Beta-lactam Allergies: Misadventures of Misreporting

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Disclosures

• Nothing to disclose
Objectives

1. Explain the public health concerns of misreported allergies
2. Distinguish between different types of drug reactions
3. Systematically evaluate a reported drug allergy
   - Specifically, an allergy to penicillin
4. Develop a plan for the management of a patient with a reported penicillin allergy
REPORTED BETA-LACTAM ALLERGIES ARE A MAJOR PUBLIC HEALTH ISSUE

Broad class of antibiotics that includes penicillins
Characterized by beta-lactam ring

Examples:
Penicillins, aminopenicillins, cephalosporins, carbapenems, monobactams, and beta-lactamase inhibitors

Drugs of choice for several indications!
Beta-Lactam Allergies: A major public health issue!

• Penicillin allergy first documented in 1946
  – Most common beta-lactam and drug class allergy
  – Reported by **up to 10% of individuals** in USA

• Prevalence of true *IgE-mediated* allergy
  – Only 10-15% of patients with a reported penicillin allergy
  – Most common between ages 20-49
  – Anaphylaxis in 1 to 2 per 10,000 treated patients
But why is this a major public health issue?

- Preferred beta-lactam therapy is avoided in >50% of patients, even when a non-severe prior reaction is reported
  - Alternatives often less effective, more costly, and more toxic

- Beta-lactams (nafcillin/cefazolin) superior to vancomycin for methicillin-susceptible S. aureus (MSSA) bacteremia
  - Retrospective cohort, 267 patients
  - Mortality: Adjusted HR of 0.21 (95% CI: 0.09-0.47)
A MAJOR Public Health Issue.

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jeffres et al</strong></td>
<td>Clinical failure with beta-lactam (BL) or non-beta-lactam (NBL) with BL allergy in G- bacilli bloodstream infections</td>
<td>433 in BL group 119 in NBL group</td>
<td>▲ Clinical failure in NBL (38.7% vs 27.4%, p=0.03)</td>
</tr>
<tr>
<td>Retrospective Multicenter</td>
<td></td>
<td></td>
<td>▲ Length of stay in NBL (30.9 vs 21.5 days, p=0.065)</td>
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<td></td>
<td></td>
<td></td>
<td>▾ Appropriate empiric abx (74.8% vs 91.7%, p&lt;0.001)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Overall Hypersensitivity rate: 2.9%</td>
</tr>
<tr>
<td><strong>Macy et al</strong></td>
<td>Outcomes with and without penicillin “allergy” at admission</td>
<td>Matched 51,582 hospitalizations with penicillin allergy</td>
<td>▲ Length of stay: 0.59 days (95% CI, 0.47-0.71)</td>
</tr>
<tr>
<td>Retrospective Matched cohort study</td>
<td></td>
<td></td>
<td>▲ C. difficile: 23.4% (95% CI, 15.6% to 31.7%)</td>
</tr>
<tr>
<td></td>
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<td>▾ MRSA: 14.1% (95% CI, 7.1% to 21.6%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>▾ VRE: 30.1% (95% CI, 12.5% to 50.4%)</td>
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Antibiotics and Risk of Community-acquired *C. diff*

<table>
<thead>
<tr>
<th>Class</th>
<th>Odds Ratio vs. no antibiotics</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>16.80</td>
<td>7.48 to 37.76</td>
</tr>
<tr>
<td>Fluoroquinolones (e.g. ciprofloxacin, levofloxacin)</td>
<td>5.50</td>
<td>4.26 to 7.11</td>
</tr>
<tr>
<td>Cephalosporins, monobactams (e.g. aztreonam), and carbapenems (e.g. meropenem)</td>
<td>5.68</td>
<td>2.12 to 15.23</td>
</tr>
<tr>
<td>Penicillins</td>
<td>2.71</td>
<td>1.75 to 4.21</td>
</tr>
<tr>
<td>Macrolides (e.g. azithromycin, erythromycin)</td>
<td>2.65</td>
<td>1.92 to 3.64</td>
</tr>
<tr>
<td>Sulfonamides and trimethoprim (e.g. SMX/TMP)</td>
<td>1.81</td>
<td>1.34 to 2.43</td>
</tr>
<tr>
<td>Tetracyclines (e.g. doxycycline)</td>
<td>0.92</td>
<td>0.61 to 1.40</td>
</tr>
<tr>
<td>ANY ANTIBIOTIC</td>
<td>3.55</td>
<td>2.56 to 4.94</td>
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</table>

Highest risk is amongst drug classes commonly used in patients with a reported penicillin allergy.
Key Points

- Up to 90% of reported penicillin allergies are not true allergies
- Beta lactams often avoided in the presence of an allergy
- Unverified beta-lactam allergies represent a major public health issue

Compromise optimal medical care

Higher costs

Increased antibiotic resistance

Increased toxic effects
Why do we care? (and what can we do?)

• We need to be able to distinguish to optimally treat patients
• Clarification of beta-lactam allergies
  – Detailed patient interview
  – Cross-reactivity concerns
• Treating a patient with a reported penicillin allergy
  – Penicillin skin testing?
  – Graded drug challenge vs. desensitization
Types of Drug Reaction

**Type A**
- 85-90% of all adverse effects
- Predictable from pharmacologic properties of the drug
- Ex) Diarrhea from antibiotics, hypoglycemia from insulin

**Type B**
- 10-15% of drug reactions
- Hypersensitivity reactions
- Signs/symptoms differ from the pharmacologic action of drugs and cannot be predicted

Hypersensitivity (Type B) Reactions

**Type I: IgE-mediated**
- Minutes to hours
- Up to 72 hours
- **Urticaria (hives)**
- **Angioedema**
- **Bronchospasm**
- **Anaphylaxis**

**Type II: Cytotoxic**
- > 72 hours
- **Hemolytic anemia**
- **Thrombocytopenia**
- **Granulocytopenia**

**Type III: Immune complex**
- 10-21 days
- **Serum sickness**
- **Interstitial nephritis**
- **Arthralgia**
- **Lymphadenopathy**

**Type IV: Cellular mediated (delayed)**
- 2-4 days
- **Contact dermatitis**
- **Drug fever**
- **SJS**
- **DRESS**

Why are there so many reported allergies?

• Type A reactions misreported as an allergy
• Penicillins can cause all 4 Type B drug reactions
• Childhood allergies:
  – Rashes and viral infection
  – Unclear history
• Family history
  – No predictable pattern to inheritance
Key Points

- Penicillins can cause several different types of drug reactions

- **Up to 90%** of drug reactions are **non-allergic** in nature
  - Often misreported as allergies!

- Type I hypersensitivity reactions are **immediate** and are mediated by drug-specific IgE antibodies
  - Distinct from other types of reactions
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• Treating a patient with a reported penicillin allergy
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Obtaining a Detailed History

• What penicillin did you take?
• What symptoms did you experience?
  – How long into therapy did you experience these symptoms?
  – How long ago did this reaction happen?
  – What other medications were you taking when you had this reaction?
• Have you taken a penicillin since this reaction?
  – Have you ever taken a cephalosporin?
WHAT PENICILLIN DID YOU TAKE?
WHAT SYMPTOMS DID YOU EXPERIENCE?

- Wheezing, throat or mouth swelling, hives/rash?
- Did you have to go to the hospital or emergency room?
- If a rash occurred what did it look like?
Hives (Urticaria) vs. Rash

**IgE-mediated**
- Type I Hypersensitivity
- Do not give the same drug
- Skin testing can confirm

https://www.aad.org/public/diseases/itchy-skin/hives

**Not IgE**
- Graded challenge
- Skin test not predictive
- Will NOT result in anaphylaxis if re-challenged

HOW LONG INTO THERAPY DID THIS OCCUR?
Hypersensitivity (Type B) Reactions

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- DRESS

HOW LONG AGO DID THIS HAPPEN?
Childhood allergies

- Viral illness can present with rash
- Higher risk of Type IV reaction with viral infections and exacerbation of autoimmune disease
- Children with EBV receiving aminopenicillins have demonstrated non-reproducible rashes
  - 90% of patients receiving ampicillin with EBV demonstrated non-pruritic morbilliform rash
Is it safe now?

Patients may “outgrow” allergy

• Even with a well-documented allergy, hypersensitivity may not persist over time due to loss of anti-PCN IgE antibodies
  o 10 years: ~50% will lose allergy
  o 15 years: ~75% will lose allergy
HAVE YOU TAKEN PENICILLIN SINCE THEN?
WHAT HAPPENED?
• Or other penicillins? (amoxicillin, nafcillin, etc.)

WHAT ABOUT A CEPHALOSPORIN?
WHAT HAPPENED?
• Use both trade names and generic names
• Ask about IV and PO antibiotics
• Other beta-lactams: carbapenems, monobactams (aztreonam), etc.
Cross-reactivity: Cephalosporins

• Early reports: Up to 41%!! (Mostly in the 10-20% range)
  – Until 1982, cephalosporins were contaminated with penicillin
  – Non-allergic ADEs reported as drug allergies (Type A)
  – Cephalothin was commonly used
• Multiple drug allergy syndrome
• 1-3% incidence of reaction independent of penicillin allergy
Determinants of IgE-mediated Penicillin Allergy

• Penicillin immunologically inert
  – Formation of hapten is necessary
• Converted to reactive intermediates under physiologic conditions
  – Ring opening
  – Degradation in the GI tract
• Major determinant responsible for > 75% of reactions

Cephalosporins do NOT form these!!

NEJM 2006;354:601-609
Side Chain Theory

6-Position: Differentiates all penicillins (Ampicillin, Piperacillin, Oxacillin, etc.)

7-Position: Alters microbiologic properties
• Determines penicillin cross-reactivity

3-Position: Alters PK properties
• May determine cross-reactivity among cephalosporins

Penicillin Core Structure

Cephalosporin Core Structure

http://en.wikipedia.org/wiki/Penicillin
http://en.wikipedia.org/wiki/Cephalosporin

PennState Health
Milton S. Hershey Medical Center
Side-Chain Similarities

• Similarities between the penicillin 6-position and cephalosporin 7-position may cause cross-reactivity

<table>
<thead>
<tr>
<th>Patient Allergic To:</th>
<th>Avoid:</th>
</tr>
</thead>
</table>
| Penicillin          | Cephalothin (1st)  
|                     | Cephalodrine (1st)  
|                     | Cefoxitin (2nd)     |
| Amoxicillin         | Cefadroxil (1st)   
|                     | Cefprozim (2nd)     |
| Ampicillin          | Cephalalexin (1st) 
|                     | Cephadrine          
|                     | Cephalolycin        
|                     | Cefaclor (2nd)      |
| Ceftazidime         | Aztreonam          |
No cross-reactivity with cephalosporins in patients with penicillin allergy

- **Objective:** Evaluation of cross-reactivity between penicillin and cephalosporins
- **Methods:** Observational, retrospective study
- **Results:** 22 patients evaluated (10 cutaneous, 12 cardio/resp rxn)
  - Allergy – 7 Amoxicillin, 14 Amox/Clav, 1 Penicillin
  - Ceftriaxone and ceftazidime skin tests negative for all patients
- **Conclusions:** Certain cephalosporins are safe for patients with penicillin allergy (third and fourth generation)
So is there cephalosporin cross-reactivity?

• True incidence: 0-5%
  – Similar side chains: higher risk
  – Minimal cross-reactivity with 2\textsuperscript{nd}, 3\textsuperscript{rd}, 4\textsuperscript{th} generations
Other Beta-lactam Cross-reactivity

• Carbapenems (e.g. meropenem, ertapenem, imipenem)
  – Early reports: 47.4%!!
    • Flawed design using imipenem-cilastatin skin test, no actual doses given
  – Recent prospective studies: <1% !!

• Monobactams (aztreonam)
  – Essentially 0% cross-reactivity
  – Shares a side chain with ceftazidime!

Cross-reactivity: Summary

**Cephalosporins**
- 2% of penicillin skin test positive patients will react
- 0.1% in patients without severe reaction

**Carbapenems**
- < 1% cross-reactivity

**Aztreonam**
- Negligible cross-reactivity

References:
WHAT OTHER MEDICATIONS WERE YOU TAKING?
Why do we care? (and what can we do?)

• We **need** to be able to distinguish to optimally treat patients

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  – Detailed patient interview
  – Cross-reactivity concerns

• Treating a patient with a reported penicillin allergy
  – Penicillin skin testing?
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Suspected Type I reaction

- **Penicillin skin testing** is diagnostic
- **Desensitization** or “induction of drug tolerance”
- Consider alternative antibiotics based on the history and severity of reaction
  - History of tolerating other beta-lactams?
  - 3rd, 4th generation cephalosporins, monobactams, and carbapenems
  - Be mindful of side chains
Penicillin Skin Test

- Evaluates IgE-mediated allergy
  - Not Types II-IV, Type A, or idiosyncratic
  - AVOID if history of SJS or TEN, extreme hypersensitivity
- Useful for ruling out allergy
  - Negative predictive value: 97-99%
  - Positive predictive value: 50%
- Can be done in an outpatient setting
- Now recommended in antimicrobial stewardship guidelines

Pharmacother 2013;33:856
Clin Infect Dis 2016;62:e51-77
Penicillin Skin Test

Skin puncture
If positive, stop
If negative, continue testing

Intradermal injection
If positive, stop
If negative or ambiguous, continue to challenge

Graded challenge
If positive, stop
If negative, continue with normal drug dosing

*Avoid H1-antihistamines and vasopressors for 48 hours before
Penicillin Skin Test

- Four substances:
  - Minor determinants: Penicillin G
  - Major determinant: Benzyl penicilloyl polylysine (Pre-Pen®)
  - Negative control: saline
  - Positive control: histamine

https://penallergytest.com/procedure/
Negative Penicillin Skin Test

- <5% risk of reaction after penicillin administration
  - Negative predictive value for tolerance is 99%
- Cephalosporin administration with minimal concern for reaction
  - Regardless of severity
  - Consider graded challenge, but not necessary
- Rate of re-sensitization very low
  - For penicillin, cephalosporin, and beta-lactam
- Remove the allergy and educate patient

Positive Penicillin Skin Test

• 50% or higher incidence of reaction after penicillin administration
• Consider alternative antibiotic and avoid first generation cephalosporins
  – 2nd, 3rd, 4th generation cephalosporins may still be safe
  – Carbapenems and monobactams likely safe
• If no alternative therapy, consider desensitization
  – Induction of drug tolerance appears safe in patients with Type 1 allergy
<table>
<thead>
<tr>
<th></th>
<th>Graded Drug Challenge</th>
<th>Desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History of allergy</strong></td>
<td>Vague, unlikely IgE-mediated</td>
<td>Proven, clear allergic events (hives, angioedema, anaphylaxis)</td>
</tr>
<tr>
<td><strong>Reason to perform and</strong></td>
<td>Disprove hypersensitivity, Confirm ability</td>
<td>No alternative therapies, Generate temporary tolerance</td>
</tr>
<tr>
<td><strong>goal</strong></td>
<td>to receive penicillin</td>
<td></td>
</tr>
<tr>
<td><strong>Relative contraindications</strong></td>
<td>Concurrent illness</td>
<td>Uncontrolled asthma, concurrent illness, hemodynamic instability</td>
</tr>
<tr>
<td></td>
<td>Suspect true IgE allergy</td>
<td></td>
</tr>
<tr>
<td><strong>Absolute contraindications</strong></td>
<td>Non IgE-mediated event (SJS, DRESS)</td>
<td></td>
</tr>
<tr>
<td><strong>Starting dose</strong></td>
<td>1:100 therapeutic dose</td>
<td>1:1,000,000 or 1:100,000 of therapeutic dose</td>
</tr>
<tr>
<td><strong>Steps to complete test</strong></td>
<td>3-5</td>
<td>10-20</td>
</tr>
<tr>
<td><strong>Time to complete test</strong></td>
<td>1-3 hours</td>
<td>2-6 hours</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Clinic or inpatient</td>
<td>Inpatient, Emergency Department, ICU</td>
</tr>
<tr>
<td><strong>Sustainability</strong></td>
<td>Once allergy disproven, drug can be given in the future</td>
<td>Temporary, ongoing administration necessary to maintain tolerance</td>
</tr>
</tbody>
</table>
Suspected Type II-IV Allergy

• No tests exist, cross-reactivity unknown for most
  – Diagnose based on detailed history
  – Avoid *penicillin* and all related drugs (including skin testing) if Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN)

• History of non-pruritic morbilliform eruption
  – Often, not distinguishable from urticaria based on history
  – Can consider graded drug challenge with close monitoring
    • Be mindful of similar side-chain drugs
    • NOT in patients with a history of SJS/TEN
Update the record!

• Allergy history documentation is poor
• Allergy records are rarely updated to demonstrate tolerance
  – In one institution, **only 18%** of patients with a reported penicillin allergy who received a penicillin antibiotic without incident had their records updated
• Algorithms to guide penicillin allergy histories can improve documentation
A proactive approach to penicillin allergy testing in hospitalized patients

• **Objective:** Evaluate patients with penicillin allergy to remove inaccurate diagnosis and reduce use of beta-lactam alternatives

• **Methods:** Penicillin skin tests and challenges performed by clinical pharmacist

• **Results:** 228 of 252 subjects (90.5%) had penicillin allergy removed
  – 85 (38%) patients received beta-lactams

• **Conclusions:** Penicillin allergy testing effectively removed reported allergies in hospitalized patients
Beta-lactams allergies are the most commonly reported drug allergies

- Several are not truly allergic in nature

There are major public health implications of inadequate allergy documentation

- Often lead to avoidance of preferred therapy
- Poorer outcomes, higher cost, greater toxicity, higher risk of resistance

Cross-reactivity between penicillins and other beta-lactams is lower than originally thought

- Certain cephalosporins, carbapenems, and monobactams present low risk

Accurate and detailed allergy history is crucial for optimal antibiotic therapy

- Penicillin skin testing and graded drug challenges are useful diagnostic measures
- Always update the medical record when information is gained

Conclusions
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