Medicine

4. Educate prescribing physicians and hospital facility leadership on testing availability and benefits
Train the trainer

The following educational model is designed to train a team of Penicillin Testing Champions (PTC) to administer and interpret penicillin allergy skin testing. Once trained, the PTC Team is qualified to train additional staff.

1. **Complete online training module**
   - e-Learning including video demonstration on test procedure & technique, literature review and supply management
   - Quizzes to test knowledge and completion certificate

2. **Participate in penicillin allergy testing in-service training**
   - Attend hands-on training with live product
   - It is recommended that trainees practice both puncture and intradermal administration a minimum of 3 times to demonstrate proper technique. Saline may be used.
   - Completion of competency form to store in employee file
Train the trainer (Cont.)

3. Successfully administer a minimum of 3 patient tests
   - It is recommended that the tests are performed within eight weeks of training
   - Test must be negative or positive – indeterminate tests do not count toward requirement
   - Upon test completion, you should know how to remove/edit allergy documentation and how to communicate results to both prescribing physician and the patient

4. Provide hands-on training to additional providers
   - Educational materials are available for support and continuing education
What our partners are saying

Penicillin Allergy Evaluation in some form is encouraged by the CDC, National Quality Forum, Infectious Diseases Society of America, the Society for Healthcare Epidemiology, American Board of Internal Medicine via the Choosing Wisely initiative and the American Academy of Allergy, Asthma and Immunology.

**Fact Sheet on Penicillin Allergy:** Is it Truly a Penicillin Allergy? Evaluation and Diagnosis of Penicillin Allergy for healthcare professionals.²

**Core Element Four:** Actions to Support Antibiotic Use includes penicillin allergy testing as a component in the Antibiotic Stewardship in Acute Care: A Practical Playbook.⁹

In patients with a history of B-Lactam allergy, we suggest that ASP’s promote allergy assessments and penicillin skin testing when appropriate.³
What our partners are saying (Cont.)

Using structured drug allergy assessments has been associated with improved stewardship as demonstrated by antibiotic selection, reduced alternative antibiotic use, decreased length of hospital stay and costs an increased guideline adherence.³

In the context of the recently launched national antibiotic stewardship initiative, the AAAAI encourages more widespread and routine performance of penicillin skin testing for patients with a history of allergy to penicillin or another beta lactam. (eg, ampicillin or amoxicillin)⁴
Visit www.penallergytest.com to learn more and access additional resources.

1. Online Training
   - Access on-demand interactive training modules to watch testing demonstration videos on procedures, techniques and supply management and assess knowledge with quizzes.

2. Demonstration videos

3. Onsite In Service Training
   - ALK offers on-site training to review importance of validating a penicillin allergy, hands on training and a skills assessment.

4. Support Material
   - Stay up to date on testing techniques, required supplies, protocol development and patient education.
PRE-PEN®
benzylpenicilloyl polylysine injection, solution
Skin Test Antigen

DESCRIPTION:
PRE-PEN® (benzylpenicilloyl polylysine injection USP) is a sterile solution of benzylpenicilloyl polylysine in a concentration of 6.0 X 10^-5 M (benzylpenicilloyl) in 0.01 M phosphate buffer and 0.15 M sodium chloride. The benzylpenicilloyl polylysine in PRE-PEN is a derivative of poly-l-lysine, where the epsilon amino groups are substituted with benzylpenicilloyl groups (50-70%) forming benzylpenicilloyl alpha amide. Each single dose ampule contains 0.25 mL of PRE-PEN.

PRE-PEN has the following structure:

CLINICAL PHARMACOLOGY:
PRE-PEN is a skin test antigen reagent that reacts specifically with benzylpenicilloyl IgE antibodies initiating the release of chemical mediators which produce an immediate wheal and flare reaction at a skin test site. All individuals exhibiting a positive skin test to PRE-PEN possess IgE against the benzylpenicilloyl structural group which is a hapten. A hapten is a low molecular weight chemical that conjugates with a carrier (e.g. poly-l-lysine) resulting in the formation of an antigen with the hapten's specificity. The benzylpenicilloyl hapten is the major antigenic determinant in penicillin-allergic individuals. However, many individuals reacting positively to PRE-PEN will not develop a systemic allergic reaction on subsequent exposure to therapeutic penicillin, especially among those who have not reacted to penicillins in the past. Thus, the PRE-PEN skin test determines the presence of penicilloyl IgE antibodies which are necessary but not sufficient for acute allergic reactions due to the major penicilloyl determinant.

Non-benzylpenicilloyl haptens are designated as minor determinants, since they less frequently elicit an immune response in penicillin treated individuals. The minor determinants may nevertheless be associated with significant clinical hypersensitivity. PRE-PEN does not react with IgE antibodies directed against non-benzylpenicilloyl haptens.

INDICATIONS AND USAGE:
PRE-PEN is indicated for the assessment of sensitization to penicillin (benzylpenicillin or penicillin G) in patients suspected to have clinical penicillin hypersensitivity. A negative skin test to PRE-PEN is associated with an incidence of immediate allergic reactions of less than 5% after the administration of therapeutic penicillin, whereas the incidence may be more than 50% in a history-
positive patient with a positive skin test to PRE-PEN. These allergic reactions are predominantly dermatologic. Whether a negative skin test to PRE-PEN predicts a lower risk of anaphylaxis is not established. Similarly, when deciding the risk of proposed penicillin treatment, there are not enough data at present to permit relative weighing in individual cases of a history of clinical penicillin hypersensitivity as compared to positive skin tests to PRE-PEN and/or minor penicillin determinants.

**CONTRAINDICATIONS:**
PRE-PEN is contraindicated in those patients who have exhibited either a systemic or marked local reaction to its previous administration. Patients known to be extremely hypersensitive to penicillin should not be skin tested.

**WARNINGS:**
The risk of sensitization to repeated skin testing with PRE-PEN is not established. Rarely, a systemic allergic reaction including anaphylaxis (see below) may follow a skin test with PRE-PEN. To decrease the risk of a systemic allergic reaction, puncture skin testing should be performed first. Intradermal skin testing should be performed only if the puncture test is entirely negative.

**PRECAUTIONS:**

**General:**
No reagent, test, or combination of tests will completely assure that a reaction to penicillin therapy will not occur.

The value of the PRE-PEN skin test alone as a means of assessing the risk of administering therapeutic penicillin (when penicillin is the preferred drug of choice) in the following situations is not established:

1. Adult patients who give no history of clinical penicillin hypersensitivity.
2. Pediatric patients.

In addition, the clinical value of PRE-PEN where exposure to penicillin is suspected as a cause of a current drug reaction or in patients who are undergoing routine allergy evaluation is not known. Likewise, the clinical value of PRE-PEN skin tests alone in determining the risk of administering semi-synthetic penicillins (phenoxymethyl penicillin, ampicillin, carbenicillin, dicloxacillin, methicillin, nafcillin, oxacillin, amoxicillin), cephalosporin-derived antibiotics, and penem antibiotics is not known.

In addition to the results of the PRE-PEN skin test, the decision to administer or not administer penicillin should take into account individual patient factors. Healthcare professionals should keep in mind the following:

1. A serious allergic reaction to therapeutic penicillin may occur in a patient with a negative skin test to PRE-PEN.
2. It is possible for a patient to have an anaphylactic reaction to therapeutic penicillin in the presence of a negative PRE-PEN skin test and a negative history of clinical penicillin hypersensitivity.
3. If penicillin is the drug of choice for a life-threatening infection, successful desensitization with therapeutic penicillin may be possible irrespective of a positive skin test and/or a positive history of clinical penicillin hypersensitivity.
Pregnancy – Pregnancy Category C:
Animal reproduction studies have not been conducted with PRE-PEN. It is not
known whether PRE-PEN can cause fetal harm when administered to a pregnant
woman or can affect reproduction capacity. The hazards of skin testing in such
patients should be weighed against the hazard of penicillin therapy without skin
testing.

ADVERSE REACTIONS:
Occasionally, patients may develop an intense local inflammatory response
at the skin test site. Rarely, patients will develop a systemic allergic reaction,
manifested by generalized erythema, pruritus, angioedema, urticaria, dyspnea,
hypotension, and anaphylaxis. The usual methods of treating a skin test antigen-
induced reaction — the applications of a venous occlusion tourniquet proximal
to the skin test site and administration of epinephrine are recommended. The
patient should be kept under observation for several hours.

DOSAGE AND ADMINISTRATION:
SKIN TESTING DOSAGE AND TECHNIQUE
Skin testing responses can be attenuated by interfering drugs (e.g. H1-
antihistamines and vasopressors). Skin testing should be delayed until the
effects of such drugs have dissipated, or a separate skin test with histamine
can be used to evaluate persistent antihistaminic effects in vivo. Due to the risk
of potential systemic allergic reactions, skin testing should be performed in an
appropriate healthcare setting under direct medical supervision.

Puncture Testing:
Skin testing is usually performed on the inner volar aspect of the forearm.
The skin test antigen should always be applied first by the puncture technique.
After preparing the skin surface, apply a small drop of PRE-PEN solution using
a sterile 22-28 gauge needle. The same needle can then be used to make a
single shallow puncture of the epidermis through the drop of PRE-PEN. Very
little pressure is required to break the epidermal continuity. Observe for the
appearance of a wheal, erythema, and the occurrence of itching at the test site
during the succeeding 15 minutes at which time the solution over the puncture
site is wiped off. A positive reaction consists of the development within 10
minutes of a pale wheal, sometimes with pseudopods, surrounding the puncture
site and varying in diameter from 5 to 15 mm (or more). This wheal may be
surrounded by a variable diameter of erythema, and accompanied by a variable
degree of itching. The most sensitive individuals develop itching quickly, and
the wheal and erythema are prompt in their appearance. As soon as a positive
response as defined above is clearly evident, the solution over the scratch should
be immediately wiped off. If the puncture test is either negative or equivocally
positive (less that 5 mm wheal with little or no erythema and no itching), an
intradermal test may be performed.

The Intradermal Test:
Using a 0.5 to 1.0 cc syringe with a 3/8” to 5/8”long, 26 to 30 gauge, short bevel
needle, withdraw the contents of the ampule. Prepare with an alcohol swab a
skin test area on the upper, outer arm, sufficiently below the deltoid muscle to
permit proximal application of a tourniquet later, if necessary. Be sure to eject
all air from the syringe through the needle, then insert the needle, bevel up
immediately below the skin surface. Inject an amount of PRE-PEN sufficient to
raise a small intradermal bleb of about 3mm in diameter, in duplicate at least
2cm apart. Using a separate syringe and needle, inject a like amount of saline or
allergen diluting solution as a control at least 5 cm removed from the antigen test sites. Most skin reactions will develop within 5-15 minutes and response to the skin test is read at 20 minutes as follows:

**Negative response** — no increase in size of original bleb and no greater reaction than the control site.

**Ambiguous response** — wheal only slightly larger than initial injection bleb, with or without accompanying erythematous flare and slightly larger than the control site; OR discordance between duplicates.

**Positive response** — itching and significant increase in size of original blebs to at least 5mm. Wheal may exceed 20 mm in diameter and exhibit pseudopods.

If the control site exhibits a wheal greater than 2-3 mm, repeat the test, and if the same reaction is observed, a physician experienced with allergy skin testing should be consulted.

**HOW SUPPLIED:** NDC 49471-001-05

PRE-PEN® (benzylpenicilloyl polylysine injection USP) is a clear, colorless, sterile solution supplied in ampules containing 0.25 mL.

Box of 5 single dose ampules. Ampules are opened by snapping the neck of the ampule using two forefingers of each hand. Visually inspect for glass chards before use. Each ampule is for single patient use only. Discard any unused portion.

PRE-PEN is optimally stored under refrigeration (2-8 °C). PRE-PEN subjected to ambient temperatures for more than 24 hours should be discarded. As with all parenteral drug products, PRE-PEN should be inspected visually for particulate matter and discoloration prior to administration.

**Rx only**

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