Itch Not That Bad: Desensitizing Our Fear of Beta-Lactam Allergies

Prasanna Narayanan, PharmD, BCPS
Clinical Pharmacist – Internal Medicine
Mayo Clinic Hospital – Rochester

Pharmacy Grand Rounds
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Objectives

- Categorize types of hypersensitivity reactions
- Discuss potential morbidity consequences of treating patients with reported beta-lactam allergies
- Describe methods to appropriately investigate and confirm beta-lactam allergies
- Outline a practical approach to manage beta-lactam allergies
Definitions

Adverse Drug Reactions

Predictable

Unpredictable

Hypersensitivity Reactions

Allergic (Immunologic)

Non-Immunologic

Types of Allergic Drug Reactions

Immediate

Type I
- IgE Mediated
- Anaphylaxis

Delayed

Type II
- IgG mediated cell destruction

Type III
- IgG:drug immune complex deposition/complement activation
- Serum sickness, vasculitis, drug fever

Type IV
- T-Cell mediated
- Contact dermatitis, SJS, TEN, DIHS

Immediate: Delayed

Ig: Immunoglobulin
SJS: Stevens Johnson Syndrome
TEN: Toxic Epidermal Necrolysis
DIHS: Drug-Induced Hypersensitivity Syndrome

Type I IgE-Mediated Reaction Mechanism

- Vasoactive mediators released as a result of mast cell and basophil degranulation

Type I IgE-Mediated Allergic Reaction

• Immediate reaction (within one hour)
• Requires previous exposure (or to a cross reactive agent)
• Symptoms:
  • Urticaria, angioedema, wheezing
  • Anaphylaxis
• Common antibiotics:
  • Beta-lactams, sulfonamides, fluoroquinolones

Beta-Lactam Allergy

• Penicillin is the most commonly reported medication allergy
  • 10% of patients in the US

• Incidence of BL allergy among hospitalized patients in the U.S. is 17%
  • 16% penicillins, 1% cephalosporins

BL: beta-lactam

Risk Factors for BL Allergy

- Ages 20-50
- Female
- Repeated or prolonged exposures
- Parenteral administration
- Other drug allergies

- First degree relatives with allergy
- Allergic diseases (e.g., asthma)

Which of the following statements is true?

A. 25% of patients in the U.S. report a BL allergy
B. Type II allergic reactions occur within one hour
C. Type I and IV are the least common allergic reactions
D. Repeated exposure to penicillin is a risk factor for developing an allergy
Objectives

• Categorize types of hypersensitivity reactions
• Discuss potential morbidity consequences of treating patients with reported antibiotic allergies
• Describe methods to appropriately investigate and confirm allergies
• Outline a practical approach to manage antibiotic allergies
10% of the population has a reported penicillin allergy

Only 1% of the entire population has a true IgE-mediated allergy to penicillin

Potential Consequences

- Beta-Lactam Allergy
- Limited Alternative Antibiotics
- Healthcare Costs
- Resistance
- Poor Clinical Outcomes
## Increased Healthcare Costs

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Patients*</th>
<th>Cost Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li, et al</td>
<td>Cost-analysis of alternative antibiotics compared with first-line agents</td>
<td>N=102</td>
<td>1.82-2.58 fold higher total cost of antibiotics</td>
</tr>
<tr>
<td>Picard, et al.</td>
<td>Additional costs of alternative antibiotics calculated</td>
<td>N=48</td>
<td>Additional cost of $250 per patient</td>
</tr>
<tr>
<td>Sade, et al.</td>
<td>Antibiotic cost comparison with matched patients</td>
<td>N=118</td>
<td>Mean antibiotic cost 63% higher in-hospital; 38% higher cost upon discharge</td>
</tr>
</tbody>
</table>

*All hospitalized patients with beta-lactam allergy

### Increased Risk of Resistant Infections

<table>
<thead>
<tr>
<th>Result</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>1.1 (95% CI, 1.0-1.3)</td>
</tr>
<tr>
<td>VRE</td>
<td>1.3 (95% CI, 1.1-1.5)</td>
</tr>
<tr>
<td>C. difficile</td>
<td>1.2 (95% CI, 1.1-1.3)</td>
</tr>
</tbody>
</table>

VRE: vancomycin-resistant *Enterococcus*

MRSA: methicillin-resistant *S. aureus*

Appropriate Empiric Therapy

- BLs are first-line therapies for common infections
- Use of NBLs to treat gram negative infections
  - Only one high quality trial
  - Non-inferiority
  - Assessment of clinical failure
- Delay of appropriate antibiotic therapy increases mortality


NBL: Non-beta-lactam

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, retrospective, cohort analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Adult patients with a GNB BSI and BL allergy</td>
</tr>
<tr>
<td><strong>Treatment Groups</strong></td>
<td>Empiric IV antibiotics: BL (n=433) vs NBL (n=119)</td>
</tr>
</tbody>
</table>
| **Primary Outcome** | Clinical Failure (72-96 hours)  
- Tmax ≥38°C  
- New use of vasopressors  
- New use of mechanical ventilation  
- New intensive care unit admission  
- Death |
| **Secondary Outcomes** | Hypersensitivity  
- Any allergy documented after receipt of antibiotic(s)  
Rate of appropriate empiric therapy  
Hospital length of stay |

GNB BSI: gram negative bacilli bloodstream infection

BL vs. NBL

- Clinical Failure:
  - BL: 27%
  - NBL: 38%
  - P = 0.03

- Appropriate Antibiotics:
  - BL: 92%
  - NBL: 75%
  - P < 0.001

BL vs. NBL

- Rate of hypersensitivity
  - 16/552 patients (2.9%)
  - 13/16 patients received a BL

- Hospital length of stay

Higher rate of clinical failure with NBL and overall low rate of hypersensitivity supports the use of BL antibiotics from an alternative class in patients with a BL allergy

What is a possible explanation for why patients treated with NBLs have worse outcomes?

A. NBL antibiotics are less likely to be active against gram negative pathogens

B. NBL antibiotics have a higher volume of distribution

C. NBL antibiotics are contraindicated for bloodstream infections
Objectives

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Assessment of Reaction

- Side effect vs. allergic reaction
- Type I vs Type IV
- Anaphylaxis - signs/symptoms in two or more systems:

<table>
<thead>
<tr>
<th>System</th>
<th>Signs/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>hives, angioedema, flushing, itching</td>
</tr>
<tr>
<td>Respiratory</td>
<td>wheezing, shortness of breath</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>vomiting, abdominal cramping, diarrhea</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>hypotension, tachycardia, chest pain</td>
</tr>
</tbody>
</table>

- <0.015% rate of anaphylaxis (penicillin)
- <1% rate of fatal anaphylaxis (all causes)

Penicillin Skin Testing

• Preferred method of evaluation/diagnosis of Type I reactions

• Not recommended for patients without a history of a reaction or never taken penicillin

• Reagents:
  • Benzylpenicilloyl polylysine injection (PRE-PEN®)
  • Minor determinants
  • Penicillin G
  • +/- amoxicillin/cefazolin

Penicillin Skin Testing, cont’d

- **Advantages:**
  - Fast – 45 minutes total
  - Reliable – negative predictive value >95%
  - Safe – children and pregnant women

- **Considerations:**
  - Antihistamine use
  - Proper technique
  - Reagents can be difficult to maintain
  - Cost/insurance coverage

Antimicrobial Stewardship

• Waning sensitivity
  • Gradual loss of IgE antibodies
  • 50% lose sensitivity in 5 years; 80% in 10 years

• <0.1% of 25 million people with penicillin allergy undergo skin testing

• Pre-operative skin testing reduces unnecessary use of vancomycin

Consider penicillin skin testing referrals when possible

Graded/Oral Dose Challenge

• Patients less likely to be allergic and in need of a penicillin in immediate future
  • Non-life threatening reaction/vague history lacking features of IgE response
  • >10 years ago with no re-exposure

• Confirms absence of allergy

• Higher risk than skin testing

• Example of oral dose challenge: amoxicillin 250 mg once

Which of the following statements is true?

A. Graded challenges are recommended in patients with a history of IgE-mediated reactions
B. Penicillin sensitivity wanes over time
C. Penicillin skin testing is associated with a low negative predictive value
D. Anaphylaxis commonly results in death
Objectives

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Cross-Reactivity
Cross-reactivity - Cephalosporins

- Traditionally thought to be ~10%
- Limitations of past studies

**Campagna, et al. 2012**
- Literature review 1950-2012
- Overall cross-reactivity 1% with first generation cephalosporins
- Negligible with 3rd/4th generation cephalosporins
- 2.5% in patients with confirmed penicillin allergy

### Identical Side Chains

<table>
<thead>
<tr>
<th>R₁-Group Side Chains</th>
<th>Amoxicillin</th>
<th>Ampicillin</th>
<th>Ceftriaxone</th>
<th>Ceftazidime Aztreonam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefadroxil Cefprozil</td>
<td>Cephalixin</td>
<td>Cefaclor</td>
<td>Cefotaxime</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cefpodoxime</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R₂-Group Side Chains</th>
<th>Cephalexin</th>
<th>Cefuroxime</th>
<th>Cefoxitin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefadroxil</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Penicillin**

**Cephalosporin**

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Cross-reactivity - Carbapenems

Systematic review PCN-allergic patients (N=838)

<table>
<thead>
<tr>
<th>History of IgE-mediated penicillin reaction</th>
<th>Proven</th>
<th>Suspected</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Suspected</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Possible</td>
<td>1</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

IgE-mediated carbapenem reaction

PCN: penicillin

Cross-reactivity - Aztreonam

• Less immunogenic than other BLs

Gaeta, et al. 2015

• 212 penicillin skin test positive patients
• Carbapenem/aztreonam skin tests followed by graded challenge if negative
• No positive skin tests or reactions to challenges

• Disadvantages:
  • Efficacy/limited coverage
  • Shortages

Desensitization

- Proven (skin test positive) or highly suspected to have Type I allergic reaction to BLs
- No alternative antibiotics available
- Temporarily alters immune response during course of therapy
- Oral route preferred
- Generally performed inpatient (ICU)

ICU: intensive care unit

Desensitization Protocol Example

- **Penicillin G IV**

<table>
<thead>
<tr>
<th>Every 15 minutes</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>20 units</td>
<td>16,000 units</td>
</tr>
<tr>
<td>40 units</td>
<td>30,000 units</td>
</tr>
<tr>
<td>80 units</td>
<td>60,000 units</td>
</tr>
<tr>
<td>160 units</td>
<td>110,000 units</td>
</tr>
<tr>
<td>300 units</td>
<td>200,000 units</td>
</tr>
<tr>
<td>600 units</td>
<td>400,000 units</td>
</tr>
<tr>
<td>1,200 units</td>
<td>1,600,000 units</td>
</tr>
<tr>
<td>2,000 units</td>
<td><strong>After 60 minutes</strong></td>
</tr>
<tr>
<td>4,000 units</td>
<td>3,200,000 units</td>
</tr>
</tbody>
</table>

- Begin full goal dose 60 minutes after previous dose
Drug Avoidance

- Complete avoidance in limited situations
  - Avoid BLs with similar side chains
- Severe hypersensitivity syndromes
  - SJS, TEN, DIHS, serum sickness, AIN, hemolytic anemia
  - Avoid using the offending agent
  - Skin testing is not recommended

AIN: acute interstitial nephritis

Approach to Patients with “PCN Allergy”

**Inpatient**
- Need for antibiotics
  - **Urgent, allergy cannot be verified**
    - Recommend later generation cephalosporin or carbapenem
  - **Non-urgent**
    - Consider allergy consult and/or skin testing

**Outpatient**
- Skin testing
  - **Skin test +**
    - Avoid specific BL/agents with similar side chain
  - **Skin test -**
    - Safe to use all BLs, consider dose challenge
  - **Skin test indeterminate or unavailable**
    - Oral challenge based on history
Carbapenems are safe to use in patients with a history of an immediate hypersensitivity reaction to penicillins.

A. True
B. False
Summary

• Penicillin is the most common drug allergy but true IgE mediated reactions are rare
• Consequences of treating BL allergic patients include increased cost, resistance, and poor clinical outcomes
• Allergies should be properly investigated and confirmed through history and skin testing
• Cephalosporins and carbapenems are safe alternatives in most “PCN-allergic” patients
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Questions?

Prasanna Narayanan, PharmD, BCPS
Clinical Pharmacist – Internal Medicine
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narayanan.prasanna@mayo.edu

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