Beta-Lactam allergies and the role of penicillin skin testing

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Disclosures

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- My comments are my best recommendations and are not officially the position of the AAAAI.
Beta-Lactam allergies and the role of penicillin skin testing

- **Penicillin skin testing**
  - Is useful in predicting IgE mediated reactions to penicillin class antibiotics.
  - Need to be followed by an oral challenge if skin test negative.
  - Does not help predict cephalosporin or other beta-lactam reactions and should not be done for these indications.

- **Cephalosporin skin testing**
  - Is only useful in predicting specific IgE mediated reactions to the specific cephalosporin used for testing.

- **Other Beta-lactam skin testing**
  - Is only useful in predicting specific IgE mediated reaction to the specific other beta-lactam used.
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Who can you test or challenge?
- Patients who have a history of anaphylaxis, respiratory problems, hives, local swelling at the site of injection, other rashes, gastrointestinal symptoms, unknown index symptoms, and other mild symptoms not specifically excluded below

Who should not be tested or challenged?
- Anyone with a history compatible with Stevens-Johnson Syndrome, toxic epidermal necrolysis, hemolytic anemia, nephritis, severe hepatitis, or oral and/or skin blisters associated with or attributed to previous penicillin class antibiotic use
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- Patients with a history of penicillin allergy who are skin test negative will have an adverse reaction about 3% of the time to any oral antibiotic.
- Cephalosporins are safely used in penicillin skin test positive individuals.
- Penicillin allergy is becoming less frequent. Currently less than 5% of history positive individuals are skin test-positive or oral challenge-positive if skin test-negative.
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- Oral challenges are a safe way of evaluating children with most beta-lactam associated rashes. Cephalosporins are safely used in penicillin skin test positive individuals.
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- Commercial anti-penicillin FEIAs (Phadia)
  - Penicilloyl G – c1
  - Penicilloyl V – c2
  - Amoxicilloyl – c6

- Very poor correlation to skin test and oral challenge results
- Not clinically useful
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- Reactions to oral penicillins in skin test positive individuals can start up to 24 hours after ingestion.
- Females are not more likely to be penicillin skin test positive than males if 5 mm is used as the cut off for a positive penicillin skin test.
- Puncture positive individuals are extremely allergic and have high rates of testing associated reactions.
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- Use Pre-Pen as supplied.
- Use native penicillin at 0.01 molar.
- Use amoxicillin at 0.01 molar (3.6 mg/ml).
- The high rates of false positives noted in the European literature is associated with using amoxicillin at 20 to 25 mg per ml which is 6 to 7 time more concentrated than recommended. The limit of solubility of amoxicillin in water at pH = 7 is 4 mg/ml.
- Use cephalosporins and other beta-lactams at 0.01 molar.
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- Oral challenge are essential after skin testing to avoid false negative skin testing and to identify T-cell mediated reactors.
- Skin testing with the minor determinants, penicilloate and penilloate, is not necessary.
- Challenge with amoxicillin 250 mg orally and observe for 1 hour.
- Give an oral challenge prior to parenteral penicillin use.
- Delayed onset T-cell reactions typically occur within 2-3 days.
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- **Potassium Penicillin G**
  - FW = 372.48 gm/mole
  - Supplied as 5 million unit vials = 3.134 gm
  - 1mg of Potassium Penicillin G = 1595 units
  - 0.01 Molar Potassium Penicillin G = 3.725 mg/ml or 5941 units/ml
  - Can be stored for 1 week in at 4° C as a concentrated stock solution
  - Make new working dilutions daily.
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- **Amoxicillin**
  - Amoxicillin [A8523 - Sigma-Aldrich.com] (C16H19N3O5S) (FW 365.4)
  - Weigh out 0.3654 gms of Amoxicillin
  - Dissolve in 80 ml of Tris buffered normal saline at pH 7.4.
  - Re-adjust pH to 7.4, bring to 100 ml total volume with buffer.
  - Pass through a sterile 0.22 μm filter.
  - Aliquot into sterile 1 ml vials @ 0.2 ml/vial.
  - Each 100 mls will make 500 unit dose vials.
  - Store at -70°C
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- A buffered saline negative control and a histamine (1 mg/ml for prick tests and 0.1 mg/ml for intradermal tests) positive control are placed at the start of each round of tests.
- Drops of each reagent are placed on the outer surface of the upper arm and pricked using a different DUOTIP-TEST® device for each drop.
- Following a 15 minute waiting period, skin prick reactions are read and recorded.
- The mean diameter of the wheal over the mean diameter of the flare or surrounding erythema is measured in millimeters.
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- Positive responses consist of a wheal of 5 mm or more in diameter with surrounding erythema greater than the wheal, a negative response to the control solution, and a positive response to histamine.
- If all tests are negative by skin prick then intradermal (ID) testing is performed using the outer surface of the other upper arm.
- Using the same reagents, 0.02 mls of each reagent is administered ID through individual 27 gauge tuberculin syringes.
- ID tests are also read and recorded after 15 minutes.
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- Positive responses consist of a wheal of 5 mm or more in diameter with surrounding erythema greater than the wheal, a negative response to the control solution, and a positive response to histamine.
- If any puncture test was positive, no ID tests are done with any of the remaining negative reagents.
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Penicillin Skin Testing

Penicillin skin test individuals with a history of an adverse reaction that is potentially IgE mediated. Do not perform penicillin skin test if there is a history of a blistering rash, oral lesions, drug induced anemia or hepatitis associated with a penicillin class antibiotic exposure, or if no history of penicillin exposure. Penicillin skin testing is not useful in evaluating cephalosporin associated reactions. Do not perform penicillin skin test if a penicillin class antibiotic has been used and tolerated since the index reaction.

Test performed by: ________________ Test ordered by: ________________
Last Name: ________________________ Patient #: ______________________
First Name: ________________________ Date of test: __ / __ / _____
Date of birth: _____ / _____ / _____ Gender: (M / F)
Date of index penicillin adverse reaction: _____ / _____ / _____
Infection index penicillin used for: (URI, otitis media, sinusitis, pneumonia, skin, VD, other list __________________________)
Route of administration: (oral / parenteral)
Time to onset: (< 1 hour / 1-24 hours / 25 – 72 hours / > 73 hours)
Type of index reaction: (fixed rash, lesions > 24 hours / hives, lesions < 24 hours / angioedema / shortness of breath / hypotension / GI / other list __________________________)
Treatment of index reaction: (stopped penicillin only / antihistamine / epinephrine / systemic steroid / other list __________________________)
Place and read all puncture tests prior to placing any intradermal tests. Positive tests are defined as wheal ≥ 5 mm with flare > wheal. Do not record test if saline control positive or histamine control negative.

Puncture

<table>
<thead>
<tr>
<th>Time placed: _____</th>
<th>Time read: _____</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Penicilloyl-polylysine</td>
<td>_____</td>
</tr>
<tr>
<td>2) Penicillin (0.01M)</td>
<td>_____</td>
</tr>
<tr>
<td>3) Amoxicillin (0.01M)</td>
<td>_____</td>
</tr>
<tr>
<td>4) Buffer Control</td>
<td>_____</td>
</tr>
<tr>
<td>5) Histamine</td>
<td>_____</td>
</tr>
</tbody>
</table>

Intradermal

<table>
<thead>
<tr>
<th>Time placed: _____</th>
<th>Time read: _____</th>
</tr>
</thead>
<tbody>
<tr>
<td>6) Penicilloyl-polylysine</td>
<td>_____</td>
</tr>
<tr>
<td>7) Penicillin (0.01M)</td>
<td>_____</td>
</tr>
<tr>
<td>8) Amoxicillin (0.01M)</td>
<td>_____</td>
</tr>
<tr>
<td>9) Buffer Control</td>
<td>_____</td>
</tr>
<tr>
<td>10) Histamine</td>
<td>_____</td>
</tr>
</tbody>
</table>

Skin test reaction: (None / list ____________) Treatment given: (None / list ____________)
Oral Challenge: (Penicillin 500mg, Amoxicillin 250mg) Time: ____________
Challenge reaction: (None / list ____________) Time of onset: ____________
Treatment given: (None / list ____________)
Delayed reaction reported: (None / list ____________ ) Time to onset: _______
<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Males (95% CI)</th>
<th>Females (95% CI)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfa class</strong></td>
<td>2.23%&lt;sup&gt;a&lt;/sup&gt; (1.91, 2.59)</td>
<td>3.42%&lt;sup&gt;a&lt;/sup&gt; (3.13, 3.74)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Penicillins</strong></td>
<td>1.11%&lt;sup&gt;b&lt;/sup&gt; (1.01, 1.24)</td>
<td>1.45%&lt;sup&gt;b&lt;/sup&gt; (1.34, 1.57)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
<td>0.47%&lt;sup&gt;d&lt;/sup&gt; (0.36, 0.62)</td>
<td>1.27%&lt;sup&gt;d&lt;/sup&gt; (1.11, 1.46)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td>0.60%&lt;sup&gt;d&lt;/sup&gt; (0.49, 0.72)</td>
<td>1.08%&lt;sup&gt;d&lt;/sup&gt; (0.96, 1.21)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td>0.52%&lt;sup&gt;d&lt;/sup&gt; (0.38, 0.72)</td>
<td>1.34%&lt;sup&gt;c&lt;/sup&gt; (1.13, 1.58)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Quinolones</strong></td>
<td>0.52%&lt;sup&gt;d&lt;/sup&gt; (0.42, 0.65)</td>
<td>1.01%&lt;sup&gt;d&lt;/sup&gt; (0.89, 1.14)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
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References

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References