Beta-lactam Allergies
Facts vs. Fears

Meghan Jeffres, PharmD
Assistant Professor, Department of Clinical Pharmacy
University of Colorado Skaggs School of Pharmacy

Statement of Disclosures

• No financial disclosures
• Clinical disclosures: I love a beta-lactam
Objectives

• Identify risk of cross-reactivity among beta-lactams
• Discuss utility of penicillin-skin testing for patients labeled as penicillin allergic
• Review medical negligence cases involving beta-lactam use in penicillin allergic patients

Points of Agreement

• Majority penicillin allergy labels are inaccurate
• Being labeled as penicillin allergic is bad for you
  - use of secondary (non-beta-lactam) antibiotics
  - incidence of resistant infections
  - incidence of treatment failure
  - healthcare costs
Paul 55 year old male with CAP

- CC: shortness of breath, cough, and fever x 3 days
- PMH: diabetes mellitus – A1c 8.9
- Vitals: 38.5, 135/90, 98, 22, 91% RA
- Allergy: Penicillin – tongue swelling

Do you recommend ceftriaxone + azithromycin or a respiratory fluoroquinolone?

CAP = community acquired pneumonia, CC = chief complaint, PMH = past medical history, RA = room air

Cross-reactivity between beta-lactams

- Historical data
  - Penicillin-cephalosporin 10%
  - Penicillin-carbapenem 5%
  - Cephalosporin-carbapenem 25%

Side chain clinical evidence

- Outpatient clinic, Italy
- N=214 – documented delayed hypersensitivity to penicillins
- Skin and patch testing
  - *No reaction to cefuroxime, ceftriaxone, or aztreonam*
  - N=40 (19%) reaction to:
    - Cephalexin (n=31) ➔ Ampicillin side chain similar
    - Cefaclor (n=39) ➔ Ampicillin side chain similar
    - Cefadroxil (n=17) ➔ Amoxicillin side chain similar
Side chain clinical evidence

- Hospital, Spain
- N=24 – immediate allergic reactions to cephalosporins
  - Skin test or radioallergosorbent (RAST) positive
- N=9 with ≥ 2 cephalosporin allergy
  - 8/9 allergic to cefotaxime, ceftriaxone, and/or cefuroxime (similar R1 chain)


PCN-CEPH crib notes

- Risk of cross-reactivity with similar side chain:
  - PCN-CEPH ≈ 20%
  - CEPH-CEPH ≈ 40%
- Cefazolin – no side chain similarities

Similar side-chains
- Penicillin, ampicillin, amoxicillin, and cephalexin
- Penicillin and cefoxitin
- Cefotaxime, ceftriaxone, cefuroxime, ceftazidime, cefepime
- Ceftazidime and aztreonam

Stacia 36 year old female with colitis

- CC: abdominal pain, fever, chills
- Vitals: 38.7, 145/99, 102, 18, 96% RA
- Allergy: Penicillin – edema, hives
- Blood culture and susceptibilities from previous month

What do you select for empiric therapy?

<table>
<thead>
<tr>
<th>E. Coli</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>S</td>
</tr>
<tr>
<td>Amp/sulb</td>
<td>R</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>R</td>
</tr>
<tr>
<td>Cefepime</td>
<td>R</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>S</td>
</tr>
<tr>
<td>Meropenem</td>
<td>S</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>R</td>
</tr>
</tbody>
</table>

RA = room air, S = susceptible, R = resistant

Use of carbapenem in penicillin allergy

- Meta-analysis of PCN allergic patients, n=838

“cross-reactivity... very low, but caution is still advised”

### Carbapenems and immediate PCN reaction

- PCN skin test positive pts, n=212
  - mix of penicillin derivatives
- Reaction history
  - Anaphylaxis 71%
  - Urticaria 15%
  - Urticaria + angioedema 10%
  - Erythema 3%
- Skin test positive
  - Imipenem – 0%
  - Meropenem – 0%
  - Ertapenem – 0%
- IV challenge, n=211
  - Imipenem – 0%
  - Meropenem – 0%
  - Ertapenem – 0%

PCN = penicillin; IV = intravenous


### Carbapenems and delayed PCN reaction

- T-cell mediated reactions + PCN skin test positive, n=204
  - mix of penicillin derivatives
- Reaction history
  - Rash 48%
  - Rash + edema 39%
  - Erythema 4%
- Skin test positive
  - Imipenem – 0%
  - Meropenem – 0%
  - Ertapenem – 0%
- IV challenge
  - Imipenem – 0%
  - Meropenem – 0%
  - Ertapenem – 0%

PCN = penicillin; IV = intravenous

Penicillin side chain groups

<table>
<thead>
<tr>
<th>Natural</th>
<th>Aminopenicillins</th>
<th>Penicillinase resistant</th>
<th>Carboxy‐penicillins</th>
<th>Ureido‐ and piperazine penicillins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>Ampicillin</td>
<td>Methicillin</td>
<td>Carbenicillin</td>
<td>Azlocillin</td>
</tr>
<tr>
<td>procaine</td>
<td>Amoxicillin</td>
<td>Nafcillin</td>
<td>Ticarcillin</td>
<td>Mezlocillin</td>
</tr>
<tr>
<td>benzathine</td>
<td>Oxacillin</td>
<td></td>
<td></td>
<td>Piperacillin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cloxacillin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dicloxacillin</td>
</tr>
</tbody>
</table>

Penicillin-penicillin skin test cross-reactivity

Penicillin allergic patients

<table>
<thead>
<tr>
<th></th>
<th>Nafcillin</th>
<th>Oxacillin</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin ± intradermal</td>
<td>2/10</td>
<td>4/10</td>
<td>2/10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Ampicillin</th>
<th>Carbenicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intradermal</td>
<td>44/70</td>
<td>0/14</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>70/70</td>
<td>0/14</td>
</tr>
</tbody>
</table>


Penicillin-penicillin cross-reactivity

<table>
<thead>
<tr>
<th>Skin test (+)</th>
<th>Penicillin received</th>
<th>Reaction</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pen G</td>
<td>Carbenicillin</td>
<td>Mild urticarial</td>
<td>12-24 hr</td>
</tr>
<tr>
<td>Methicillin</td>
<td>Pen G</td>
<td>Urticaria</td>
<td>6 days</td>
</tr>
<tr>
<td>Methicillin</td>
<td>Methicillin</td>
<td>Rash, nephritis</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Pen G, ampicillin, methicillin</td>
<td>Nafcillin</td>
<td>Urticaria</td>
<td>24-48 hr</td>
</tr>
<tr>
<td>Pen G</td>
<td>Carbenicillin</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Pen G</td>
<td>Carbenicillin</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Methicillin</td>
<td>Pen G</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Methicillin</td>
<td>Methicillin, oxacillin</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Sue 77 year old female with BSI

- CC: fever and confusion, during dialysis
- Vitals: 38.0, 119/62, 101, 19, 95% RA
- Allergy: Penicillin – rash (remote history)
- Empiric antibiotics:
  - vancomycin and meropenem
- Day 3 – blood cultures

<table>
<thead>
<tr>
<th>Enterococcus</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>S</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>S</td>
</tr>
</tbody>
</table>

BSI = bloodstream infection, RA = room air, S = susceptible

Sue – enterococcal BSI with PCN rash

A. Continue meropenem, D/C vancomycin
B. Continue vancomycin, D/C meropenem
C. D/C both, start ampicillin
D. D/C both, de-sensitize to ampicillin
E. D/C both, give a test dose of ampicillin
F. Perform a penicillin skin test

BSI = bloodstream infection, PCN = penicillin, D/C = discontinue
Penicillin Skin Testing

- Preferred method for diagnosis of Type I reactions
- Reagents:
  - Penicillin G
  - Benzylpenicilloyl polylsine injection (PRE-PEN®)
  - Saline
  - Histamine

http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/allergy/adverse-drug-reactions/

Penicillin skin testing by pharmacists

- Approximately 1 hour per test (interview + skin test)
- Decreased vancomycin and fluoroquinolone use

http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/allergy/adverse-drug-reactions/

NAME__
DATE ________________
MR # ________________ ADMITTING DX ________________
ORDERING PHYSICIAN ____________________________
CONTACT NUMBER ____________________________
PHARMACIST ____________________________
INCLUSION CRITERIA
☐ Patients must be greater than 18 years old.
☐ Patients are eligible for the protocol if they have a listed history of a reaction to any penicillin antibiotic.
☐ The ordering Physician feels that the information provided from the skin test would be beneficial for the reasons outlined above.
☐ No exclusion criteria are met.
☐ Histamine 1 or 2 receptor antagonists are to be withheld for 24 hours prior to procedure (order written by Pharmacist).

EXCLUSION CRITERIA
☐ Patient has a recent (within last 5 years) report of an immediate (urticaria, etc.) reaction to a penicillin antibiotic, including anaphylaxis.
☐ Patient has a report of a hypersensitivity reaction other than a type I reaction (hemolytic anemia, interstitial nephritis, Stevens–Johnson syndrome, etc.).
☐ It is determined by medication history that the patient has an intolerance (e.g., stomach upset) to a penicillin antibiotic, not a true allergy.
☐ Patient has severe immunosuppression; does not include patients with diabetes or those using corticosteroids.
☐ Patient does not have enough amenable skin surface on the arms to perform the test accurately.
☐ Patient is pregnant.

Wall et al. AJHP. 2004;61(12):1271-1275.
Penicillin Skin Testing by ID Fellows

11 months – 90 patients assessed, 76 (85%) tested

<table>
<thead>
<tr>
<th>Results</th>
<th>n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PST positive</td>
<td>3 (4)</td>
</tr>
<tr>
<td>PST negative</td>
<td>64 (84)</td>
</tr>
<tr>
<td>Invalid</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Change in antibiotic therapy</td>
<td>54/67 (81)</td>
</tr>
<tr>
<td>Narrow spectrum</td>
<td>34/54 (63)</td>
</tr>
<tr>
<td>More effective antibiotics</td>
<td>43/54 (61)</td>
</tr>
<tr>
<td>Cheaper</td>
<td>33/54 (61)</td>
</tr>
<tr>
<td>Updated allergy status</td>
<td>59 (88)</td>
</tr>
</tbody>
</table>

Survey of Fellowship directors
- N=50 (32% response rate)
- PST offered – 60%
- Performed by:
  - Allergy/immunology – 94%
  - Pharmacy – 3%
  - Out-patient only – 3%
- Fellows should be involved in PST – 56%
- PST service involving ID fellows would benefit patient care and antibiotic stewardship – 70%


Penicillin Skin Testing – Inpatient Setting

Benefits
- 60-90 minutes
- Negative predictive value >95%
- Safe in children and pregnant women
- Increases beta-lactam utilization
- Cost-savings

Limitations
- Low clinical utility
- Identification of IgE reactions only
  - Does not de-label patient
- Antihistamine and other medication interactions
- Contraindicated in SJS/TEN, organ or hemolytic adverse reactions

SJS = Stevens-Johnson Syndrome,
TEN = toxic epidermal necrolysis

Skin, PO, and IV challenges shows a lack of allergic reaction with dis-similar side chains
*limited data within penicillin class

Changes to practice:
- Do not accept penicillin, cephalosporin, or carbapenem as an allergy – get a specific medication
- Use dis-similar cephalosporin or carbapenems
- Update allergy label when beta-lactam is tolerated
- Update/replace pharmacy software

Legal liability is the reason I do not prescribe or recommend a beta-lactam in a patient with a beta-lactam allergy.

☑ True ☑ False
Patients with a known penicillin allergy, received a beta-lactam, experienced an adverse reaction

Black line: Total cases filed per decade
Dashed line: Number of cases in which the defendant prevailed
Dotted line: Number of cases in which the plaintiff prevailed

In the hypothetical medical system, patients are treated by two separate, but equally important groups: the providers who order the antibiotics and the infectious diseases experts who change them. These are their stories.....
Case 1: Boone v. William Backus Hospital

FACTS

• 4 year old boy (Boone) presented to the ED with signs and symptoms of otitis media
• Allergy history: penicillin and sulfa; immediate reaction
• Given: 250mg injection of ceftriaxone IM and 5ml acetaminophen with codeine elixir
• In ED – vomiting, sweating, became pale – nurse states symptoms caused by injections and safe to take child home

ED = emergency department; IM = intramuscular

Case 1: Boone v. William Backus Hospital

FACTS

• Outside of ED child began to vomit violently
• Mother went back to the ED – asks several people for help and is turned away
• Home – continued vomiting, lips and gums turn white
• Returned to hospital – lethargic and non-responsive – dies that night
• Autopsy – hemolysis due to allergy reaction to ceftriaxone

☑️ Liable ☐ Not Liable
Case 1: Legal Outcome

• Motions:
  • Defense successfully moved for summary judgment
  • Plaintiff appealed case to Connecticut Supreme Court
  • Court upheld trial court

Case 2: Killeen v. Reinhart

FACTS

• 20-ish year old woman, 6 months pregnant presents to obstetrician with an asthma attack in 1971
• Admitted to obstetrics ward – SOB, coughing, vomiting
• Asthma symptoms initially improved followed by quick deterioration
• Given cephalothin for possible pulmonary infection
  • 1st generation, similar structure to cephalexin
• Died within 24 hours of symptom deterioration

SOB = shortness of breath
Jury Members

- Assume you wrote and/or filled the prescription for cephalothin. Would you:
  - ☑ Settle
  - ☑ Go to trial

Case 2: Legal Outcome

- 3 physicians settled before trial for $265,000
- Hospital went to trial
  - General verdict against the hospital for $650,000
- Hospital appealed
  - Appellate court remanded the case back to the trial court
  - Judge stated "it cannot be concluded that the administration of cephalothin was so clearly contraindicated as to cast liability upon the hospital’s staff to have failed to question the doctors’ use of this medication"
Time-traveling hypothetical expert witness

• Penicillin allergic patients

<table>
<thead>
<tr>
<th></th>
<th>Ampicillin, n=70</th>
<th>Cephalothin, n=123</th>
<th>Carbenicillin, n=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intradermal</td>
<td>63%</td>
<td>43%</td>
<td>0%</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>100%</td>
<td>92%</td>
<td>0%</td>
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Beta-lactam Allergies
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