

**Penicillin Skin Testing: Frequently Asked Questions
Benzylpenicilloyl Polylysine (Pre-Pen®) and Diluted Penicillin G**

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**VA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN
Pharmacist Executives**

Benzylpenicilloyl polylysine (Pre-Pen®) was FDA approved in 2009 for the assessment of sensitization to penicillin in those patients suspected, based upon previous experience, of having a clinical hypersensitivity to penicillin. Penicillin skin testing is the most reliable way to evaluate patients for IgE-mediated penicillin allergy. Skin testing is conducted using benzylpenicilloyl polylysine (major determinant), penicillin G diluted with normal saline to 10,000 units/ml (minor determinant), a positive and negative control. Testing with both the major and minor determinant of penicillin can identify up to 97% of patients with an immediate hypersensitivity to penicillin.

The intent of this document is to help guide appropriate use of penicillin skin testing.

1. WHEN IS PENICILLIN SKIN TESTING INDICATED?

Penicillin skin testing can be considered in those patients with a prior history of hypersensitivity to penicillin or allergy to penicillin in situations where the provider considers penicillin the drug of choice or prefers treatment with penicillin. If skin testing is indicated, the patient should be referred to a VA Allergy Specialist or other appropriately trained physician who is experienced in the application and interpretation of PCN skin testing, as locally designated.

Although approximately 10% of patients will remain allergic to penicillin their entire lives, a large majority will stop expressing penicillin-specific IgE-mediated antibodies and can be safely treated with penicillin.

Skin testing with benzylpenicilloyl polylysine is contraindicated in patients who are known to be extremely hypersensitive to penicillin and in those patients who have experienced a systemic or marked local reaction to prior administration of benzylpenicilloyl polylysine.

Skin test response may be blunted by use of interfering drugs including H1-antihistamines and vasopressors. It is recommended that skin testing be delayed until the effect of interfering medications has dissipated (24 hrs for chlorpheniramine or fexofenadine; 4 days for diphenhydramine; 3 weeks for hydroxyzine or phenothiazines).

Additional Information:

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

The value of benzylpenicilloyl polylysine skin test alone as an indicator of assessing the risk of administering therapeutic penicillin (when penicillin is the preferred drug of choice) has not been established for the following situations:

- 1) Adult patients who give no history of clinical penicillin hypersensitivity
- 2) Pediatric patient populations

The clinical value of benzylpenicilloyl polylysine is unknown in the following circumstances:

- When exposure to penicillin is suspected as a cause of a current drug reaction.
- In patients without a history of penicillin allergy who are undergoing routine allergy evaluation or testing.
- In determining the risk of allergic reactions directed at semisynthetic penicillins (phenoxymethyl penicillin, ampicillin, carbenicillin, dicloxacillin, methicillin, nafcillin, oxacillin, amoxicillin), cephalosporin-derived antibiotics, and penem antibiotics. Individuals may have reactions directed at the R-group side chain which distinguishes the chemical structure of different penicillin-class compounds.

In addition to the results of the benzylpenicilloyl polylysine skin test, individual patient factors must be considered when deciding whether to administer penicillin. The manufacturer recommends keeping the following in mind when making penicillin treatment decisions:

- A serious allergic reaction to therapeutic penicillin may occur in a patient with a negative skin test to benzylpenicilloyl polylysine.
- It is possible for a patient to have an anaphylactic reaction to therapeutic penicillin in the presence of a negative benzylpenicilloyl polylysine skin test and a negative history of clinical penicillin hypersensitivity.
- 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.

2. WHEN INDICATED, WHO SHOULD APPLY AND INTERPRET THE PENICILLIN SKIN TEST?

Penicillin skin testing should only be performed by personnel skilled in the application and interpretation of this type of skin testing and prepared to treat potential severe allergic reactions, including anaphylaxis.

The VA Medical Advisory Panel and VISN Pharmacist Executives recommend that testing be performed by a VA Allergy Specialist or other appropriately trained physician who is experienced in the application and interpretation of PCN skin testing, as locally designated.

3. WHEN SHOULD PENICILLIN SKIN TESTING BE CONDUCTED AND IN WHAT SETTING?

Penicillin skin testing can be done electively when a patient is well and not in immediate need of antibiotic therapy or alternatively, when a patient is in need of antibiotics and treatment with penicillin is being considered. If done electively, it is important to carefully document the results of the testing (e.g., in the problem list and as an annotation to the drug allergy history). There is lack of agreement regarding the need to perform an elective challenge with penicillin immediately after a negative penicillin skin test result.

Because of the risk for systemic allergic reactions, including anaphylaxis, skin testing should be performed in an appropriate healthcare setting supervised by healthcare providers experienced and prepared to manage these types of reactions. To reiterate, penicillin skin testing should only be performed by personnel skilled in the application and interpretation of this type of skin testing and prepared to treat potential severe allergic reactions, including anaphylaxis. The VA Medical Advisory Panel and VISN Pharmacist Executives recommend that testing be performed by a VA Allergy Specialist or other appropriately trained physician who is experienced in the application and interpretation of PCN skin testing, as locally designated.

4. HOW IS PENICILLIN SKIN TESTING PERFORMED?

Skin testing should be performed in a two-step manner:

Step 1) Puncture or prick test (inner volar aspect of the forearm): Using a 22-28-gauge needle, apply a small drop of skin test antigen to the test site, then puncture the epidermis using the same needle, do not draw any blood. Using separate needles, follow the same procedure for applying penicillin minor determinant mixture (MDM-penicillin G diluted with normal saline to a concentration of 10,000 units/ml), positive control (histamine base 1.0 mg/ml) and negative control (normal saline). Read in 15-20 minutes:

- a. If change in diameter of wheal is <3 mm than that observed with the negative control, test is negative, proceed to intradermal test
- b. If change in diameter of wheal is ≥ 3 mm that that observed with the negative control, test is positive. As soon as a positive response is observed, the solution should be wiped off the skin. Patient is **NOT** to receive penicillin.
- c. The positive control (histamine skin test) should be positive to ensure the results are not falsely negative.

Step 2) Intradermal test (upper, outer arm, sufficiently below the deltoid muscle or the inner volar aspect of the forearm) conducted only if the puncture or prick test is negative. Using a 26-30 gauge, short bevel needle, withdraw the contents of the ampule and inject a sufficient amount of benzylpenicilloyl polylysine to raise a small intradermal bleb of about 3 mm in diameter; in duplicate at least 2 cm apart. Mark the margins of initial bleb with a pen. Using separate syringes and needles, inject a like amount of penicillin G [MDM-diluted to 10,000 units/ml] in duplicate at least 2 cm apart and a single intradermal test using the negative control, spaced at least 5 cm apart from the antigen test sites. Read in 20 minutes:

- d. If there is no increase in the original bleb and no greater reaction than the negative control site, test is negative.
- e. If bleb or wheal increases >2 mm from its original size or is >2 mm larger than the negative controls, the test is positive. Patient is NOT to receive penicillin
- f. If the negative control (saline) site exhibits a wheal >2-3 cm, repeat the test. If the same reaction is observed, a provider experienced in allergy skin testing should be consulted.

Step 3) (Optional) Oral penicillin (e.g., amoxicillin 250 mg administered in a monitored setting for 45-60 minutes) challenge if both puncture and intradermal tests are negative. However, this step is considered as optional since these tests are rarely positive after negative skin testing.

5. WHAT ARE THE POTENTIAL ADVERSE EVENTS WITH PENICILLIN SKIN TESTING?

Some patients may develop an intense local inflammatory response at the skin test site. In rare cases, patients may develop systemic allergic reactions from skin testing with benzylpenicilloyl polylysine. These reactions may manifest as generalized erythema, pruritis, angioedema, and shortness of breath, hypotension and anaphylaxis. To minimize the risk of systemic reactions, a puncture skin test should be performed first. Intradermal skin testing should be performed only if the puncture test is entirely negative.

Because of the risk for systemic allergic reactions, including anaphylaxis, skin testing should be performed in an appropriate healthcare setting supervised by healthcare providers experienced and prepared to manage these types of reactions.

When treating a benzylpenicilloyl polylysine induced reaction, it is recommended that a venous occlusion tourniquet be applied proximal to the skin test site and epinephrine be administered. The patient should be kept under observation for several hours.

REFERENCES:

1. [HTTP://WWW.PREPEN.COM/FILES/PREPEN_PACKAGE_INSERT.PDF](http://www.prepen.com/files/prepen_package_insert.pdf) Benzylpenicilloyl polylysine (Pre-Pen) Product Labeling. 10/2009. ALK-Abello, Round Rock, TX 78664 (Accessed 5-22-12)
2. Bernstein IL, Li JT, Bernstein DI, et al. Allergy Diagnostic Testing: An Updated Practice Parameter. *Annals of Allergy, Asthma and Immunol* 2008;100:S1-S148.
3. Management of Persons Who Have a History of Penicillin Allergy. CDC 2010. <http://www.cdc.gov/std/treatment/2010/penicillin-allergy.htm> (Accessed 5-22-12)