Medication Allergies and Cross-Reactivity

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Disclosures

I have no relevant financial relationships or commercial interests to disclose for this presentation.
Learning Objectives

At the conclusion of this presentation, the audience member should be able to:

- Explain the pathophysiology of medication allergies and sensitivities
- Describe the risk for allergic cross-reactivity for beta lactam antibiotics, sulfa drugs, opioids, and NSAIDs
- Given a patient case, identify appropriate medication therapy taking into consideration the allergy history
PATHOPHYSIOLOGY
Allergic Drug Reactions

- **Allergic drug reaction** - adverse medication effect that involves immunologic mechanisms
  - Ex. anaphylaxis from β-lactam antibiotics, dermatitis from sulfonamides, serum sickness from phenytoin

- **Allergic-like/pseudoallergic reaction** - not proven to be immune mediated but resembling an allergic reaction
  - Ex. shock after radiocontrast media, aspirin-induced asthma, opiate-related urticaria, flushing after vancomycin

- Account for up to 15% of adverse drug reactions
Factors Related to the Occurrence and Severity of Drug Allergies

- Dose
- Duration of exposure
- Metabolism
- Protein-binding
- Route of administration
- Sensitivity of patient
  - Age
  - Genetics
  - Environmental factors
# Types of Immune Reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Descriptor</th>
<th>Mediators</th>
<th>Onset</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Anaphylactic (IgE mediated)</td>
<td>IgE, mast cells, basophils</td>
<td>Within 30 minutes</td>
<td>Anaphylaxis, urticaria, laryngeal edema, wheezing</td>
</tr>
<tr>
<td>II</td>
<td>Cytotoxic</td>
<td>Cell-bound Ag, IgM, IgG</td>
<td>5-12 hours</td>
<td>Hemolytic anemia, interstitial nephritis, cytopenias</td>
</tr>
<tr>
<td>III</td>
<td>Immune complex</td>
<td>Ag-Ab complexes, complement</td>
<td>3-8 hours</td>
<td>Serum sickness, glomerular nephritis</td>
</tr>
<tr>
<td>IV</td>
<td>Cell-mediated (delayed)</td>
<td>T cells</td>
<td>1-3 days</td>
<td>Contact dermatitis</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Precise mechanism unknown</td>
<td></td>
<td>Any time</td>
<td>Fever, hepatitis, interstitial pneumonitis, rash, Stevens-Johnson syndrome</td>
</tr>
</tbody>
</table>
Pathogenesis of type I hypersensitivity

- Allergen
  - CD4
  - IL-4

  ↓

- Memory cell
- Plasma cell
- Sensitised mast cell
- Fc receptor for IgE
- IgE

  Allergen

  →

  - Vasoactive amines
- Smooth muscle
- Blood vessel
- Mucous gland
- Platelets
- Sensory nerve endings
- Eosinophil

Goldstey RA et al. Immunology 5th Ed, 2003, p 363
Anaphylaxis

- Acute, life-threatening allergic reactions involving multiple organ systems
  - Dermatologic
  - Respiratory
  - Gastrointestinal
  - Cardiovascular

- Accounts for 1500 deaths per year in the US

- Occurs within 30 minutes of exposure

- Monitor for late phase reaction for 12 hours
Treatment of Anaphylaxis

- **Discontinue offending agent!**
- **Epinephrine** 1:1,000 0.5 mg IM
  - Can be repeated in 15 minutes x 1
  - Counteracts bronchoconstriction and vasodilation
- **Steroid (hydrocortisone 250mg IV)**
  - Reduces risk of late-phase reaction
- **Antihistamine** (diphenhydramine 25-50mg IV)
- **IV fluids**
- **Vasopressors for refractory hypotension**
Anaphylactoid Reactions

- Similar to anaphylaxis in clinical signs/symptoms
- May produce direct release of inflammatory mediators rather than through IgE
- Ex. vancomycin-induced “red man syndrome”
BETA LACTAM ANTIBIOTICS
Penicillin Allergy

- **Major determinant**
  - Penicilloyl group, accounts for 85-90% of penicillin breakdown product

- **Minor determinants**
  - Other chemical byproducts of penicillin

- **Risk factors for IgE reaction**
  - Multiple short courses of penicillin, especially via parenteral and topical route
  - Allergic diseases
  - Age (most common between ages 20-49)

Beta Lactam Chemical Structure

Amoxicillin, a penicillin

Aztrenam, a monobactam

Imipenem, a carbapenem

FIGURE 1. Chemical structure of penicillin
Aminopenicillin-induced exanthema allows treatment with certain cephalosporins or phenoxyethyl penicillin

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Aminopenicillins

- Up to 100% of patients with viral infection have ampicillin-induced rash (not IgE-mediated)
- Cohort of 71 patients with non-IgE mediated hypersensitivity to aminopenicillins
  - All patients underwent skin testing and graded challenge
  - 97.2% tolerated cephalosporins (cefpodoxime or cefixime)
  - 71.8% tolerated penicillin
- May cross-react with cephalosporins with aminobenzyl side chain (i.e. cephalexin)

Figure 1. Side chains of β-lactams. Left-hand column, R side chains of different penicillins; right-hand column, R1 side chains of different cephalosporins.
Cephalosporins

- Cross-reactivity with penicillin allergy is up to 10%
  - Higher incidence with 1st generation cephalosporins
  - Patients with negative skin test are at no higher risk than general population

- Management
  - Positive skin test – avoidance or desensitization
  - Mild reaction to penicillin – proceed with caution
Carbapenems

- Incidence of hypersensitivity 0.3-2.3%
- Cross-reactivity
  - Proven, suspected, or possible IgE mediated reaction to β-lactams: 1.6 to 5.9%
  - Proven IgE mediated reaction to β-lactams: 0.5%
  - Positive PCN skin test: 0.06 to 1.9%
  - Negative PCN skin test: no reaction
- Management
  - In patients with proven IgE mediated reactions to β-lactams, consider graded challenge in ICU

Monobactams (Aztreonam)

- No clinical cross-reactivity between β-lactam antibiotics and aztreonam

- Exceptions:
  - Cystic fibrosis patients can develop sensitization reactions
  - Ceftazidime shares similar structure, use in caution with ceftazidime allergy
Penicillin Skin Testing

- Pre-Pen® contains benzylpenicilloyl, the major determinant of penicillin allergies
- Puncture testing vs. intradermal testing
- Negative control required, positive control can be considered
- Negative test associated with risk of Type I allergic reaction < 5% **in healthy patients**

**Penicillin skin test reagents**

- Benzylpenicilloyl-polylysine (Pre-Pen full strength)
- Penicillin G (10,000 U/mL)
- Penicillin minor determinants (mixture, 10–2 M)
- Ampicillin (1–3 mg/mL)
- Amoxicillin (1–3 mg/mL)
- Cephalosporin (1–3 mg/mL)
- Saline solution (negative control)
- Histamine (positive control)

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*One drop of each reagent is used for the prick tests; 0.02 mL is used for the intradermal tests.*

†Penicillin G concentration of 10,000 U/mL needs to be prepared daily.

‡Penicillin minor determinant mixtures are available only at some research centers. Ideal concentration for skin test may vary.*
Graded Challenge vs. Desensitization

**Graded Challenge**
- Test doses given to ensure no reaction
- Ex. 1%, 10%, 100% of total dose
- Use if low likelihood of true allergy

**Desensitization**
- Many small doses given to prevent anaphylactic reaction
- Many steps, labor intensive
- Use if true allergy is suspected
### Intravenous protocol for penicillin desensitization

<table>
<thead>
<tr>
<th>STEP*</th>
<th>SOLUTION (U/mL) †</th>
<th>DOSE (mL)</th>
<th>DOSE (U)</th>
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<tr>
<td>1</td>
<td>100</td>
<td>0.1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>0.2</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>0.4</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>0.8</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>1,000</td>
<td>0.15</td>
<td>150</td>
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<td>6</td>
<td>1,000</td>
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<td>0.4</td>
<td>4,000</td>
</tr>
<tr>
<td>11</td>
<td>10,000</td>
<td>0.8</td>
<td>8,000</td>
</tr>
<tr>
<td>12</td>
<td>100,000</td>
<td>0.15</td>
<td>15,000</td>
</tr>
<tr>
<td>13</td>
<td>100,000</td>
<td>0.30</td>
<td>30,000</td>
</tr>
<tr>
<td>14</td>
<td>100,000</td>
<td>0.60</td>
<td>60,000</td>
</tr>
<tr>
<td>15</td>
<td>100,000</td>
<td>1.00</td>
<td>100,000</td>
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<td>16</td>
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<td>17</td>
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</tr>
<tr>
<td>19</td>
<td>1,600,000</td>
<td>25</td>
<td>1,600,000</td>
</tr>
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<td>25</td>
<td>3,200,000</td>
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<tr>
<td>21</td>
<td>5,000,000</td>
<td>25</td>
<td>5,000,000</td>
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</tbody>
</table>

*Each step is administered at 15-minute intervals
†Use penicillin G for dilutions in 0.9% sodium chloride
Case #1

JT is a 56 yom with a history of DM, HTN, and HLD. He presents with MSSA bacteremia secondary to a diabetic foot infection. He has a history of penicillin allergy.

How would you manage his infection?
SULFONAMIDES
Sulfonamide-Associated Reactions

- Anaphylaxis
- Angioedema
- Erythema multiforme
- Flushing
- Photosensitivity
- Pustular eruption
- Urticaria
- Bullous eruption
- Erythroderma
- Fixed drug eruption
- Lupus erythematosus
- Psoriasis
- Vasculitis
- Exanthema
- Aphthous stomatitis
- Erythema nodosum
- Exfoliative dermatitis
- Sweet’s syndrome
- Pruritus
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Serum sickness
- Hepatitis
- Hemolytic anemia

Sulfonamides and Loop Diuretics

FIGURE 4. Sulfamethoxazole (SMX) molecule structure.

FIGURE 5. Furosemide molecule structure.
Absence of Cross-Reactivity between Sulfonamide Antibiotics and Sulfonamide Nonantibiotics

Cross-Reactivity of Sulfonamide Antibiotics and Nonantibiotics

- Retrospective cohort study of 20,279 patients who received a sulfonamide antibiotic followed by a sulfonamide nonantibiotic within 60 days

<table>
<thead>
<tr>
<th>Table 1. Sulfonamide Nonantibiotic Drugs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Acetohexamide</td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
</tr>
<tr>
<td>Benzbthiazide</td>
</tr>
<tr>
<td>Bumetanide</td>
</tr>
<tr>
<td>Chlorothiazide</td>
</tr>
<tr>
<td>Chlorpropamide</td>
</tr>
<tr>
<td>Chlorothalidone</td>
</tr>
<tr>
<td>Clopamide</td>
</tr>
<tr>
<td>Clorexolone</td>
</tr>
</tbody>
</table>
Figure 1. Primary Analysis of a Cohort of Patients Who Had Received a Sulfonamide Antibiotic and Who Subsequently Received a Sulfonamide Nonantibiotic.

A narrow outcome was defined by the occurrence of reactions such as urticaria, anaphylactic shock, erythema multiforme, and drug allergy. A broad definition also included asthma, eczema, and unspecified adverse effects of a drug. For a complete list, see Supplementary Appendix 1, available with the full text of this article at http://www.nejm.org.
Cross-Reactivity of Sulfonamide Antibiotics and Nonantibiotics

- Most common reactions observed
  - Asthma (70.1%)
  - Eczema (14.1%)
  - Adverse drug reaction (11.4%)
- 18 patients had symptoms consistent with type I hypersensitivity
- Previous reaction to a sulfonamide antibiotic was associated with a 2.8 times higher likelihood of having a reaction to the nonantibiotic
  - Similar risk was observed for patients with a sulfonamide allergy who received penicillin

Ethacrynic Acid

- Non-sulfa loop diuretic
- Approx. $3000 per dose for IV
- 1:1 conversion from IV:PO
- Higher incidence of ototoxicity compared to other loop diuretics
- Reserve for patients with allergic reactions to loop diuretics
Case #2

AP is a 72 yof with a history of MI s/p CABG, CHF, HTN, and HLD. Her medication allergies include trimethoprim/sulfamethoxazole (Bactrim®). When asked she says it causes rash.

When you order furosemide 40 mg IV in PowerChart you get an alert saying she has a sulfa allergy. What do you do?
OPIOIDS
Terminology

- Opiate – drugs derived from opium poppy
  - Morphine, codeine, heroin
- Opioid – natural and synthetic drugs with morphine-like activity
  - Hydromorphone, oxycodone
- Many opiates and opioids are histamine releasers and can cause anaphylactoid reactions

Structure of morphine and some chemically-related naturally occurring or semi-synthetic clinically-important opioid drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Substituent at position</th>
<th>Bond(s) at positions 7-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>-OH -OH -H -CH₃</td>
<td>Double</td>
</tr>
<tr>
<td>Codeine</td>
<td>-OCH₃ -OH -H -CH₃</td>
<td>Double</td>
</tr>
<tr>
<td>Heroin</td>
<td>-OCOCH₃ -OCOCH₃ -H -CH₃</td>
<td>Double</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>-OH =O -H -CH₃</td>
<td>Single</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>-OH =O -OH -CH₃</td>
<td>Single</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>-OCH₃ =O -H -CH₃</td>
<td>Single</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>-OCH₃ =O -OH -CH₃</td>
<td>Single</td>
</tr>
<tr>
<td>Buprenorphine*</td>
<td>-OH -OCH₃**</td>
<td>Single</td>
</tr>
<tr>
<td>Naloxone</td>
<td>-OH -OH -CH₂CH=CH₂</td>
<td>Single</td>
</tr>
</tbody>
</table>

* Has a 1-hydroxy-1,2,2-trimethylpropyl substituent at C-7. ** Endo-ethano bridge between C-6 and C-14.
Anaphylactoid Reaction

- **NOT** IgE-mediated
- Mast cells release histamine
- Histamine release causes:
  - Increased heart rate
  - Increased force of myocardial contraction
  - Vasodilation → flushing & hypotension
  - Itching
- More common with morphine, codeine, and meperidine
- Premedicate with antihistamines
Opioid Allergy

- Type I reactions are very rare
  - Limited to case reports with morphine, heroin, meperidine, and fentanyl
  - Fentanyl is most commonly reported
  - <0.1% incidence with tramadol
  - Only 1 report confirmed IgE antibodies

- Opioids account for ~1% of drugs implicated in perioperative anaphylaxis

- Use caution with intradermal testing due to known histamine release with some opioids

Management of Reported Opioid Allergies

- Obtain thorough history
  - Cardiovascular collapse and bronchospasm more common in anaphylactic reactions
  - Cutaneous symptoms more common in anaphylactoid reactions
- Use appropriate skin tests and/or challenge tests
- Consider IgE antibody immunoassays or serum tryptase level
- Use non-opioid analgesics when possible
- Cross-reactivity with true Type I allergies is poorly understood

Case #3

LP is a 25 yof who presents to the ED with a tibia-fibula fracture after an ATV accident. When you offer her hydromorphone for pain, she says she can’t take it because she is allergic to morphine.

What do you do?
ASPIRIN AND NSAIDS
NSAID Mechanism of Action
Aspirin: Respiratory Reactions

- **Symptoms**: bronchospasm, rhinorrhea, conjunctival injection, periorbital edema, generalized flushing
- **Onset**: 2-3 hours after ingestion
- **Risk factors**: asthma (4-21%), nasal polyps (35-52%), or both (65%)
- **Mechanism**: COX-1 inhibition depletes PGE2 and increases leukotriene production
- **Cross-reactivity**:
  - Will cross react with other nonselective NSAIDs that inhibit the COX-1 enzyme
  - COX-2 selective NSAIDs can be safely used
  - Limit APAP doses to < 1000 mg and salsalate to < 2 g

Aspirin: Skin Reactions

- **Symptoms**: urticaria, skin eruptions
- **Onset**: within 4 hours of ingestion. Symptoms will diminish in 24-48 hours but can continue for up to 2 weeks
- **Risk factors**: atopy, female sex, intermittent NSAID use for pain relief
- **Mechanism**: COX-1 inhibition PGE2 and increases leukotriene production
- **Cross-reactivity**:
  - Will cross react with other nonselective NSAIDs that inhibit the COX-1 enzyme
  - Up to 4% of patients may cross react with COX-2 selective NSAIDs

Aspirin: Anaphylaxis

- **Symptoms**: urticaria, angioedema, bronchospasm, hypotension
- **Onset**: within 30 minutes
- **Risk factors**: previous exposure to the drug
- **Mechanism**: IgE antibody production
- **Cross-reactivity**: will not cross-react except for those with nearly identical structures

Management of Aspirin Sensitivity

- Skin testing not routinely done
- Manage underlying disease state (i.e. asthma)
- Desensitization
  - Can be considered for aspirin-induced asthma or IgE-mediated reaction
  - Decreases leukotriene production and extracellular histamine levels
  - Will return to sensitivity within 2-4 days
  - Confers “cross-desensitization” to other nonselective NSAIDs
- Leukotriene antagonists

Case #4

LF is a 63 yom with a h/o asthma, DM, HTN, HLD, and PVD who presents with unstable angina and is going to go for PCI with probable stent placement. He has been unable to tolerate aspirin in the past due to severe bronchospasm.

What do you do?
RADIOCONTRAST MEDIA
Radiocontrast Media

- Cause allergic-type reactions in up to 12% of patients
  - 1-3% have delayed skin reactions over 5-7 days
  - Anaphylactic reactions occur in up to 0.04% of patients
  - Can cause dose-dependent hypotension

- Mechanism: histamine release and mast cell triggering (IgE or direct activation)

- Higher risk in women, atopic patients, and with older agents

- Seafood allergy does **NOT** predispose to allergic reaction!

- May premedicate with steroids or antihistamines
Conclusions

- A thorough history is imperative to distinguish between IgE mediated and allergic-type reactions.

- Patients with a history of drug allergy are more likely to be allergic to other medications, even those which are structurally unrelated.

- Consider risks and benefits of exposure to medications in the same class in patients with IgE mediated allergic reactions.
Medication Allergies and Cross-Reactivity

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