Penicillin Allergy: Does it Exist?
A review of penicillin allergy and other allergic conditions that will change the way you practice

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Disclosures

- **Grants:** Shire, Regeneron, CSL Behring
- **Speaker’s Bureau:** CSL Behring, Genentech, Teva, Astrazeneca, Regeneron
Outline

- Overview of allergy/clinical immunology
- Drug allergy
  - Penicillin allergy
  - Local anesthetic allergy
- Upper airway pathology
- Contact dermatitis
- Latex allergy
- Management
  - Acute
  - Long term
What We Treat

- Chronic rhinitis
  - Allergic and non-allergic
- Chronic sinusitis
- Asthma
- Adverse reactions to foods
- Atopic dermatitis
- Contact dermatitis
- Adverse reactions to drugs
  - PCN allergy
- Urticaria/angioedema
- Anaphylaxis
- Sting insect allergy
- Immunodeficiency
  - Primary and secondary
- Eosinophilia
  - Eosinophilic esophagitis
- Miscellaneous
  - Mastocytosis
  - Vaccinology
  - Vasculitis
  - Vocal cord dysfunction
Our Specialty

- Rhinitis
- Asthma
- Eczema
- Food Allergy
Skin Testing

Allergen solution is placed on skin

Positive test: Skin is red and itchy

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ROCHESTER REGIONAL HEALTH
Classification of Drug Reactions

Penicillin Allergy

- Most commonly reported medication allergy
- Public health implications
  - Alternative antibiotics regimens are not reflective of the standard of care
  - Increased cost of care
  - Increased risk of complications
  - Increased length of inpatient hospitalization
- > 90% of “PCN allergic” individuals can safely tolerate PCNs and related antibiotics
Penicillin Allergy

- 10% of individuals will experience a delayed, maculopapular rash with amoxicillin
- Nearly 100% of individuals with EBV will experience a rash if exposed to PCN

<table>
<thead>
<tr>
<th>Loss of Allergy Over Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since Rxn</td>
</tr>
<tr>
<td>Resolution</td>
</tr>
</tbody>
</table>
Viral Exanthem Versus Urticaria
PCN Allergy Evaluation

Did You Know?

- Penicillin allergy has been linked to longer and costlier hospital stays.

- Ninety percent of patients who claim a penicillin allergy are not truly allergic. They can safely take penicillin and related antibiotics.

- Patients with a penicillin allergy are more likely to be prescribed other antibiotics. These may be more expensive, less effective and more likely to cause greater side effects.

- Some alternative antibiotics can lead to severe diarrhea caused by a germ called *Clostridium difficile*, also known as *C. diff*.

To discuss penicillin skin testing with an allergist or to set up an appointment:

Allergy, Immunology and Rheumatology Office Locations

**Rochester/Alexander Park**
222 Alexander St.
Ste. 3000
Rochester, NY 14607

**Greece**
2300 West Ridge Rd.
Fifth Floor
Rochester, NY 14626

**Penfield/Linden Oaks**
10 Hagen Dr.
Ste. 20
Rochester, NY 14625

P 585.922.8350
F 585.922.8355

PCN Allergy Skin Testing

- Major determinant: BPO (benzyl penicilloyl)
- Minor determinants: penicilloate, penilloate, PCN G
- Well studied and validated skin test reagents
  - NPV nearly 100% for anaphylaxis
  - NPV ~97% for IgE mediated allergy
  - PPV ~60%
- No role for in vitro IgE testing or ELISA
Our Experience

**Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients screened</td>
<td>2465</td>
<td></td>
</tr>
<tr>
<td>Patients with reported PCN allergy</td>
<td>363</td>
<td>14.7%</td>
</tr>
<tr>
<td>Patients completing PCN evaluation</td>
<td>185</td>
<td>51.0%</td>
</tr>
<tr>
<td>Males (%)</td>
<td>117</td>
<td>32.2%</td>
</tr>
<tr>
<td>Females (%)</td>
<td>246</td>
<td>67.8%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.3 ± 25.3</td>
<td></td>
</tr>
<tr>
<td>New patient evaluation</td>
<td>207</td>
<td>57%</td>
</tr>
</tbody>
</table>

**Chief Complaint**

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCN/drug allergy</td>
<td>82</td>
<td>22.6%</td>
</tr>
<tr>
<td>Chronic rhinitis/sinusitis</td>
<td>80</td>
<td>20.0%</td>
</tr>
<tr>
<td>Asthma</td>
<td>70</td>
<td>19.3%</td>
</tr>
<tr>
<td>Food allergy</td>
<td>43</td>
<td>11.8%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>31</td>
<td>8.5%</td>
</tr>
<tr>
<td>Other</td>
<td>57</td>
<td>15.7%</td>
</tr>
</tbody>
</table>

**Time Since Reported Reaction**

- < 1: 23 (9.1%)
- 1 to < 5: 63 (24.4%)
- 5 to < 10 Years: 58 (24.4%)
- 10+: 191 (75.9%)
- Unknown: 28 (11.3%)

**Reported Reaction History**

- Interfering Medications: 171 (68.8%)
- Time Constraint: 109 (44.0%)
- Scheduled for PST or DC: 13 (5.3%)
- Other: 9 (3.6%)
- Delayed Reaction: 9 (3.6%)
- Anxiety/Needle Fear: 8 (3.2%)
- Recent Reaction: 8 (3.2%)
- Recent Positive PST: 8 (3.2%)

Ramsey and Mustafa. JACI IP 2018. 6(5): 1756.
# Graded Challenge Versus PCN SPT

| Randomized PCN Allergy Evaluations | | | |
|------------------------------------|---------------------------------|---------------------------------|
|                                    | PCN SPT                         | Graded Challenge                | Difference                    |
| Patients                           | 80                              | 79                              |                               |
| PST Positive / GC Fail             | 10 (12.5%)                      | 3 (3.8%)                        | 8.7% (p=0.079)                |
| PST Negative / GC Pass             | 70 (87.5%)                      | 76 (96.2%)                      |                               |
| Time (minutes)                     |                                 |                                 |                               |
| Mean, SD                           | 72.7 (5.3)                      | 66.7 (4.8)                      | 6.0 (p< 0.001)                |
| Median, IQR                        | 73.5 (68.8-75.3)                | 66.0 (62-70)                    | 7.5 (p< 0.001)                |
| Cost                               |                                 |                                 |                               |
| Each                               | $393.66                         | $53.66                          | $340.00                       |
| Total                              | $29,092.80                      | $4,239.14                       | $24,853.66                    |

Mustafa et al. AAAAI Annual Meeting 2019 Abstract.
Penicillins and Cephalosporins

- 2% cross reactivity in patients with + PCN SPT
- Cross reactivity decreases from 1st to 4th generation

Staicu et al. All All Asthma Immunol 2017. 119: 42.
Penicillin Allergy – Practical Points

- Clinical history drives decision making
- Evaluation of all patients should be considered
  - History with red flag symptoms
  - Patient with multiple medical comorbidities
  - Patient with multiple reported drug allergies
- Evaluation can be done in roughly one hour
Local Anesthetic Allergy

- Vast majority of reactions are vasovagal in nature, a toxic reaction, or result of concurrent epinephrine use
- Rarely, if ever, are reactions IgE mediated
- IgE mediated reactions will nearly always have dermatologic manifestations
## Classification of Local Anesthetics

- Benzoic acid esters have significant cross reactivity.
- Group II agents do not cross react with one another.
- Agents in group II are generally less sensitizing than benzoic acid esters.
- Diagnosis is based on skin testing.

<table>
<thead>
<tr>
<th>Benzoic Acid Esters (Group I)</th>
<th>Amide/Misc Structures (Group II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzocaine</td>
<td>Bupivacaine</td>
</tr>
<tr>
<td>Butamben picrate</td>
<td>Dibucane</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>Dydonine</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Etiodocaine</td>
</tr>
<tr>
<td>Procaine</td>
<td>Levobupivacaine</td>
</tr>
<tr>
<td>Proparacaine</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>Mepivacaine</td>
</tr>
<tr>
<td></td>
<td>Pramoxine</td>
</tr>
<tr>
<td></td>
<td>Prilocaine</td>
</tr>
<tr>
<td></td>
<td>Ropivacine</td>
</tr>
</tbody>
</table>

Table adapted from Patterson’s Allergic Disease.
Drug Allergy Evaluation

Lutz et al. AAAAI Annual Meeting 2019 Abstract.
Management of IgE Mediated Drug Allergy

- Avoidance of offending drug or use of an equally efficacious alternative
- Induction of temporary tolerance
  - Can be performed quickly in the acute setting

<table>
<thead>
<tr>
<th>Beta-lactam concentration (mg/mL)*</th>
<th>Dose number*</th>
<th>Amount givenΔ (mL)</th>
<th>Dose given (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1</td>
<td>0.1</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.2</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.4</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.8</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.6</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3.2</td>
<td>1.60</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>6.4</td>
<td>3.20</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>1.2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>2.4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>4.8</td>
<td>24</td>
</tr>
<tr>
<td>50</td>
<td>11</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>4</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>8</td>
<td>400</td>
</tr>
</tbody>
</table>

* Dilutions prepared from antibiotic syrup, 250 mg/5 mL.
  * Dose approximately doubled every 15 min.
Δ Drug amount given in 30 mL water or flavored beverage.

Allergic Rhinitis and Upper Airway Pathology

- Otitis media with effusion
- Tubal dysfunction
- Adenoid hypertrophy

Allergic rhinitis

- Viral infection
- Laryngitis
- Sinusitis
- Nasal polyps

Hellings et al. Allergy 2006; 61: 656.
Nasal Obstruction

Chronic rhinitis → Nasal obstruction → Obligate mouth breathing → Facial and dental changes

Adenoidectomy → Reduced size of adenoids → Change from mouth to nose breathing → Tongue position raised → Lips closed → Facial and dental changes

Nasal Obstruction and Head Posture

- Plugging the nares leads to immediate change in cranio-vertebral angle
- The jaws move apart, by elevation of the maxilla and depression of the mandible
- When the obstruction is removed, posture immediately returns to normal

Consequences of Nasal Obstruction

- Significant reduction of the palatal surface area and volume leading to changes in palatal morphology
- Increased palatal depth/height, both in primary dentition and mixed dentition phase
  - No change in transverse dimensions of the palate
- Increased prevalence of class II malocclusion and open bite
- Reduced nasopharyngeal and oropharyngeal space
- Increased prevalence of a mandibular retrusion
- Significant constriction of the maxillary arch
Therapeutic Options

Medical Management
- Nasal corticosteroids
- Nasal antihistamines
- Leukotriene receptor antagonists
- Systemic antihistamines
- Nasal anti-cholinergic agents

Immunotherapy
- Traditional subcutaneous IT
- FDA-approved sublingual IT
  - Dust mites
  - Grass
  - Ragweed
Contact Dermatitis

Local

Angular Cheilitis
Possible Sensitizing Agents

- “The incidence of adverse reactions to dental treatment and dental products is difficult to estimate but seems to be low considering the number of dental treatments undertaken in westernized countries.”

<table>
<thead>
<tr>
<th>Possible Contact Allergens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiseptics</td>
</tr>
<tr>
<td>Latex gloves/dams</td>
</tr>
<tr>
<td>Metals</td>
</tr>
<tr>
<td>Acrylcs</td>
</tr>
<tr>
<td>Impression material</td>
</tr>
<tr>
<td>Adhesive agents</td>
</tr>
<tr>
<td>Local anesthetics</td>
</tr>
<tr>
<td>Mouthwashes</td>
</tr>
<tr>
<td>Cements</td>
</tr>
<tr>
<td>Toothpaste</td>
</tr>
</tbody>
</table>

Patch Testing

Fonacier et al. JACI IP 2015. 3: S1.
Latex Allergy

IN BRIEF
- Most patients allergic to natural rubber latex are able to be treated in general dental practice.
- Some patients will have moderate to severe reactions even when precautions are taken.
- General dental practitioners are not yet fully aware of the problems associated with allergy to natural rubber latex.

The provision of dental care for patients with natural rubber latex allergy: are patients able to obtain safe care?

Survey Results

- 765 respondents
- 512 (67%) had a patient with latex allergy
- 290 (38%) aware of the spectrum of clinical presentation
- 528 (69%) would accept latex allergic patients
  - Most common reason to deny care was discomfort with treating reactions

Table 3 Percentage of dental respondents who correctly identified important potential hazards, and the percentage who would use a NRL free alternative (if willing to accept NRL sensitised patients).

<table>
<thead>
<tr>
<th>Identified potential hazard</th>
<th>Sample size N = 764</th>
<th>Would use NRL free Sample size N = 705</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gloves</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Rubber dam</td>
<td>77</td>
<td>47</td>
</tr>
<tr>
<td>Local anaesthetic cartridge</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Prophy polishing cup</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>O₂ giving equipment</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

## Latex Allergy for the Dentist

<table>
<thead>
<tr>
<th>Sources of Latex in the Dental Office</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gloves</td>
</tr>
<tr>
<td>Rubber dams</td>
</tr>
<tr>
<td>Amalgam carriers</td>
</tr>
<tr>
<td>Anesthetic plungers</td>
</tr>
<tr>
<td>IV tubing/bags</td>
</tr>
<tr>
<td>Syringe stoppers</td>
</tr>
<tr>
<td>Medicine dropper bulbs</td>
</tr>
<tr>
<td>Bandages and tape</td>
</tr>
<tr>
<td>Prophy cups</td>
</tr>
<tr>
<td>Stethoscopes</td>
</tr>
</tbody>
</table>
Latex Allergy

- Incidence increased in the 1980s but has since sharply declined with the use of latex-free materials
- Risk factor for sensitization is frequent exposure
  - Heath care workers
  - Individuals with chronic bladder care
- Spectrum of clinical reactions
  - IgE mediated allergic reaction
  - Non-immune Irritant reaction
  - Allergic contact dermatitis
- Diagnosis based on history
  - No validated skin test reagents, specific IgE testing with poor sensitivity
Anaphylaxis

<table>
<thead>
<tr>
<th>Skin</th>
<th>Respiratory</th>
<th>Gastrointestinal</th>
<th>Cardiovascular</th>
<th>Neurological</th>
</tr>
</thead>
<tbody>
<tr>
<td>hives, swelling, itching, warmth, redness</td>
<td>coughing, wheezing, shortness of breath, chest pain or tightness, throat tightness, trouble swallowing, hoarse voice, nasal congestion or hay fever-like symptoms, (sneezing or runny or itchy nose; red, itchy or watery eyes)</td>
<td>nausea, stomach pain or cramps, vomiting, diarrhea</td>
<td>dizziness/ lightheadedness, pale/blue colour, weak pulse, fainting, shock, loss of consciousness</td>
<td>anxiety, feeling of “impending doom” (feeling that something really bad is about to happen), headache</td>
</tr>
</tbody>
</table>

Other
uterine cramps
Management of Acute Reactions

- Intramuscular epinephrine
  - Not diphenhydramine or any other antihistamines
- Absolute contraindication to epinephrine
  - None
- Relative contraindication to epinephrine
  - None
- Comorbidities to be aware of
  - Coronary artery disease
Mediators of Anaphylaxis

- Leukotrienes
- Prostaglandins
- Kinins
- Platelet activating factor
- Interleukins
- Tumor necrosis factor
- Histamine

Diphenhydramine (Benadryl)
Management with Epinephrine

- **α₁-adrenergic receptor**
  - Vasoconstriction
  - Peripheral vascular resistance
  - Mucosal edema

- **α₂-adrenergic receptor**
  - Insulin release

- **β₁-adrenergic receptor**
  - Inotropy
  - Chronotropy

- **β₂-adrenergic receptor**
  - Bronchodilation
  - Vasodilation
  - Glycogenolysis
  - Mediator release

Management with Epinephrine

Epinephrine

Antihistamines

Simons et al. JACI 1998. 101; 33.
Jones et al. Ann All Asth Immunol 2008. 100(5); 452.
Anaphylaxis – Points to Consider

- ~20% of reactions have a biphasic response
- Previous reactions do NOT predict the severity of future reactions
- No diagnostic tools to predict the severity of reactions
- Referral to allergist for evaluation is recommended
Summary

- 10% of individuals report PCN allergy, and 95% can safely tolerate PCNs
- Evaluation of drug allergy can be done safely and relatively quickly
- Allergic rhinitis leads to nasal obstruction and contributes to changes in facial structure
- Latex allergy is very uncommon
- Epinephrine is the only therapy for anaphylaxis
Thank You

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