THE GATEWAY
TO THE FUTURE OF PHARMACY

MPA
MISSOURI PHARMACY ASSOCIATION

IIIPA
Illinois Pharmacists Association
Drug Allergy: A “Rash”ionale for Treatment

Heather A. Powell, PharmD, BCPS
Assistant Professor of Clinical Sciences
Roosevelt University College of Pharmacy

Jordan O. Powell, PharmD
Clinical Pharmacist – Remote Order Verification
Advocate Health Care
Disclosure and Conflict of Interest

Heather and Jordan Powell declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings and honoraria.
Pharmacist Objectives

At the conclusion of this program, the pharmacist will be able to:

1. Recognize hallmark signs and symptoms of IgE-mediated allergic reactions.
2. Select appropriate and effective pharmacologic treatments for drug allergy reactions.
3. Discuss the risks and benefits of implementing angiotensin II receptor blocker therapy after experiencing angiotensin-converting enzyme-inhibitor angioedema.
4. Describe the cross-reactivity of various antibiotic classes for patients with documented beta-lactam antibiotic allergies.
Technician Objectives

At the conclusion of this program, the technician will be able to:

1. Recognize hallmark signs and symptoms of IgE-mediated allergic reactions.
2. Describe pharmacologic treatments for drug allergy reactions.
3. Discuss the risks and benefits of implementing angiotensin II receptor blocker therapy after experiencing angiotensin-converting enzyme-inhibitor angioedema.
4. Describe the cross-reactivity of various antibiotic classes for patients with documented beta-lactam antibiotic allergies.
Which of the following is *not* an IgE-mediated reaction?

A. Urticaria
B. Anaphylaxis
C. Angioedema
D. Stevens Johnson Syndrome
Which of the following situations would warrant use of an oral steroid for a patient with contact dermatitis?

A. Dermatitis covering >20% of BSA
B. Erythema and pruritus
C. Dermatitis limited to areas not including the face or feet
D. Duration < 4 days
Angiotensin Receptor Blocker (ARB) administration is an absolute contraindication for anyone with documented Angiotensin Converting Enzyme Inhibitor (ACE-I) induced angioedema.

A. True
B. False
The cross-reactivity of an IgE-mediated drug reaction occurring upon administration of a cephalosporin in a patient with a true penicillin allergy is approximately what percentage?

A. 2%
B. 10%
C. 40%
D. 100%
Drug Allergy: A “Rash”ionale for Treatment
# Adverse Drug Reactions (ADRs)

<table>
<thead>
<tr>
<th>Type A (Predictable)</th>
<th>Type B (Unpredictable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose dependent</td>
<td>Dose independent</td>
</tr>
<tr>
<td>Related to known pharmacologic actions of the drug</td>
<td>Unrelated to known pharmacologic mechanism</td>
</tr>
<tr>
<td></td>
<td>Occurs only in susceptible individuals</td>
</tr>
</tbody>
</table>
### Type B ADRs

<table>
<thead>
<tr>
<th>Subclass</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug intolerance</td>
<td>Undesirable pharmacologic effect that occurs at low, sometimes sub-therapeutic doses, without underlying abnormalities of metabolism, excretion, or bioavailability</td>
</tr>
<tr>
<td>Drug idiosyncrasy</td>
<td>Abnormal or unexpected effect that is unrelated to the intended pharmacologic action of the drug</td>
</tr>
<tr>
<td>Drug allergy</td>
<td>Immunologically mediated responses that result in production of drug-specific antibodies, T cells, or both</td>
</tr>
<tr>
<td>Pseudo-allergy</td>
<td>Manifestations mimic IgE-mediated allergic reactions but are due to direct release of mediators from mast cells and basophils; do not require a preceding period of sensitization</td>
</tr>
</tbody>
</table>
Drug Allergy Diagnosis Considerations

1. The symptoms and physical findings are compatible with an immune drug reaction
2. Temporal relationship between administration of the drug and an adverse event
3. Class and/or structure of the drug have been associated with immune reactions
4. Patient received the drug (or a cross-reacting drug) on 1 or more occasion
5. No other clear cause for the presenting manifestations
6. Skin test and/or laboratory findings are compatible with drug hypersensitivity
Drug Allergy Classifications

- Gell-Coombs Classification
  - Type I: IgE-mediated
  - Type II: Cytotoxic
  - Type III: Immune complex
  - Type IV: Cellular mediated

- Mixed Drug Reactions
  - Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome
  - Steven’s Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)
  - Red Man’s Syndrome

References:
## IgE-mediated

<table>
<thead>
<tr>
<th>Mechanism:</th>
<th>Release of mediators (histamine, prostaglandins, leukotrienes, acid hydrolases, neutral proteases, proteoglycans, cytokines) from sensitized basophils and mast cells on contact with allergens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset:</td>
<td>Within minutes of exposure</td>
</tr>
</tbody>
</table>
| Common drugs: | Biologics  
Antibiotics  
Heparin  
Protamine  
Insulin |
| Examples: | Urticaria  
Bronchospasm  
Anaphylaxis  
Angioedema |

Anaphylaxis

Life threatening systemic hypersensitivity reaction upon contact with an allergen

**Signs/Symptoms**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td>Mucous membrane swelling, hoarseness, stridor, wheezing</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>Tachycardia, hypotension, chest pain</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td>Pruritus, urticaria, angioedema, flushing</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>N/V, pain, diarrhea, dysphagia</td>
</tr>
<tr>
<td><strong>Central Nervous System</strong></td>
<td>Aura of impending doom, dizziness, headache, confusion, seizure</td>
</tr>
</tbody>
</table>

Anaphylaxis: Treatment

• **Airway Support**
  - Respiratory collapse:
    - Intubate
    - Nebulized β2 agonists (albuterol)
    - Administer 1-5 mg glucagon IV over 5 minutes for those on β-blockers not responding to epinephrine
    - Oxygen

• **Remove the allergen (if possible)**
• **Place in the supine position**
Anaphylaxis: Treatment

• Epinephrine
  o $\alpha_1, \beta_1, \beta_2$ adrenergic agonist $\rightarrow$ vasoconstriction and bronchodilation
  o Prompt, early use should be considered given long onset of antihistamines and corticosteroids even in patients with mild symptoms
  o Dosing:
    ▪ Self-injectors $\rightarrow$ IM or SubQ depending on brand: 0.3 mg into the anterolateral aspect of the middle third of the thigh every 10-20 minutes until arrival at ED

• Circulatory collapse: IV normal saline

Anaphylaxis: Treatment

• Antihistamines (H₁ or H₂) – optional
  o Not useful for acute manifestations
  o H₁: No direct evidence to support their use in this population
    → evidence extrapolated from use in urticarial or allergic rhinitis
    ▪ 25 – 50 mg diphenhydramine if IV
    ▪ 10 mg cetirizine if PO
  o H₂: Not supported by RCT evidence

• Glucocorticoids - optional
  o Not useful for acute manifestations but thought to control prolonged symptoms
    ▪ 1-2 mg/kg (max 125 mg) IV methylprednisolone (or PO equivalent)
  o Do not administer if symptoms are managed by epinephrine alone

Angioedema

- Diffuse vasodilation and increased vascular permeability
- Signs/Symptoms:
  - Asymmetric, non-pitting edema of the subcutaneous or submucosal tissues of the lips, tongue, and face
  - Diffuse abdominal pain and diarrhea
- Treatment:
  - Airway support
  - Drug discontinuation

Image: https://commons.wikimedia.org/wiki/File:Angioedema2013.JPG
# ACE-I Induced Angioedema

<table>
<thead>
<tr>
<th>Mechanism:</th>
<th>Bradykinin elevation (inflammatory vasoactive peptide) (\rightarrow) diffuse vasodilation and increased vascular permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time frame:</td>
<td>May occur at any time (\rightarrow) Will take at least 24 hours to resolve post drug discontinuation</td>
</tr>
<tr>
<td>Incidence:</td>
<td>0.1 – 0.7% of all recipients (\rightarrow) Not related to specific agent or dose</td>
</tr>
</tbody>
</table>

ACE-I Angioedema Treatment

- Airway Support
- Icatibant (FIRAZYR®)
  - selective bradykinin β2 receptor antagonist
  - Off-label use
- Antihistamines
- Fresh Frozen Plasma
- Corticosteroids?
TRANSCEND Trial

• Angiotensin II receptor blocker (ARB) or placebo in ACE-I intolerant patients
  – Primary outcome was **not** ARB tolerance, but the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure
  – “Intolerability” was mostly due to cough (88.2%), not angioedema (1.3%)
  – Treatment-period angioedema occurrence not significantly different in ARB (0.07%) vs placebo (0.10%) groups (p > 0.05)
  – Study not powered for sub-group analysis

ARBs following ACE-I Angioedema

• Controversial
  – Unreliable results from the TRANSCEND trial
• Risk of developing ARB induced angioedema after ACE-I angioedema ranges anywhere from 2-17% risk

Recommendation: Reserve for patients with definite indications for ARBs, avoid use if patient needed airway support for angioedema
Drug Allergy Classifications

- **Gell-Coombs Classification**
  - Type I: IgE-mediated
  - Type II: Cytotoxic
  - Type III: Immune complex
  - Type IV: Cellular mediated

- **Mixed Drug Reactions**
  - Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome
  - Steven’s Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)
  - Red Man’s Syndrome

### Cellular mediated

<table>
<thead>
<tr>
<th>Example</th>
<th>Contact dermatitis (topical induction and elicitation of sensitization by a drug is limited to the skin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms:</td>
<td>Delayed cutaneous eruptions (maculopapular exanthems, vesicles, and crusted lesions)</td>
</tr>
</tbody>
</table>
| Common drugs: | Topical bacitracin  
Neomycin  
Glucocorticoids  
Local anesthetics  
Antihistamines  
Oral penicillins and sulfonamides |
Cellular Mediated Allergy Treatment

- Drug/Irritant discontinuation
- Aluminum acetate compresses, calamine lotion, and/or colloidal oatmeal compresses or baths for pruritus reduction
Cellular Mediated Allergy Treatment

• Topical Corticosteroids
  o Long term use should be avoided
  o Potency depends on vehicle and increases if steroid is applied after shower/bath and/or if application site is covered
Cellular Mediated Allergy Treatment

• Topical Corticosteroids (cont.)
  o High potency
    ▪ For dermatitis NOT involving the face or flexural areas once or twice daily for 2-4 weeks
    ▪ Should be used for long-term control of chronic dermatitis of the hands, feet, or non-flexural areas once daily 3x/week on alternate days
  o Medium or low-potency
    ▪ For dermatitis of the face and flexural areas once or twice daily for 1-2 weeks
# Cellular Mediated Allergy Treatment

<table>
<thead>
<tr>
<th>Steroid Vehicle</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| **Ointment**    | (+) lubrication and occlusion  
(+) absorption | Cannot use in hairy areas  
May cause maceration and folliculitis on intertriginous areas  
Greasy |
| **Creams**      | (+) lubrication  
Vanish into the skin  
Drying effects for exudative inflammation | Less potent than ointments  
Contain preservatives |
| **Lotions**     | Least greasy and occlusive  
Contain alcohol for drying effects  
Good for hairy areas where they can penetrate easily and leave little residue | Less potent than ointments and creams |
| **Gels**        | Quick drying effects for exudative inflammation  
Good for hairy areas where they can penetrate easily and leave little residue | Less potent than ointments and creams |
<table>
<thead>
<tr>
<th>Topic Steroid Potency</th>
<th>Generic</th>
<th>Vehicles available</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultra high (I)</strong></td>
<td>Augmented betamethasone dipropionate 0.05% Clobetasol propionate 0.05% Diflorasone diacetate 0.05% Fluocinonide 0.1% Flurandrenolide 4 mcg per m² Halobetasol propionate 0.05%</td>
<td>Ointment, gel Ointment, cream, lotion, gel Ointment Cream Tape Ointment, Cream</td>
</tr>
<tr>
<td><strong>High (II)</strong></td>
<td>Amcinonide 0.1% Augmented betamethasone dipropionate 0.05% Desoximetasone 0.25% and 0.05% Diflorasone diacetate 0.05% Fluocinonide 0.05% Halcinonide 0.1%</td>
<td>Ointment Cream, lotion Ointment, cream, gel Cream Ointment, cream, gel Ointment, cream</td>
</tr>
<tr>
<td><strong>Medium to high (III)</strong></td>
<td>Betamethasone dipropionate 0.05% Fluticasone propionate 0.005%</td>
<td>Cream Ointment</td>
</tr>
<tr>
<td>Topic Steroid Potency</td>
<td>Generic</td>
<td>Vehicles available</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Medium (IV and V)</td>
<td>Betamethasone valerate 0.1% Desoximetasone 0.05% Fluticasone propionate 0.05% Hydrocortisone butyrate 0.1% Hydrocortisone probutate 0.1% Hydrocortisone valerate 0.2% Mometasone furoate 0.1% Triamcinolone acetonide 0.1%</td>
<td>Cream, lotion Cream Cream Ointment Cream Ointment, cream Ointment, cream, lotion Ointment, cream, cream, lotion</td>
</tr>
<tr>
<td>Low (VI)</td>
<td>Alclometasone dipropionate 0.05% Desonide 0.05% Fluocinolone 0.01% Hydrocortisone butyrate 0.1%</td>
<td>Ointment, cream Ointment, cream, lotion, gel Cream</td>
</tr>
<tr>
<td>Least potent (VII)</td>
<td>Hydrocortisone 1% and 2.5%</td>
<td>Ointment, cream, lotion</td>
</tr>
</tbody>
</table>
Cellular Mediated Allergy Treatment

- **Oral Corticosteroids**
  - Prednisone 0.5-1 mg/kg (max 60 mg/day) for 7 days then tapered over two weeks for dermatitis >20% of BSA or when disabling (hands, feet, genitalia)

- **Topical tacrolimus**
  - Use for contact dermatitis that is chronic and resistant to topical steroids or induced by topical steroids
Drug Allergy Classifications

• Gell-Coombs Classification
  – Type I: IgE-mediated
  – Type II: Cytotoxic
  – Type III: Immune complex
  – Type IV: Cellular mediated

• Mixed Drug Reactions
  – Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome
  – Steven’s Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)
  – Red Man’s Syndrome
DRESS Syndrome

- Drug-induced, multi-organ inflammatory response that may be life-threatening

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Cutaneous eruptions (exanthems, erythema multiforme, purpura)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Eosinophilia</td>
</tr>
<tr>
<td></td>
<td>Hepatic and renal dysfunction</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Facial edema</td>
</tr>
<tr>
<td><strong>Time frame:</strong></td>
<td>2 – 8 weeks after therapy initiation</td>
</tr>
<tr>
<td><strong>Common Drugs:</strong></td>
<td>Anticonvulsants (carbamazepine, phenytoin, lamotrigine)</td>
</tr>
<tr>
<td></td>
<td>Sulfa drugs</td>
</tr>
<tr>
<td></td>
<td>Allopurinol</td>
</tr>
<tr>
<td></td>
<td>Minocycline</td>
</tr>
<tr>
<td></td>
<td>Abacavir</td>
</tr>
<tr>
<td></td>
<td>Hydroxychloroquine</td>
</tr>
</tbody>
</table>
DRESS Syndrome

DRESS Syndrome Treatment

• Drug discontinuation
• Symptoms may worsen after drug therapy is discontinued and may persist for weeks to months (average recovery time is 6-9 weeks)
• Warm, humid environment with gentle skin care
• Corticosteroids
  – Questionable efficacy
  – High or super high potency topical corticosteroids 2-3x/week for relief of pruritus and skin inflammation

Drug Allergy Classifications

- **Gell-Coombs Classification**
  - Type I: IgE-mediated
  - Type II: Cytotoxic
  - Type III: Immune complex
  - Type IV: Cellular mediated

- **Mixed Drug Reactions**
  - Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome
  - Steven’s Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)
  - Red Man’s Syndrome

Steven’s Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)
## Steven’s Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)

### Symptoms
- Confluent purpuric macules on face and trunk
- Severe, mucosal erosions on more than one mucosal surface with fever and organ involvement
- SJS is less severe with < 10% of body surface involved
- TEN involves detachment of > 30% of body surface with mucosal membrane involvement

### Time frame:
4 - 28 days after therapy initiation

### Common Drugs:
- Sulfonamides
- Cephalosporins
- Imidazole agents
- Quinolones
- Aromatic anticonvulsants (Carbamazepine, ethosuximide, lamotrigine, oxcarbazepine, phenobarbital, and primidone)
- Valproic acid
- Glucocorticoids

---

SJS and TEN Treatment

- Drug discontinuation
- Wound care/referral to burn unit
- Fluids and nutrition
- Pain control
- Systemic corticosteroids (prednisone 1 mg/kg/day)
  - Controversial due to increased infection/mortality risk
  - Use within 3 days of onset at high doses
- IVIG (1mg/kg per day for 3 days)
  - Controversial due to no high-quality evidence
  - Use within 24-48 hours of onset
Drug Allergy Classifications

• Gell-Coombs Classification
  – Type I: IgE-mediated
  – Type II: Cytotoxic
  – Type III: Immune complex
  – Type IV: Cellular mediated

• Mixed Drug Reactions
  – Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome
  – Steven’s Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)
  – Red Man’s Syndrome
Red Man’s Syndrome

Red Man’s Syndrome

- Vasoactive mediator (histamine) release from non-specific mast cell activation due to IV vancomycin administration causing an ADR that mimics an allergic reaction

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Erythema and flushing of the face, neck, trunk, and/or upper extremities</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
</tr>
</tbody>
</table>

| Time frame:               | May be immediate              |

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Slow infusion rate to over 1.5 – 2 hours and increase the dilution volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-OR-</td>
</tr>
<tr>
<td></td>
<td>Slow infusion rate to ≤ 10 mg/min or run a 1 gm dose over 100 minutes (whichever is a slower infusion)</td>
</tr>
<tr>
<td></td>
<td>Antihistamines (H1 and H2)</td>
</tr>
</tbody>
</table>

Penicillin (PCN) Allergy

- Up to 10% of the population has a documented PCN allergy
  - Up to 90% of these patients are not at risk of IgE mediated reactions
  - Immunogenicity wanes over time
  - Product of previously impure drug formulations

Penicillin (PCN) Allergy

Cross-reactivity of β-lactams:
- More dependent on side chains
- Cephalosporins (2nd or 3rd generation): ~1-2.5%
  - Avoid early generations with AMOXICILLIN allergy (R-group side chain)
- Carbapenems: ~ 0.9 -1%

Penicillin (PCN) Allergy

• Immediate (Type 1/IgE mediated) reactions are relative contraindications for re-exposure to PCNs
  – Urticaria, angioedema, pruritis, flushing, anaphylaxis, hypotension, edema, wheezing
  – Occur within 1 – 4 hours of drug exposure

• Late reactions warrant clinical judgement before re-exposure to PCNs depending on severity
  – Rash (maculopapular or morbilliform or contact dermatitis), RBC, WBC, and platelet destruction, and serum sickness
  – Occur days to weeks after drug exposure
  – Not predicted by skin tests

Post-Test Question #1

Which of the following is not an IgE-mediated reaction?

A. Urticaria
B. Anaphylaxis
C. Angioedema
D. Stevens Johnson Syndrome
Which of the following is *not* an IgE-mediated reaction?

A. Urticaria
B. Anaphylaxis
C. Angioedema
D. Stevens Johnson Syndrome
Which of the following situations would warrant use of an oral steroid for a patient with contact dermatitis?

A. Dermatitis covering >20% of BSA
B. Erythema and pruritus
C. Dermatitis limited to areas not including the face or feet
D. Duration < 4 days
Post-Test Question #2

- Which of the following situations would warrant use of an oral steroid for a patient with contact dermatitis?
  - A. Dermatitis covering >20% of BSA
  - B. Erythema and pruritus
  - C. Dermatitis limited to areas not including the face or feet
  - D. Duration < 4 days
Angiotensin Receptor Blocker (ARB) administration is an absolute contraindication for anyone with documented Angiotensin Converting Enzyme Inhibitor (ACE-I) induced angioedema.

A. True
B. False
Angiotensin Receptor Blocker (ARB) administration is an absolute contraindication for anyone with documented Angiotensin Converting Enzyme Inhibitor (ACE-I) induced angioedema.

A. True
B. False
The cross-reactivity of an IgE-mediated drug reaction occurring upon administration of a cephalosporin in a patient with a true penicillin allergy is approximately what percentage?

A. 2%
B. 10%
C. 40%
D. 100%
The cross-reactivity of an IgE-mediated drug reaction occurring upon administration of a cephalosporin in a patient with a true penicillin allergy is approximately what percentage?

A. 2%
B. 10%
C. 40%
D. 100%
Take Home Points

- Airway support should be the first step taken for IgE-mediated allergic reactions.
- Choosing an appropriate topical steroid based on vehicle, potency, and application site is crucial to preventing unwanted side effects for contact dermatitis.
- A history of ACE-I induced angioedema is not an absolute contraindication to treatment with an ARB but should likely be considered as one if the airway was compromised.
- Of the 10% of the population with a reported penicillin allergy, 90% of these patients will tolerate a penicillin without an IgE-mediated allergic reaction.
Resources & References

Speaker Contact Information

- Heather A. Powell, PharmD, BCPS
  - hpowell01@roosevelt.edu

- Jordan O. Powell, PharmD
  - jopowell15@gmail.com