



Penicillin Allergy Skin Testing

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Disclosures

- I have nothing to disclose



Why do penicillin allergy testing?

- Most patients (>95%) who think they are allergic to penicillin are not
- Most labels start at age 3 or earlier and stick
- Most diagnoses are not true penicillin allergy
- Those that were true fade over time (almost all gone by 10 years)
- Significant personal and public health outcomes result from the label
- Large burden of labels in US and internationally requires a coordinated effort
- WIDESPREAD EDUCATION IS PIVOTAL



Penicillin Allergy Skin Testing

- **WHO**

- Almost anyone with a past history of an immediate or accelerated reaction temporarily associated with a penicillin that has potentially allergic symptoms
 - rash, itching, respiratory symptoms, hemodynamic instability, nausea/abdominal pain in association with other symptoms
- Patients with isolated nausea, vomiting, diarrhea, headache are not allergic and can be reassured or go straight to oral challenge
- Patients with serious delayed reactions with severe cutaneous reactions or fever/hepatitis, etc. should be excluded



Adverse Effects of Penicillin Allergy Labels

- **What** are the consequences of a penicillin allergy label:
 - Less effective drug = antimicrobial treatment failures and higher mortality
 - More surgical site infections
 - More antimicrobial treatment failures
 - Longer hospital stay and greater health care costs
 - infection with multidrug resistant organisms (MRSA, VRE, C. diff) = negative consequences for individual and public health (risk for spread to other individuals)



How Can Addressing the Penicillin Allergy Help?

- Validated testing exists that can help safely remove the penicillin allergy label
- This includes skin testing and an oral challenge
- The chance of having a “reaction” in the face of negative testing is <1% (safer than all other allergy testing) and most reactions are mild
- Hence penicillin allergy testing is primarily used for its high negative predictive value.



“Toolkit” for Penicillin Allergy Testing (HOW)

- **Trained staff**
- Skin prick applicators for epidermal prick testing
- Tuberculin skin test syringes for intradermal testing
- Appropriate reagents, including:
- Bare minimum:
 - Histamine (positive control)
 - Saline (negative control)
 - The penicillin allergy major determinant (commercial version Pre-Pen)
- Additional reagents that we typically use:
 - Penicillin G
 - Ampicillin (North America), Amoxicillin used frequently in Europe and Australia either as commercialized or “in house made” reagents
- For intradermal testing of these should be available in sterile formulation.
 - There are commercially available kits that include these reagents
 - Or some institutions have pharmacy compounding services that can make them.
- **Anaphylaxis kit for management of allergic reactions**



Example of an anaphylaxis kit



Key components = epinephrine, a bronchodilator, a steroid (hydrocortisone, prednisone), antihistamine (H1 + H2) (cetirizine and diphenhydramine (Benadryl), famotidine)



Example: Anaphylaxis kit ingredients

Includes:

Medications:

- Epinephrine 0.3mg dose, multiple
- Albuterol inhaler
- Cetirizine tablets 10mg
- Diphenhydramine oral solution 12.5 mg/5 ml
- Diphenhydramine injectable 50mg/ml
- Famotidine oral tablets 20mg
- Hydrocortisone injection 100mg/ml
- Prednisone 20mg oral tablets
- Saline flushes 10ml
- Normal Saline 1000ml
- Glucagon

Equipment:

- 25 gauge 1" needle
- 25 gauge 1 1/2" needle
- Filter needle/straw
- 1 ml syringes
- 3 ml syringes
- Alcohol pads
- IV start kit
- Infusion set
- Extension set
- Microclave connector
- 22G Jelco
- 24G Jelco



HOW: Preparing for Skin Testing

- Ideally, patients should pause use of any drugs that have anti-histaminic properties
- This can also include tricyclic anti-depressants (eg. doxepin and amitriptyline and antipsychotics).
- Each clinic should have a list of drugs to avoid prior to testing.
- Many drugs DO NOT have to be avoided (E.g. SSRI antidepressants, proton pump inhibitors, most drugs for diabetes and hypertension)
- Beta-blockers may need to be held up to 48 hours prior to testing
 - Depends on patient history (risk for true anaphylaxis)
 - Response to treatment for anaphylaxis (eg epinephrine) is blunted in patients on beta-blockers however in most low risk patients the risk of stopping the beta-blocker may outweigh any risk of not stopping them.



HOW: Performing Skin Prick Testing

- First perform a standard baseline physical examination with vital signs and peak flow measurements
 - Ideally document or note any pre-existing skin rashes and condition of skin (easy bruising, dermatographism etc).
- Optimal site is the volar surface of the forearm or the extensor surface of the upper arm
- Next, prepare the skin to be tested using a sterile alcohol swab
 - Make sure the skin you are testing is clean, dry, and intact
- Mark the sites where you plan to place your allergen tests using a marker (we can show picture of this) that will remain for 24 hours or so (for delayed reactions)



Skin Prick Testing - HOW

- Concentrations of reagents have been validated in previous studies on controls and patient populations
 - appropriate strength to be non-irritating and non-histamine releasing in the absence of allergy
- Test is performed using a standard epidermal allergy applicator and a drop of each reagent
- Placed using a simple technique with a small amount of pressure
- Skin prick testing for immediate drug reactions is interpreted at 15-20 minutes after placement, comparing reagents to controls



Intradermal Testing

- Intradermal testing is placed using a tuberculin syringe, but the volume used (0.02 ml) is small and the technique differs (only a tiny bleb is raised)
- These results are also interpreted at 15-20 minutes after placement, comparing reagents to controls.



Intradermal test application



Interpretation of Penicillin Allergy Skin Testing

- How good are my controls?
- Histamine control:
 - Your histamine skin prick control should be clearly positive. This includes a wheal size greater than 3mm and erythematous flare around it.
 - Common reasons for negative histamine: Placement location, inhibition by patient medications
- Saline control
 - Your saline control should be clearly negative.
 - Common reasons for positive saline : dermatographism, chronic urticaria



Positive Penicillin Allergy Skin Test



Terminology:

Wheal: The raised portion of the test, measured across its widest diameter

Flare: The erythematous portion of the test, measured across its widest diameter



Positive Penicillin Allergy Skin Test

- Read at 15-20 minutes after placement
- Differing guidelines for a positive test:
 - Wheal of at least 5 mm with flare greater than wheal
 - Wheal > 3 mm from baseline with a flare at least 5 mm greater than baseline



Pitfalls of Penicillin Allergy Testing

- False positives: Up to 50% in some series. Clinical history is important.
 - Rarely there may be need to proceed to a double blind challenge
- False negatives
 - Patients on prolonged antihistamines and critically ill patients (empty mast cells) at highest risk.
 - When skin testing is negative most reactions that occur with lower dose oral challenge (e.g. 250 mg of amoxicillin) are very mild

IMPORTANT POINT: Antihistamines may be a cause for a false negative reaction but they will not prevent a true IgE-mediated reaction on oral challenge



Safety of Testing

- Basic penicillin testing is incredibly safe and can be performed routinely in most allergy practices in the US
- Testing procedure can be completed within 2 hours
- At end of testing with negative results can rule out risk for an immediate reaction to penicillins



Post-procedure observation and care

- Photographic documentation of skin testing is advised when possible (most EHR now accommodate this)
- Topical diphenhydramine and hydrocortisone can be applied to positive histamine control and other positive skin testing to control short lived symptoms such as pruritus



Oral challenge to penicillin or amoxicillin

- Allergists do not consider penicillin allergy skin testing to be the gold standard for penicillin allergy label removal.
 - The most important question is “Does the patient tolerate the drug?”
- All negative skin tests should be followed by some form of oral challenge to a penicillin to definitively prove safety.
 - Good tolerance of amoxicillin rules out immediate hypersensitivity to penicillins
 - The patient’s risk of a future delayed skin reaction is not excluded, but is the same as the 2-5% risk of the general population.



After-Visit Care for a Patient with Negative Testing

- Remove the label from the EHR!
- Provide patient with documentation for their outside providers and pharmacy
- Ideally communicate findings directly to patient's pharmacy from clinic
- Negative testing means that patient does not have a risk of an immediate reaction; risk of delayed rash is at population baseline of 2-5%



Post-visit care for Patient with Positive Penicillin Skin Testing

- Reinforce label and its severity in the EHR
- Provide patient with documentation for their outside providers and pharmacy
- Ideally communicate directly with patient's pharmacy, from clinic
- Even positive tests can wane with time and re-testing in 5 years should be considered
- With low severity histories consider false positive skin test
- With high severity histories there should be communication to avoid all penicillins, cephalosporins, carbapenems until further skin testing and a specialty assessment can be done done
 - Consider the potential for cross-reactivity based on shared R1 side chains (E.g. ampicillin and cephalixin)



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