Drug Allergy: Cost, Containment and Reduction of Use

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Objectives

• Recognize adverse outcomes and costs associated with drug allergy.
• Understand the pathogenesis of common drug hypersensitivity reactions and diagnostic options.
• Recognize the challenges associated with management of multiple drug allergies.
• Discuss approaches to reduce the cost and adverse effects associated with drug allergy.
Adverse Drug Reactions

- Any noxious, unintended, and undesirable effect of a drug.

**Type A reactions**

- Predictable

- Dose dependent

- Related to the pharmacology of drug

- 80-90% of adverse drug reactions

- example: drug with anti-cholinergic effects causing urinary retention

**Type B reactions**

- Unpredictable, unrelated to known pharmacologic action

1. **Intolerance:** pt develops a known side effect at a lower dose of med than expected.

2. **Idiosyncratic:** pharmacogenomic effect: pt has a reaction based on the way their body processes a drug – secondary to they genetics (i.e. aspirin).

3. **Immunologic/Hypersensitivity.**
Why is it Important to Characterize Adverse Drug Reactions and Drug Allergy?

- Non-immunologic reactions or mild hypersensitivity reactions does not complete preclude use of drug again.
- Use of alternative agents may be more expensive, less efficacious, and/or have more side effects.
- Having a history of antibiotic allergy (real or not) is associated with unexpected adverse outcomes.¹
  - Longer hospital stays
  - Increased mortality
  - Increased drug resistant infections
- Most patients carrying a label of “drug allergy” do not have true hypersensitivity; may be needlessly avoiding drug.
- Management of patients with multiple drug allergies can be difficult.

# Gell-Coombs classification of Immune Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Gell-Coombs classification</th>
<th>Mechanism</th>
<th>Examples of adverse penicillin reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Anaphylactic (IgE-mediated injury)</td>
<td>Acute anaphylaxis, Urticaria</td>
</tr>
<tr>
<td>II</td>
<td>Complement-dependent cytolysis (IgG/IgM)</td>
<td>Hemolytic anemias, Thrombocytopenia</td>
</tr>
<tr>
<td>III</td>
<td>Immune complex damage</td>
<td>Serum sickness, Drug fever, Some cutaneous eruptions and vasculitis</td>
</tr>
<tr>
<td>IV (also types IV a-d)</td>
<td>‘Delayed’ or cellular hypersensitivity</td>
<td>Contact dermatitis, Morbilliform eruptions, Interstitial nephritis, SJS/TEN, Hepatitis</td>
</tr>
</tbody>
</table>
What Makes a Drug an Allergen?

Risk Factors

Drug Factors
- Chemical Properties of Drug
- Frequency, Dose of Drug
- Route of Adm. (IV > PO)
- Size, immunogenicity

Patient Factors
- Age, sex
- Allergic history
- Genetic Predisposition

Disease Factors
- Alt. of Metabolic Pathway
- Immune system “turned on” or Immunodysfunction

Age and Gender as Risk Factors

Penicillin Allergy by Gender

- Male: 33%
- Female: 67%


Jhaveri, P and Ishmael, F
Manuscript in preparation
Allergic Profile of Antibiotics

**HIGH**
- Beta lactams
  - Amino-penicillins
  - Other penicillins
  - 1\textsuperscript{st} gen cephalosporins
  - Carbapenems
  - 2\textsuperscript{nd} & 3\textsuperscript{rd} gen cephalo.
  - Monobactams, etc.
  - Cefaclor
- **Sulfonamides**
  - Antimicrobials

**MODERATE**
- Anti-tuberculous drugs
  - Vancomycin
- Aminoglycosides

**LOW**
- Macrolides
  - Erythromycin
  - Clarithromycin
  - Azythromycin
- **Quinolones**
  - Moxifloxacin
  - Levofloxacin
  - Ciprofloxacin
- **Tetracyclines**
  - Metronidazole
  - Clindamycin
## Prevalence of Specific Antibiotic Allergy at HMC

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Total #</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Lactams</td>
<td>23004</td>
<td>44.72</td>
</tr>
<tr>
<td>Sulfa</td>
<td>14069</td>
<td>27.35</td>
</tr>
<tr>
<td>Macrolide</td>
<td>5632</td>
<td>10.95</td>
</tr>
<tr>
<td>Quinolone</td>
<td>3793</td>
<td>7.37</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>2204</td>
<td>4.29</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1039</td>
<td>2.02</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>693</td>
<td>1.35</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>552</td>
<td>1.07</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>310</td>
<td>0.60</td>
</tr>
<tr>
<td>Anti-mycobacterial</td>
<td>58</td>
<td>0.11</td>
</tr>
<tr>
<td>Linezolid</td>
<td>38</td>
<td>0.07</td>
</tr>
<tr>
<td>Other</td>
<td>29</td>
<td>0.06</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>11</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Total # Antibiotic Allergies</strong></td>
<td><strong>51432</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
Hypersensitivity to other Classes of Drugs

 Likely to cause hypersensitivity  
• Latex  
• Aromatic anticonvulsants  
• Anesthetics/muscle relaxants  
• NSAIDs  
• Opioids  
• Radiocontrast agents  

 Unlikely to cause hypersensitivity (but often implicated)  
• Local anesthetics (lidocaine)  
• Antihypertensives  
  – B-blockers  
  – diuretics  
  – ACE-Inhibitors (angioedema is a rare, but real side effect)  
• Glucocorticoids  
• Vaccines
Penicillin Allergy

• Most frequently reported drug allergy (rate 3-10%).
• About 90% of patients labeled as penicillin allergic are not truly allergic.
• Prevalence of true allergy is about 1-3%.
• Personal history of atopy (allergic rhinitis, eczema, food allergy) increases risk.
• Even in patients with true allergy, about 80% will lose their allergy within 10 years.
Clinical Features

• Classic history – prior use of penicillins without difficulty. Subsequent course results in symptoms after first dose.

• Dose and route of administration may increase risk and severity (high dose, IV, repeated administration more likely to induce).

• Skin findings: hives, angioedema (in contrast to non-IgE mediated reactions tend to be macular).

• Systemic symptoms: bronchospasm, GI sx, cardiovascular collapse.
Why is Penicillin Allergy Important?

- First line agent for many infections, inexpensive, efficacious.
- Widely used – almost all Americans will have multiple doses of penicillins by adulthood.
- Highly cross-reactive within the penicillin family (need to avoid the whole class).
- May be cross-reactive with other beta-lactam antibiotics such as cephalosprins.
- Chemically reactive – prone to causing hypersensitivity.
- Reported allergy is high but most are not allergic.
- Adverse effects associated with penicillin allergy.
Adverse Outcomes in Patients with Penicillin Allergy Admitted with Pneumonia

Adverse Outcomes in Patients with Penicillin Allergy Admitted with Bacteremia

Association of Antibiotic Allergy With Severe Infections

Association of Antibiotic Allergy With Drug Resistant Infections

<table>
<thead>
<tr>
<th>MRSA (methicillin-resistant staph. Aureus)</th>
<th>VRE (vancomycin-resistant enterococcus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCN Allergy</td>
<td>PCN Allergy</td>
</tr>
<tr>
<td>Other Abx Allergy</td>
<td>Other Abx Allergy</td>
</tr>
</tbody>
</table>

- * indicates statistical significance

Adverse Outcomes Associated with Penicillin Allergy

• Clear associations and rationale for why PCN allergy is important
• Nature of association unclear
• Can accurately diagnosing patients with penicillin allergy be beneficial?
Can Penicillin Allergy be Accurately Diagnosed?

• Depends on the mechanism
IgE Mediated Drug Allergy

Drug serum protein

Neo-antigen recognized as foreign, IgE antibody generated

IgE binds to receptors on surface of mast cells and basophils

Mediator release, Allergic symptoms

Repeat drug exposure
Skin Testing for Penicillin Allergy

- Consists of two components: Pre-Pen: a conjugated penicillin to a polylysine group (mimics hapten carrier) and native penicillin G.
- Pre-Pen is the only conjugated reagent for antibiotic testing. Now available again for testing.
- Administered as a skin prick or intradermal test.
- If IgE is present on skin mast cells, mediator release causes formation of a wheal and flare response.
Penicillin skin testing

- Sensitivity using the combination of conjugated penicillin and penicillin G is around 95-97%.
- If skin prick testing and intradermal testing are both negative, an oral challenge is performed using penicillin or amoxicillin (250-500 mg).
- A combination of negative skin test and challenge effectively rules out IgE-mediated allergy.
- A positive skin test or challenge confirms IgE-mediated allergy and penicillins should be avoided.
- High level of cross-reactivity within penicillin family.
Is Skin Testing Useful for Other Drugs?

• There are limited diagnostic tests available.
• Sensitivity to other small molecules drugs is low:
  — no agents other than PCN that mimic hapten-carrier.
  — may be useful if test is positive.
• High sensitivity skin testing can be performed for:
  — complete antigens (do not need to form haptens): recombinant proteins, vaccines, insulin.
  — functionally multivalent compounds: succinylcholine and quaternary amines.
Other Diagnostic Tests

• In vitro testing – none that are standardized or useful clinically.

• Gold standard is provocation testing (drug challenge).
  – Administer implicated drug at increasing doses (1:100, 1:10, 1:1).
  – Objective reaction confirms hypersensitivity.
  – Only done if pre-test probability of true allergy is LOW.
What Happens if a Patient is Truly Penicillin Allergic?

- Physicians are more likely to give vancomycin\(^1\).
- Vancomycin allergy is rising, and diseases such as vancomycin resistant enterococcus is increasing\(^2\).
- Other beta-lactams should be considered: monobactams are safe\(^3\); carbapenems\(^4,5\) are likely safe.
- We still don’t know if cephalosporins are safe, but newer data suggests a low rate of cross-reactivity with penicillins.

\(^2\)Ishmael et al. Manuscript in preparation
\(^3\)Drug Allergy Practice Parameters. Ann Allergy Asthma Immunol. 2010
\(^4\)Romano et al. Annals of Internal Med. 2007
\(^5\)Atanaskovic-Markovic M et al. Allergy 2008
Physicians are Not Aware of Safe Alternatives in Penicillin Allergy

<table>
<thead>
<tr>
<th>Answer Options</th>
<th>Urticaria, % responses:</th>
<th>Anaphyaxis history, % response</th>
<th>Positive SPT, % response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>46.8</td>
<td>22.9</td>
<td>30.3</td>
</tr>
<tr>
<td>Monobactam</td>
<td>56</td>
<td>38.5</td>
<td>47.7</td>
</tr>
<tr>
<td>1st generation cephalosporin</td>
<td>37.6</td>
<td>5.5</td>
<td>22.9</td>
</tr>
<tr>
<td>2nd generation cephalosporin</td>
<td>45.9</td>
<td>9.2</td>
<td>29.4</td>
</tr>
<tr>
<td>3rd generation cephalosporin</td>
<td>52.3</td>
<td>10.1</td>
<td>37.6</td>
</tr>
<tr>
<td>4th generation cephalosporin</td>
<td>49.5</td>
<td>9.2</td>
<td>33</td>
</tr>
<tr>
<td>Would need further testing</td>
<td>22.9</td>
<td>40.4</td>
<td>15.6</td>
</tr>
<tr>
<td>None of the above</td>
<td>9.2</td>
<td>24.8</td>
<td>18.3</td>
</tr>
<tr>
<td>Other</td>
<td>3.7</td>
<td>3.7</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Type IV Hypersensitivity Reactions

Antigen Presenting Cell

Native drug or Hapten-carrier

MHC

T-cell Receptor

T-cell

Macrophages

Neutrophils

Eosinophils

Cytotoxic T-cells
T-cell Mediated Drug Reactions

**Severity**

- **Mild**
  - Macular rash
  - Can safely use again

- **Moderate**
  - Macular rash + fever/other combination of symptoms/rash
  - More extensive
  - Avoid drug, ?? use again if clinical need exists

- **Severe**
  - DRESS (Drug Rash With Eos & Systemic Sx)
  - Stevens-Johnson (SJS)
  - Toxic epidermal Necrolysis (TEN)
  - Never use drug again, or same class
T-Cell Induced Reactions

Most common reaction is a macular drug eruption:

• Characterized by delayed reactions, patient on drug for ~1 week when rash begins.
• Usually self limited.
• May be able to treat through rash if clinically indicated.
• Can use the same agent again (or same class).

Mild Reactions are Usually Not Reproducible

• Only 6-7% of drug rashes are reproducible with oral challenge in children that developed a rash with penicillin use.

• These with positive reactions on challenge were mild.

• Many reactions may be due to a co-existing infection (i.e. patient with mononucleosis that develops a rash after receiving ampicillin).

Severe T-cell Reactions

• More severe reactions characterized by:
  • Fever
  • Mucous membrane involvement
  • Involvement of other organ systems:
    – CBC abnormalities
    – Elevation in LFTs, decreased renal function
  • Target lesions, bullous rash
• These are signs of a more severe drug reaction (SJS, TEN, DRESS: definitely avoid implicated medication, refer to ER, allergy consult

Diagnostic Tests for T-cell Reactions

• Even more limited options vs IgE-mediated reactions

• Patch testing (similar to contact dermatitis testing): low sensitivity and specificity.

• In vitro testing:
  – no good commercially available tests.
Multiple Drug Allergies

- Patients often have allergies listed to 2 or more medications.
- Difficult to manage patients with multiple drug allergies.
- Reactions are not usually true hypersensitivity reactions.
- Often due to incorrect classification of drug reactions (Type “A” reactions labeled as allergy).
Multiple Drug “Allergies” are Common

<table>
<thead>
<tr>
<th>Number of “Allergies”</th>
<th>Individuals</th>
<th>Percent Reporting</th>
<th>Population Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57,310</td>
<td>62.2%</td>
<td>13.9%</td>
</tr>
<tr>
<td>2</td>
<td>19,997</td>
<td>21.7%</td>
<td>4.9%</td>
</tr>
<tr>
<td>3</td>
<td>7994</td>
<td>8.7%</td>
<td>1.9%</td>
</tr>
<tr>
<td>4</td>
<td>3467</td>
<td>3.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>5</td>
<td>1552</td>
<td>1.7%</td>
<td>0.4%</td>
</tr>
<tr>
<td>6</td>
<td>786</td>
<td>0.9%</td>
<td>0.2%</td>
</tr>
<tr>
<td>7</td>
<td>447</td>
<td>0.5%</td>
<td>0.1%</td>
</tr>
<tr>
<td>8</td>
<td>240</td>
<td>0.3%</td>
<td>0.06%</td>
</tr>
<tr>
<td>9</td>
<td>127</td>
<td>0.1%</td>
<td>0.03%</td>
</tr>
<tr>
<td>10+</td>
<td>275</td>
<td>0.3%</td>
<td>0.07%</td>
</tr>
<tr>
<td>Totals</td>
<td>92,195</td>
<td>100%</td>
<td>22.4%</td>
</tr>
</tbody>
</table>

Hershey Medical Center


Jhaveri, P and Ishmael, F Manuscript in preparation
Demographics of Patients Multiple Drug Allergies

- More likely to be female
- Increases with age
- Increases with BMI
- Association with dx of anxiety
- Associated with increased health care utilization

Hershey Medical Center

Increased Healthcare Utilization in Patients with Multiple Drug Allergies

Healthcare utilization of MDIS cases compared with health plan members with and without any drug “Allergy” during 2009

<table>
<thead>
<tr>
<th>Health care utilization and outcomes during 2009</th>
<th>Severe MDIS cases</th>
<th>Moderate MDIS cases</th>
<th>Health plan members with any drug “Allergy”</th>
<th>Health plan members with no drug “Allergy”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total prescriptions (m ± SD) n = 537 (0.023%)</td>
<td>40.0 ± 27.3</td>
<td>26.3 ± 21.1</td>
<td>16.5 ± 17.3</td>
<td>7.5 ± 10.9</td>
</tr>
<tr>
<td>Total antibiotics (m ± SD)</td>
<td>0.80 ± 1.99</td>
<td>0.57 ± 1.46</td>
<td>0.41 ± 1.13</td>
<td>0.27 ± 0.80</td>
</tr>
<tr>
<td>Total narcotics (m ± SD)</td>
<td>0.64 ± 2.63</td>
<td>0.50 ± 2.44</td>
<td>0.34 ± 1.86</td>
<td>0.17 ± 1.24</td>
</tr>
<tr>
<td>Total anti-depressants (m ± SD)</td>
<td>0.11 ± 0.70</td>
<td>0.12 ± 0.76</td>
<td>0.08 ± 0.62</td>
<td>0.04 ± 0.41</td>
</tr>
<tr>
<td>New antibiotic class “allergies” (m ± SD)</td>
<td>0.10 ± 0.36</td>
<td>0.06 ± 0.26</td>
<td>0.03 ± 0.18</td>
<td>0.01 ± 0.11</td>
</tr>
<tr>
<td>New non-antibiotic class “allergies” (m ± SD)</td>
<td>0.43 ± 0.88</td>
<td>0.18 ± 0.49</td>
<td>0.08 ± 0.32</td>
<td>0.02 ± 0.16</td>
</tr>
<tr>
<td>New total drug class “allergies” (m ± SD)</td>
<td>0.52 ± 0.99</td>
<td>0.24 ± 0.58</td>
<td>0.11 ± 0.38</td>
<td>0.03 ± 0.20</td>
</tr>
<tr>
<td>Outpatient visits (m ± SD)</td>
<td>26.6 ± 19.5</td>
<td>15.4 ± 14.9</td>
<td>10.2 ± 11.6</td>
<td>6.1 ± 7.7</td>
</tr>
<tr>
<td>Emergency department visits (m ± SD)</td>
<td>1.5 ± 2.8</td>
<td>0.7 ± 1.7</td>
<td>0.4 ± 1.1</td>
<td>0.3 ± 0.7</td>
</tr>
<tr>
<td>Days of hospitalization (m ± SD)</td>
<td>12.4 ± 46.1</td>
<td>6.3 ± 39.2</td>
<td>3.3 ± 28.2</td>
<td>1.1 ± 14.9</td>
</tr>
<tr>
<td>Radiology procedures (m ± SD)</td>
<td>7.1 ± 7.1</td>
<td>3.8 ± 4.5</td>
<td>2.2 ± 3.3</td>
<td>0.8 ± 1.9</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.

*P < .0001 for all categories comparing health plan members with and without any drug “allergy” and all categories comparing severe with moderate MDIS, except as noted.

*aP = NS.

Total courses of these various classes of medications dispensed during 2009.

Total visits, days, or procedures during 2009.
Etiologies of Multiple Drug Allergy Syndrome

• Misclassification of side effects as a allergy.
• Conditioned responses – subjective symptoms rather than true reactions.
  – i.e. patient complains of sensation of throat closure with multiple chemically unrelated drugs.
• Multiple antibiotic syndrome – weak and non-specific reactions to multiple medications.
  – Patients develop rashes with many different antibiotics.
  – Limited to skin only, not dangerous.
Multiple Drug Allergies Case 1

- Case Presentation: 60 y/o female with common variable immunodeficiency and need for recurrent antibiotic therapy presents with hives after receiving the first dose of each of the following antibiotics:
  - amoxicillin-clavulante (penicillin)
  - cefdinir (3rd generation cephalosporin)
  - azithromycin (macrolide)
  - levofloxacin (quinolone)
  - doxycycline (tetracycline)
  - trimethoprim-sulfamethoxazole (sulfonamide)
Multiple Drug Allergy Syndrome

• This is a non-specific immune response, sometimes triggered by infection.
• Appears to be a T-cell process; non-specific pre-activation of T-cells that are weakly reactive to drugs, have a low threshold for activation.
• Reactions are limited to rash/hives only - can safely tolerate antibiotics with pre-medication with antihistamines.
• Skin test to penicillin: r/o IgE mediated allergy.
• Challenges may be useful.
• Patients are likely to develop hives again with any antibiotic. Offer reassurance.

Daubner et al. Allergy 2011
Multiple Drug Allergies Case 2

• 55 y/o male that presented for a drug allergy workup to a number of different medications:
  – Omeprazole: bloating and diarrhea
  – Ranitidine: headache
  – Atorvastatin: numbness in fingers
  – Metoprolol: fatigue
Multiple Drug Allergies Case 3

• 35 y/o female with a history of sensation of throat closure with multiple medications:
  – Multiple NSAIDs
  – Penicillin
  – Azithromycin
  – Thiazide diuretics

• No rashes, no angioedema or other symptoms.
Conditioned Responses

• Laryngeal edema can be seen with true drug hypersensitivity.
• But.. it can also be a subjective finding. In the absence of objective findings and with multiple unrelated medications, it suggests absence of true allergy.
• Difficult to manage these patients.
• Often, patients have had a true reaction to one agent in the past and now fear every medication.
• Placebo controlled graded challenges to drugs and use of laryngoscopy can be helpful to prove that these are not real reactions.
A Diagnostic Algorithm for Adverse Drug Reactions

Detailed history and physical exam

Consistent with type A reaction(s)
- Consider a dose reduction
- Alternative family member
- Don’t list as “allergy”

Consistent with hypersensitivity
- More severe rash
  - Avoid medication and class.
  - Consider allergy referral or ER referral

Combined Features or History unclear
- Mild sx (i.e. mild macular rash)
  - Consider using same medication or class member again
- More severe rash
  - Avoid medication and class.
  - Consider allergy referral or ER referral

Consistent with IgE reaction
- Avoid Medication and related class.
  - Refer to Allergy

Can refer to allergy for PCN skin testing if ambiguous.

Refer to Allergy
- Skin testing if appropriate graded challenges
Challenges Associated With Management of Drug Allergies

• Overuse of antibiotics/use of wrong class.
• Lack of good diagnostic tests.
• Poor understanding of side effects vs. true drug hypersensitivity (both patients and physicians).
• Complicated mechanisms and variability of drug responses.
Physician Approaches to Minimize Impact of Drug Allergies

- Appropriate/limited use of antimicrobial agents.
- Detailed history taking for drug reactions.
- Distinguish between “type A” reactions vs. true hypersensitivity.
- Re-introduction when appropriate.
- Avoidance of medications in cases consistent with true or more severe hypersensitivity reactions.
- Referral to Allergy for testing/challenges.