Penicillin Allergy: Why the Epidemic is Leading to Poor Clinical Outcomes

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Disclosures

• I have no actual or potential conflict of interest in relation to this presentation.
Objectives

- Characterize and stratify penicillin allergic reactions
- Review the clinical data on clinical decision making in patients with penicillin allergies
- Be able to identify which patients should have further evaluation after a drug-related adverse event

Presentation Outline

- Case presentation
- Defining drug allergies
- Penicillin allergies
  - Prevalence
  - Importance of penicillin allergy label
  - Evaluation methods
### Case Presentation

<table>
<thead>
<tr>
<th>Case</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>RJ</td>
<td>18 yo male with newly diagnosed syphilis.</td>
</tr>
<tr>
<td>DK</td>
<td>32 yo female with AML s/p chemotherapy that presents with neutropenic fever.</td>
</tr>
<tr>
<td>RS</td>
<td>63 yo male with a history of diabetes and ESRD s/p DDKT on chronic immunosuppression that presents with pneumonia.</td>
</tr>
</tbody>
</table>

All have a distant history of penicillin allergy.

### How Common are Adverse Drug Events?

#### Allergy Label
- 36% of patients have a listed allergy in their EMR
  - 43% of these had multiple allergies
  - 4-7% have MDIS
- Risk factor: Drug exposure

#### Adverse Events
- Adverse drug events occur in up to 25% of prescriptions
  - 13% of these were serious
- Allergic reactions (immunologically mediated) account for only 5-10% of all ADEs
Classifying Adverse Drug Events

**Type A Reactions**
- Predictable – Due to known pharmacodynamics of the drug (dose-dependent)
- Based more on drug than host
- >85% of ADEs
- Examples
  - Sedation with diphenhydramine
  - Diarrhea with amoxicillin
  - Bleeding due to warfarin

**Type B Reactions**
- Unpredictable
- Based more on host than drug
- ~15% of ADEs
- Examples
  - Hypersensitivity reactions
  - Pseudoallergies

Variety of Drug Reactions

<table>
<thead>
<tr>
<th>Examples of Drug Allergies</th>
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</thead>
<tbody>
<tr>
<td>IgE-mediated</td>
<td>Pneumonitis</td>
<td>Urticaria multiforme</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>AIN</td>
<td>Erythema multiforme</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Drug-induced lupus</td>
<td>AGEP</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>FDE</td>
<td>Infusion reactions</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>Contact dermatitis</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>Serum sickness-like</td>
<td>Acne</td>
<td>Angioedema</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Photosensitivity</td>
<td>IgE-mediated anaphylaxis</td>
</tr>
<tr>
<td>Arthus reaction</td>
<td>SDRIFE</td>
<td>Non-IgE-mediated anaphylaxis</td>
</tr>
<tr>
<td>DRESS</td>
<td>Drug exanthema</td>
<td>IgG-mediated anaphylaxis</td>
</tr>
<tr>
<td>SJS</td>
<td>Drug fever</td>
<td>MRGPRX2-mediated</td>
</tr>
<tr>
<td>TEN</td>
<td>Bullous pemphigoid</td>
<td>Pemphigus vulgaris</td>
</tr>
</tbody>
</table>
Penicillin Allergy Labels

- 8-10% of the US population carries a history of penicillin allergy
  - >95% will tolerate penicillin use after evaluation
- Waning sensitivity to penicillin
  - 50% lose sensitivity by 5 years
  - 80% lose sensitivity by 10 years
- Subsequent penicillin use after negative testing does not increase risk of sensitization


Effects of Penicillin Allergy Label

- Use of inferior/toxic antibiotics
- Increase in length of stay
- Increase in adverse effects
- Antibiotic resistance

Use of inferior/toxic antibiotics
Increase in length of stay
Increase in adverse effects
Antibiotic resistance
Antibiotic Exposure

![Antibiotic Exposures in Hospitalized Patients](image)

**Outcomes: PCN Allergy Label**

1. Higher rate of treatment failures
2. Increased prevalence of Clostridium difficile, MRSA, and VRE
3. Increased future healthcare utilization
   - Longer hospital length of stay
   - Higher rate of readmission
4. Increased healthcare dollars
5. Higher rates of surgical site infections

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Treatment Failure with Alternative Antibiotics

- GNB bacteremia (Jeffres et al.)
  - Non-β-lactam failure rate: 39%
  - β-lactam failure rate: 27%
- MSSA bloodstream infections (McDanel et al.)
  - β-lactams had a 35% lower mortality rate for definitive treatment compared to vancomycin

C difficile, MRSA, and VRE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Increase in Prevalence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Diff</td>
<td>23.4%</td>
</tr>
<tr>
<td>MRSA</td>
<td>14.1%</td>
</tr>
<tr>
<td>VRE</td>
<td>30.1%</td>
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</tbody>
</table>

Surgical Site Infections

When controlled for surgery type, age, sex, race, American Society of Anesthesiologists class, procedure duration, and wound class, 51% increased risk of a SSI in patients that have a PCN allergy label (p<0.04).


Anesthesiologist Perspective

- Up to 60% of anesthesiologists will not give β-lactam antibiotics to penicillin-allergic patients
  - Medical-legal concerns
- Studies have supported:
  - Penicillin allergy evaluation prior to surgery
  - Cephalosporins without prior evaluation/testing (in penicillin allergic patients)

Choosing Wisely Campaign

Don’t overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation.

https://www.choosingwisely.org

Penicillin Testing (Inpatient)

665 underwent evaluation

627 underwent skin testing protocol

596 passed PO challenges
Penicillin allergy removed from chart

600 negative skin tests

10 positive/indeterminate skin tests

17 negative histamine controls

12 cleared based on history alone

4 cleared by direct challenge

4 failed PO challenges
No further action
Who Should We Be Evaluating?

• Everyone!

• High risk patients and high utilizers of the healthcare system
  • Chronic disease (CF, diabetes, COPD, asthma)
  • Immunosuppressed (chemotherapy, autoimmune, transplant)
  • Immunodeficient (HIV, primary immunodeficiency)
  • Malignancy

How Should We Test Patients?

• Inpatient vs Outpatient?
• Skin testing vs Direct Provocation Challenge?
• Allergist vs Non-allergist?
Inpatient Vs Outpatient Evaluation

- Traditionally, penicillin allergy evaluation has occurred in the outpatient setting
- Outpatient:
  - Allergist primary practice in the outpatient setting
  - Can perform multiple evaluations simultaneously
  - Difficult to schedule testing
- Hospitalized patients:
  - Incidence of penicillin allergy is higher (up to 15%)
  - Older, more ill and greater need for antibiotics
  - Testing could alter antibiotic therapy immediately

Penicillin Skin Testing

- Modified protocol
  - Skin prick and intradermal testing
    - Penicilloyl-polylysine
    - Penicillin G
  - Observed (graded) oral amoxicillin challenge
- NPV of 97-100%
  - PPV not well established

Direct Provocation Testing

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Penicillin SPT</th>
<th>DC</th>
<th>Difference</th>
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</thead>
<tbody>
<tr>
<td>Patients</td>
<td>80</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>PST Positive/DC fail, n (%)</td>
<td>10 (12.5)</td>
<td>3 (3.8)</td>
<td>8.7% (P = .079)</td>
</tr>
<tr>
<td>PST Negative/DC pass</td>
<td>70 (87.5)</td>
<td>76 (96.2)</td>
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</tbody>
</table>

- DC reactions were all minor cutaneous reactions
- False positive results from SPT

SPT: Skin Prick Test

Mild Reactions
- Minor rash (not hives)
- Delayed (>2 hours), maculopapular rash (Type IV HSR)
- Remote, unknown reaction (patient cannot recall)

IgE-Mediated HSR
- Immediate (<2 hours)
  - Anaphylaxis
  - Angioedema
  - Hives/urticaria
  - Wheezing
  - Laryngeal Edema
  - Hypotension

Severe Non-IgE-Mediated Reactions
- Stevens-Johnson Syndrome
- Toxic Epidermal Necrolysis
- Serum Sickness/SSLR
- Acute Interstitial Nephritis (AIN)
- Drug Rash Eosinophilia with Systemic Symptoms (DRESS)
- Drug Fever
- Drug-induced Hepatitis

Significant underlying conditions?
- Pregnancy
- Moderate to severe pulmonary disease
- Moderate to severe cardiac disease
- Hemodynamic instability

OHSU Penicillin Allergy Evaluation Protocol

- >10 years ago?
- <10 years ago?
- Significant underlying conditions?
  - Yes
    - Avoid Penicillins
  - No
    - Graded Oral Amoxicillin Challenge
      - Neg
        - Referral for Evaluation and Penicillin Skin Testing by Allergy/ID/Pharmacy
      - Pos
        - Avoid Penicillins

Risk Stratifying PCN Allergy Patients

- No consensus with high variability between studies
  - Time since reaction
  - Symptoms (cutaneous only)
  - Severity of reaction
- UK Tertiary Center Study – Multivariate regression analysis
  - Self reported history of anaphylaxis
  - Patients’ recall of index penicillin
  - Time of less than 1 year since index reaction

Allergist or Non-Allergist?

- Both should be involved!

- Lower risk patients -> Non-Allergist
  - Penicillin Allergy Toolbox
  - Evaluation and Management of Penicillin Allergy: A Review
    - Shenoy ES, Macy E, and Rowe T.

- Higher risk patients -> Allergist
Take Home Points

• Always question drug allergies
  • Especially penicillin
• Penicillin allergy labels can drastically alter clinical outcomes and lead to more expensive care
• Performing inpatient and/or outpatient penicillin evaluations (history, testing) is safe and reliable in removing penicillin allergy labels

Questions?

Combined Clinic for Severe Sinus Disease
ENT & Allergy

Clinic for Asthma & Allergic Diseases
Updates on Cephalosporin Allergies

- Most commonly used antibiotic in US hospitals
- 1.3-1.7% of patients report ADRs to cephalosporins
- Can cause all types of HSRs
  - SSLR (11% of cases)
  - AIN (9% of cases)
  - SCAR (5% of cases)
  - Anaphylaxis (4% of cases)
- 60% of patients lose cephalosporin sensitivity after 5 years


Cephalosporin Testing

- Skin testing (prick and ID)
  - Limited data on sensitivity and specificity
  - False positive rate in healthy population (1421 patients): 5.2%
  - Perioperative anaphylaxis: Skin testing has high PPV
    - Danish study showed 7 of 7 patients had a positive DPT after positive skin test
    - Wide range of concentrations used
- Skin testing (delayed ID and patch)
- In vitro sIgE testing
  - Limited commercially availability and limited data
- Direct provocation testing

Historically, cross-reactivity has been overestimated.

Recent meta-analysis (PCN Allergic):
- Aminocephalosporins: 16.5%
- Intermediate-similarity-score: 5.6%
- Low-similarity-score: 2.11%

R1 and R2 side chains.

Penicillin Relabel

Interventions to Maintain Penicillin Allergy Label Removal

1. Pharmacist counseling at the time of negative test
   • Active removal of allergy, procedure note documentation

2. Pharmacist counseling at post-discharge visit
   • Telephone call or face to face visit

3. Best practice advisory in the electronic medical record
   • Alerting providers to the negative penicillin allergy test result on attempt to add back allergy

4. Wallet card given to patient documenting negative testing
   • Given at time of negative test documentation

I am NOT Allergic to Penicillin

Penicillin Skin Testing (Prick and Intradermal) followed by an oral graded Amoxicillin Challenge was performed at Oregon Health and Science University (OHSU) on: ____________________________.

RESULTS: Negative (No Reaction)

Test performed by ____________________________.

<table>
<thead>
<tr>
<th>Allergy Information</th>
<th>I am NOT Allergic to Penicillin</th>
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<tbody>
<tr>
<td>Name: ______________________</td>
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<tr>
<td>Date of Birth: ______________</td>
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<tr>
<td>Allergies:</td>
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