Clarifying antibiotic allergies: skin testing, allergy interviews, and delabeling

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Disclosures

- I have nothing to disclose related to the contents of this presentation.
Pharmacist Objectives

• Explain the “side chain theory” of antibiotic cross-reactivity.
• Conduct an antibiotic allergy interview.
• Review the process, benefits, and limitations of penicillin skin testing.
• Explain the importance of “delabeling” penicillin allergies to prevent negative health consequences.
Technician Objectives

• List potential health consequences for patients labeled with a penicillin allergy.
• Conduct an antibiotic allergy interview.
• Review the process, materials, and storage requirements for penicillin skin testing components.
Impact of penicillin allergies on patient outcomes

- Increased utilization of broad-spectrum antibiotics
- Increased C. difficile rates
- Increased length of stay
- Increased mortality
- Increased risk of surgical site infection
- Increased monetary costs
- Prolonged time to first dose of antibiotic
- Increased 30 and 180 day readmission

History of Fluoroquinolones

1962
- First FQ introduced

2008
- Boxed warning: worsening MG

2011
- Enhanced label warning from FDA: possible permanent side effects – joint pain, tendon rupture, tendinitis, anxiety, depression, and AMS

2013
- Updated labeling: potentially irreversible peripheral neuropathy

2016
- BBW: tendinitis/tendon rupture

2018
- Safety communication: adverse psychiatric effects and hypoglycemic risks
- FDA warning: increased risk of ruptures or tears in the aorta
## Classification of Drug Allergies

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>Presentation</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>IgE</td>
<td>Anaphylaxis, urticaria, hives, bronchospasm, laryngeal edema</td>
<td>Immediate (0-1 hours)</td>
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<tr>
<td></td>
<td></td>
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<td>Accelerated (within 72 hours)</td>
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<tr>
<td>Type 2</td>
<td>IgG, IgM, immune complex</td>
<td>Hemolytic anemia, leukopenia, thrombocytopenia, drug induced nephritis</td>
<td>&gt;72 hours</td>
</tr>
<tr>
<td>Type 3</td>
<td>IgG, IgM, immune complex</td>
<td>Serum sickness, drug fever, rash, itch, joint pain, fever, swollen lymph nodes</td>
<td>1-14 days</td>
</tr>
<tr>
<td>Type 4</td>
<td>T-cell mediated</td>
<td>Contact dermatitis</td>
<td>&gt;72 hours</td>
</tr>
</tbody>
</table>

Question 1

• What percentage of patients report a penicillin allergy in the US?
  a) 20%
  b) 10%
  c) 5%
  d) 1%
Let’s look at the stats

https://twitter.com/jeffpearson/status/1083577528835547136
Background

- Most common drug allergy reported in the US
- Often experienced early in life
- Easy to falsely diagnose
- Impact of time?
- When PCN skin testing is performed on patients with reported PCN allergies, >90% are found not to be allergic

Trubiano JA, Adkinson NF, Phillips EJ. JAMA. 2017;318(1):82-83
CROSS REACTIVITY AND THE SIDE CHAIN THEORY
Cephalosporin cross-reactivity with penicillins

- Overestimated due to presence of PCN in original formulations
- Early literature confounded by nonallergic ADRs
- The American Academy of Allergy, Asthma & Immunology defines the risk of cross reactivity between penicillins and cephalosporins as <5%
- All cephalosporins are not created equal

The Side-Chain Theory

- 6-position PCN side chain
- 7 or 3 position cephalosporin side chains

The Side-Chain Theory

3, similarity at the cephalosporin 3–position side chain; 7, similarity at the cephalosporin 7–position side chain; 6/7, similarity at the penicillin 6–position side chain and the cephalosporin 7–position side chain.

Question 2

• Based on the side chain theory / table below, would cefazolin be safe to administer to a patient with a history of an allergy to amoxicillin?

Common beta-lactams with side chain similarities

- Amoxicillin and Ampicillin
  - Cefaclor, cefadroxil, cefprozil, cephalexin, cefatrizine, cephradine
- Of note, cefazolin, ceftriaxone, and cefepime do not share side chain similarities with PCNs
  - Ceftriaxone and cefepime do share side chain similarities with other cephalosporins however

Side Chain Summary

“When current clinical data are combined with structural activity relationship side-chain analysis, it appears that, for select cephalosporins without side-chain similarities, the relative risk of prescribing these antibiotics in a non-IgE-mediated penicillin-allergic patient is no greater than the low inherent allergic risk of the products themselves.”

CONDUCTING ANTIBIOTIC ALLERGY INTERVIEWS
Questions to clarify PCN allergy

- Do you have any allergies?
  - Sometimes medical record doesn’t match the patient’s memory
- What happened when you took the drug?
  - What was the reaction?
  - Common type I reaction symptoms: Urticaria, pruritus, angioedema, wheezing, shortness of breath
  - Non hypersensitivity events: Nausea, vomiting, diarrhea, headache
- Did the reaction occur after the 1\textsuperscript{st} dose or the 10\textsuperscript{th} dose?
  - Immediate (IgE mediated) versus delayed onset (non-IgE mediated)

Trubiano JA, Adkinson NF, Phillips EJ. JAMA. 2017;318(1):82-83
Questions to clarify PCN allergy

• How was the reaction managed?
  – If epinephrine and antihistamines resolved the reaction within a few hours, reaction may have been IgE mediated

• How many years ago did the reaction occur?
  – 50% of patients with IgE-mediated reactions lose sensitivity within 5 years, and 80% lose sensitivity within 10 years

• Have you tolerated similar antibiotics with no reaction?

Trubiano JA, Adkinson NF, Phillips EJ. JAMA. 2017;318(1):82-83
Tips to supplement allergy histories

- Review patients’ antibiotic usage at your institution
- Review claims history
- Bring a list of commonly used beta-lactams to read to the patient
- Reach out to community pharmacies for fill histories
Algorithm

• See attached handout for an example decision-making algorithm when interviewing patients with penicillin allergies.
Let’s Practice

• Get into pairs to role play 2 different penicillin allergy interview scenarios. One person will be the patient, and one will be the pharmacist/technician.
• Spend about 5 minutes on each scenario.
• After scenario one, switch roles.
PENICILLIN SKIN TESTING
Penicillin skin testing

WHAT IS IT?

• Most reliable and safe method to assess type I (IgE-mediated) reactions only

• Bioassay performed on the skin, which detects presence of allergen-specific IgE on a patient’s mast cells

• Mast cell activation → positive skin test (“wheal and flare”) reaction within 15-20 minutes

• American Academy of Allergy, Asthma, and Immunology (AAAAI) recommend skin testing for all patients believed to be allergic to penicillin.
Penicillin skin testing

- WHO TO TEST?
  - History of type 1 reaction
  - Unclear allergy histories (To exclude type 1 reactions)
  - NO ROLE IN TESTING THOSE WITH SJS OR TEN
  - Should NOT be performed in weeks immediately following anaphylactic episode
Penicillin skin testing

• HOW TO TEST?

https://www.penallergytest.com/implementation-2/train-the-trainer-program/
Penicillin skin testing

• Now what?
  – UPDATE THE PATIENT’S RECORDS
  – Educate the patient
  – Make antimicrobial recommendation, if necessary
Question 3

• A 26-year-old pregnant woman has syphilis. She recalls an “itchy rash” and trouble breathing after taking penicillin 4 years ago; she thinks the rash appeared about 3 days into the course of penicillin. The team wants to perform a PRE-PEN test to see if this represents a true penicillin allergy. Do you agree with the use of penicillin skin testing for this patient?
The results come back as follows:

Skin prick:

Intra-dermal:

• How would you interpret the results?
• What antimicrobial therapy would you recommend?
Pros/cons of penicillin skin testing?

• What do you think?
DEELABELING
What is “delabeling”?  

- Removing an existing penicillin allergy label from a patient’s chart in individuals found not to be allergic
Evidence in the literature

  - 784 patients allergic to penicillins in an outpatient clinic in Israel
  - PCN skin testing performed, followed by oral challenge. Letters sent to provider recommending delabeling from medical file, if appropriate
  - 88% of patients deemed “not allergic”
  - 70% of patients used PCNs at least once after the testing
  - 51% carried label in their medical record despite negative testing
Evidence in the literature

  - Case series of 100 children with negative penicillin allergy testing results from an ED
  - 46 prescriptions in 36 patients reported by PCP and/or parent within 1 year after testing
  - No child developed serious ADR after penicillin challenge
  - Total cost savings for ED: $192223
Evidence in the literature

  - 36 patients completed a penicillin skin testing protocol at a community health system in an 8-month period
  - 100% had a negative result.
  - 27/36 patients were converted to penicillin or cephalosporin
  - Reduction in use of carbapenems, aztreonam, vancomycin, and other broad-spectrum agents
  - Decrease in drug costs
Evidence in the literature

• Pharmacists performing PCN skin testing?
  – 2004, Wall et al: pharmacists conducted PST in patients with PCN allergy history. 26/26 patients received a penicillin or beta-lactam antibiotic.
  – 2015, Gugkaeva et al: pharmacist-provided PST service resulted in 40/51 patients switched to narrower-spectrum beta-lactam
  – Query of boards of pharmacies: only 12 of 38 respondents permitted this practice. In all cases, collaborative practice agreements were required.
WHAT IF WE DON’T HAVE PENICILLIN SKIN TESTING?
Evidence in the literature


  - Pharmacy driven pilot to determine the impact of beta-lactam allergy interviews on antimicrobial therapy

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<thead>
<tr>
<th>Results</th>
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<tbody>
<tr>
<td>Percentage of patients switched to beta-lactam</td>
<td>65.6% (21/32)</td>
</tr>
<tr>
<td>Number of discrepancies between EMR reported allergy and allergy obtained on interview (%)</td>
<td>11/32 (34.4%)</td>
</tr>
<tr>
<td>Number of patients experiencing hypersensitivity reaction</td>
<td>0/21</td>
</tr>
</tbody>
</table>

- Retrospective (control) group
  - Chart reviewed for documented allergy, reaction, reaction classification, non-beta lactam antibiotic ordered and duration of use

- Prospective group
  - Charts reviewed as above
  - Patients interviewed utilizing standardized questionnaire
  - EHR allergies were updated when necessary
  - Antibiotic recommendation communicated to provider if appropriate
# Results

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n=43)</th>
<th>Prospective Group (n=37)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of fluoroquinolone, mean days (SD)(^a)</td>
<td>3.7 (2.2)</td>
<td>2.7 (1.7)</td>
<td>0.027</td>
</tr>
<tr>
<td>Length of stay, median days (IQR)</td>
<td>6 (3-9)</td>
<td>5 (4-8)</td>
<td>0.73</td>
</tr>
<tr>
<td>Patient switched to beta-lactam antibiotic, no. (%)</td>
<td>n/a</td>
<td>18 (49)</td>
<td>n/a</td>
</tr>
<tr>
<td>Pharmacy recommendations accepted, no. (%) recommendations</td>
<td>n/a</td>
<td>17/18 (94)</td>
<td>n/a</td>
</tr>
<tr>
<td>Adverse reaction after switch to beta-lactam, no.</td>
<td>n/a</td>
<td>0</td>
<td>n/a</td>
</tr>
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Summary

• Penicillin allergies can have detrimental health and economic consequences

• Cross reactivity appears to be highest with similar antibiotic side chains
Summary

• Allergy interviews can help distinguish between allergies vs. adverse reactions and determine allergy type/severity

• Penicillin skin testing is the gold standard for clarifying type 1, IgE-mediated reactions
Tips for Success

• Take every opportunity to clarify allergies
• Consider printing off example “scripts” to guide allergy interviews
• Assess fill/order history for other beta-lactams
• Educate the patient and other healthcare professionals
Helpful Resources

• CDC: Evaluation and Diagnosis of Penicillin Allergy for Healthcare Professionals: Is it Really a Penicillin Allergy?
  https://www.cdc.gov/antibiotic-use/community/for-hcp/Penicillin-Allergy.html

• The Itch: An SIDP Podcast Miniseries on Penicillin Allergy https://www.sidp.org/Podcasts

• NebraskaMed Penicillin Allergy Guidance Document:
No matter the practice setting or resources, all pharmacists and technicians can serve as antimicrobial stewards by appropriately clarifying penicillin allergies.