Drug “Allergy”
A practical update

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Drug “Allergy’

- Definitions
- Incidence and prevalence
- Mechanisms
- Skin testing
- In Vitro testing
- Desensitization
- Challenges
- Selected references
Drug “Allergy”

 Definitions
  • Adverse Drug Reaction
  • Drug Allergy = IgE Mediated
  • Immunologically Meditated Reactions
    ▪ Antibody
    ▪ T-Cell
  • Direct Mast cell activation
  • Cytokine associated

Drug “Allergy”

 Prevalence
  • About 22% report at least one drug allergy
  • Females > Males
  • Old > Young
  • Antibiotics account for >50% of reports
  • Narcotics 13.9% of reports
  • NSAIDs 7.7% of reports
Drug "Allergy"

- Incidence of antibiotic allergy
  - Females about twice as high as males for most antibiotic classes, about 0.5% for males and 1.1% for females.
  - Sulfa: females 3.42%, males 2.23%
  - Penicillin: females 1.45%, males 1.11%

### Antibiotic Allergy Incidence

<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>Sulfa class</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>Penicillins</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>Tetracyclines</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>Cephalosporins</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>Macrolides</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>Quinolones</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>
Drug "Allergy"

- Multiple Drug "Allergy" Syndrome
  - Most are Female
  - Most are elderly
  - Most have depression or other serious mental illness
  - Most have no allergy
  - Most can be challenged with the drugs they truly need and tolerated them
  - Avoid unnecessary drug use as much as possible

- IgE mediated Drug Allergy
  - Antigen specific IgE mediated with mast cell degranulation
  - Predicted by skin testing
  - Predicated by direct measurement of antigen specific IgE
  - Requires intact protein antigens (MW>5000), materials that will haptenate proteins, or bifunctional small molecules that can cross link IgE
  - Requires sensitization
Drug "Allergy"

- Immunologically Mediated Reactions
  - IgG with Compliment
    - Serum sickness
    - Interstitial nephritis
    - Hemolytic anemia
    - Auto-antibodies, drug induced lupus
  - T-Cell
    - Contact Dermatitis
    - Some photo-sensitivities

- Mast Cell Activation
  - IgE via the high affinity Fcε Receptor
  - Direct Effect
    - NSAIDs, Opiates
    - IV Contrast (Hyperosmolar agents)
    - Auto antibodies (Anti-Fcε Receptor)
Drug "Allergy"

- **Cytokine**
  - Direct Effect
    - IL-2 (fatigue, flu like symptoms, edema, rashes)
  - Cytokine Release
    - IL-1 (promotes IL-2, IL-6, IL-8, and GM-CSF secretion)
    - Anti-CD-3 (kills T cells)
  - Cytokine Overproduction
    - Fas ligand
  - Cytokine mimicry
    - TGN1412, humanized monoclonal superagonist of the CD28 T cell surface receptor
  - Cytokine Inhibition
    - Anti-IL-6 receptor

Drug "Allergy"

- **TEN/SJS**
  - Risk factors predicting developing TEN or SJS in patients with Erythema Multiforme
    - Existing co-morbidities (other systemic illness)
    - History of “drug allergy”
    - Anti-epileptic medication use
    - Anti-microbial use
Drug "Allergy"

What Allergists need to be comfortable doing
- Penicillin skin testing and oral challenges
- Sulfonamide challenges
- Protein skin testing
- Local anesthetic challenges
- Aspirin and NSAID challenges and desensitization
- Cancer chemotherapeutic testing and desensitization/challenge
- Patch testing for contact sensitivities (often done in Dermatology)

Drug "Allergy"

Skin Testing
- Do not test, desensitize, or challenge
  - Toxic epidermal necrolysis
  - Stevens Johnson syndrome
  - Hemolytic anemia
  - Severe hepatitis
  - Nephritis
  - Oral and/or skin blisters
Drug "Allergy"

- Skin Testing
  - OK to test, desensitize, or challenge
    - anaphylaxis
    - respiratory problems
    - hives
    - other rashes
    - local swelling at the site on injection
    - gastrointestinal symptoms
    - unknown symptoms
    - other symptoms not specifically excluded

Drug "Allergy"

- Whole protein skin testing
  - Use honeybee venom as a model
    - Latex
    - Biological agents (recombinant proteins)
    - Enzymes
Drug "Allergy"

- **Penicillin Skin Testing**
  - Penicilloyl-poly-lysine (6 x 10^{-5} molar)
  - Native Penicillin (0.01 molar)
  - Penilloate, penicilloate, and amoxicillin are not needed
  - Commercial ELISAs are not useful
  - Oral challenges are essential

- **Penicillin Skin Testing**
  - Puncture testing prior to intradermal testing
  - Testing reactions are more common in puncture positive individuals
  - Positive tests are 5 mm or larger with erythema > wheal
  - Oral challenge all negative individuals
Drug "Allergy"

- Penicillin Oral Challenge
  - Amoxicillin 250 mg, observe for 1 hour
  - Penicillin 500 mg, observe for ½ hour then Bicillin 2.4 million units and observe for 1 hour
  - Itch without rash is not a “reaction”
  - Many reactions start up to 2 days after challenge, have patients call in to report

Drug "Allergy"

- Local anesthetic testing
  - Use lidocaine with methylparaben
  - Challenge with saline after negative skin tests

- Preservatives and Excipients
  - Polysorbate
  - Polyoxylated castor oil
Penicillin Skin Testing

**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.

## Penicillin Skin Testing

**Penicillin Skin Testing**
- Data collection Sheet
- San Diego Allergy Department

- Penicillin skin test individuals with a history of an adverse reaction that is potentially IgE mediated. Do not perform skin test if there is a history of a bystander reaction, oral lesions or angioedema associated with penicillin class antibiotic exposure, or if no history of penicillin exposure. Penicillin skin testing is not specific to evaluating cephalosporin associated reactions. Do not perform skin test if penicillin class antibiotic has been used and tolerated since the index reaction.

- Test performed by: __________
- Test ordered by: __________
- Patient's name: __________
- Date of birth: __________
- Gender: __________
- First name: __________
- Last name: __________
- KP #: __________
- Date of index penicillin adverse reaction: __________
- Date of birth: __________
- Gender: __________
- First name: __________
- Last name: __________
- KP #: __________

**Infection index penicillin used for:** (URI, otitis media, sinusitis, pneumonia, skin, UD, other list)

**Type of index reaction:**
- **Fixed rash, lesions > 24 hours**
- **Hives, lesions < 24 hours**
- **Angioedema**
- **Shortness of breath / hypotension**
- **GI**
- **Other list**

**Time to onset:**
- (< 1 hour / 1-24 hours / 24-72 hours / > 72 hours)

**Route of administration:** (oral / parenteral)

**Treatment of index reaction:**
- (stopped penicillin only / antihistamine / epinephrine / systemic steroid / other list)

**Oral Challenge:**
- (Penicillin 500mg, Amoxicillin 250mg)
- Time: __________
- Treatment given: (None / list)
- Challenge reaction: (None / list)
- Time of onset: __________

**Skin test reaction:**
- (None / list)
- Treatment given: (None / list)

**Intradermal**
- Penicilloyl-polylysine
- Penicillin (0.01M)
- Amoxicillin (0.01M)
- Buffer Control
- Histamine
- Time placed: __________
- Time read: __________
- Treatment given: (None / list)

**Puncture**
- Penicilloyl-polylysine
- Penicillin (0.01M)
- Amoxicillin (0.01M)
- Buffer Control
- Histamine
- Time placed: __________
- Time read: __________
- Skin test reaction: (None / list)

**Delayed reaction reported:** (None / 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.**

San Diego Allergy Department

Data collection Sheet

Penicillin Skin Testing

**Histamine**

**Buffer Control**

**Penicillin (0.01M)**

**Amoxicillin (0.01M)**
Drug "Allergy"

- Desensitization – for IgE mediated reactions
  - Oral if possible
  - Start with about twice the dose used for intradermal skin testing
  - Double dose every 20 minutes
  - Give continued medication
  - Repeat desensitization if lapse in coverage (> 2 half lives)

Drug "Allergy"

- Challenges for non-IgE mediated reactions (Sulfonamide model)
  - Oral if possible
  - Slowly increase dose over a period of days
  - Expect delayed onset reactions.
  - OK to do at home.
  - Stop if significant rash occurs.
Drug "Allergy"

- In Vitro Tests
  - Non-specific Tests
    - Tryptase
  - Antigen specific ELISAs
    - Latex

Drug "Allergy"

- Latex FEIAs done at KPSC
  - 6109 done 9-7-2004 to 5-5-2010
  - 808 (11.7%) were “positive” 0.35 to 118 units
  - 424 (6.1%) were > 1 unit
Penicillin Allergy Testing

<table>
<thead>
<tr>
<th>First Author (year)</th>
<th>Subjects</th>
<th>PST positive N (%)</th>
<th>RAST or FIEA positive N (%)</th>
<th>Both positive N (%)</th>
<th>PST negative Oral challenge positive N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macy (2010)</td>
<td>150</td>
<td>6 (4.0%)</td>
<td>4 (2.7%)</td>
<td>0</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Silva (2009)</td>
<td>54</td>
<td>6 (11.0%)</td>
<td>8 (14.8%)</td>
<td>1 (16.6%)</td>
<td>2 (4.9%)†</td>
</tr>
<tr>
<td>Sanz (1996)</td>
<td>149</td>
<td>44 (29.5%)</td>
<td>26 (17.4%)</td>
<td>14 (31.8%)</td>
<td>Not Done</td>
</tr>
<tr>
<td>Jarish (1981)</td>
<td>51</td>
<td>17 (33.3%)</td>
<td>12 (23.5%)</td>
<td>11 (64.7%)</td>
<td>Not Done</td>
</tr>
<tr>
<td>Basombaba (1979)</td>
<td>81</td>
<td>63 (77.8%)</td>
<td>37 (45.7%)</td>
<td>36 (57.1%)</td>
<td>Not Done</td>
</tr>
<tr>
<td>Totals</td>
<td>485</td>
<td>136 (28.0%)</td>
<td>87 (17.9%)</td>
<td>62 (45.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Drug "Allergy"

- **Selected References**
  - Macy E, Schatz M, Zeiger RS. Immediate hypersensitivity to methylparaben causing false-positive results of local anesthetic skin testing or provocative dose testing. The Permanente Journal, 2002;6:17-21
  - Macy E. Multiple Antibiotic Allergy Syndrome. Immunol Allergy Clin N Am 2004;24;533-43
Drug "Allergy"

Selected References