Penicillin Skin Allergy Testing

Penicillin allergy testing can be performed safely on hospitalized patients and suggests improved outcomes, less vancomycin use, and potential cost savings.1

Approximately 10% of the general population and up to 20% of hospitalized patients claim an “allergy” to penicillin; however, the majority of these patients are not truly allergic when assessed by skin testing.2

- In an era of rising antibiotic costs and growing antibacterial resistance, a patient’s uncertain allergy history can force a prescriber to choose a drug that may not be optimal.2
- Carrying an inaccurate diagnosis of penicillin “allergy” could adversely affect the quantity and quality of health care used.1
- Penicillin allergy skin testing improved access to the most appropriate antibiotics without having a negative impact on patient safety or outcomes.3

IMPLEMENTING PENICILLIN ALLERGY SKIN TESTING IN YOUR FACILITY MAY BRING THE FOLLOWING BENEFITS:

Combatting Drug Resistance

- Drug allergy history is associated with increased hospital use over the next several years and significantly higher rates of serious infections.3
- Recent studies state, patients claiming a penicillin allergy (compared to the control subjects) had:

  - 23% higher incidence of C. difficile1
  - 14% higher incidence of MRSA1
  - 30% higher incidence of VRE infections1

- Current literature supports the role of penicillin allergy skin testing within various practice settings as an intervention for improving patient care by reducing the use of alternative antibiotics.3
- Antibiotic-resistant infections cost the US Healthcare system in excess of $20 billion annually, as reported by the Alliance for the Prudent Use of Antibiotics.4
Reduction in Cost

- Penicillin skin testing frequently allowed for less expensive agents that would have been avoided due to a reported allergy, saving $82,000 amongst the patients involved in the study.5
- Penicillin skin testing is the most rapid, sensitive, and cost-effective modality for evaluating patients with immediate allergic reactions to penicillin.5

Antimicrobial Stewardship Support

- The increased use of penicillin skin testing may help improve antibiotic stewardship in the hospital setting.5
- Penicillin skin testing may serve as a novel tool preserving provider autonomy in antibiotic prescribing and breaking down barriers to using preferred therapeutic agents, including B-lactams, if clinically indicated.3
- Penicillin allergic patients are significantly more likely to receive fluoroquinolones, vancomycin, and clindamycin than non-allergic patients.1

Introduction of penicillin allergy skin testing may allow trained healthcare providers to prescribe cheaper, more appropriate, less toxic antimicrobial agents.

References
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 (55-70%) forming benzylpenicilloyl alpha amide. Each single dose ampule contains 0.25 mL of PRE-PEN.

PRE-PEN has the following structure:

\[
\text{R-Benzylpenicilloyl - H}
\]

**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 penicillloyl IgE antibodies which are necessary but not sufficient for acute allergic reactions due to the major penicillloyl 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 (phenoxy-methyl penicillin, ampicillin, carbenicillin, dicloxacinil, methicillin, nafillin, oxacillin, amoxicillin), cephalosporin-derivated 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.

**ADVERSE REACTIONS:**
AMMmatory response at the skin test site.

**DOSAGE AND ADMINISTRATION:**
**SKIN TESTING DOSAGE AND TECHNIQUE**
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 scratch. 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 than 5 mm wheal with little or no erythema and no itching), an intradermal test may be performed.

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**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.

**SKIN TESTING DOSAGE AND TECHNIQUE**
Skin testing responses can be attenuated by interfering drugs (e.g. H1-antihistamines and vasoressors). 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 vials. Due to the low incidence of potential systemic allergic reactions, skin testing should be performed in an appropriate healthcare setting under direct medical supervision.

**Puncture Testing:**
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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:**
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 fingers 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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