Medication Allergies

Ronald M. Ferdman, M.D., M.Ed.
Children’s Hospital Los Angeles
Division of Clinical Immunology and Allergy

Disclosure

- I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial services discussed in this CME activity.
- I do not intend to discuss an unapproved / investigative use of a commercial product / device in my presentation.

Objectives
Un-Objectives

After completion of this activity, the participant will not be able to:

• List all possible allergic reactions that may occur after any particular drug
  √ Most drugs can potentially cause most types of reactions
  √ Can’t rule-in or rule-out an adverse reaction based on the drug itself
  √ Way too many types of possible drug reactions to cover

Objectives

After completion of this activity, the participant will be able to:

• List historical questions & tests that aid in the diagnoses of drug allergies
• Recognize various clinical patterns of drug adverse reactions
• Describe the treatment options for drug allergies

Case 1
Too Little, Too Late

• 17 y/o female with CF transferred from OSH for lung transplant due to poor lung function
  – Pan-susceptible Pseudomonas isolated, but had been treated with antibiotics to which the organism was resistant due to allergy “susceptible” antibiotics

• After evaluation, received intravenous ceftazidime for 3 weeks with marked improvement in lung function

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Case 2
Horse After the Cart
• 5 year old with underlying pulmonary disease, developed respiratory failure and was intubated with influenza A pneumonia
  – influenza vaccine withheld due to history of egg allergy
• After evaluation next influenza season, vaccine administered successfully and child remained healthy all season

What’s In Common?
• A known or suspected drug or vaccine allergy prevented the patient from receiving optimal care
  – Patient had a bad outcome
  – Bad outcome might have been avoided with optimal management of drug allergy

Drug Allergies Are Over Estimated
~80-90% of patients who state they are allergic to penicillin are not
• Leads to increased usage of broader spectrum antibiotics
  – Possible increasing drug resistance
• Leads to increased cost of treatment
• Leads to use of less effective treatment

Changes in drugs increased mean treatment costs 4-fold (range, 2-11; mean, €273.47 per patient per day).

Number of patients on a single day (random) with diagnosis of drug hypersensitivity at hospital admission and after an in-depth allergy evaluation:

Mean antibiotic costs for patients labeled as penicillin allergic:
- 63% greater during inpatient stay
- 38% greater after discharge
- With no change in any outcome parameter compared to non-penicillin allergic

Adverse Drug Effects

**Type A**: Predictable (Most common ~80%)
- Dose dependent
- Related to pharmacologic actions
- Occur in otherwise healthy people
  - Side effects, secondary effects, toxic effects, interactions

**Type B**: Unpredictable
- Dose independent
- Unrelated to pharmacologic actions
- Occur only in susceptible people
  - Allergic reactions, idiosyncratic reactions

**Type C**: "Chronic"
- Uncommon
- Related to cumulative dose
  - HPA axis suppression from corticosteroids

**Type E**: "End of Use"
- Occurs soon after withdrawal of drug
  - Opiate withdrawal syndrome

**Type D**: "Delayed"
- Uncommon
- Usually dose related
- Becomes some time after use of drug
  - Teratogenesis and carcinogenesis

**Type F**: "Failure"
- Common
- Dose related, often drug interactions
  - Pregnancy despite OCP use in patient taking rifampin

Are nature and timing of reaction consistent with a drug hypersensitivity?

- Yes
  - Diagnostic test positive OR
    - No accurate test available
  - Accurate diagnostic test available and test is negative
  - - Administer in usual manner
    - Consider a "graded challenge"
  - Non-cross-reacting AND
    - Clinically equivalent drug available?
    - Yes
      - Administer alternative non-cross-reacting drug
    - No
      - Pre-treat if possible
        - Induce tolerance if possible

- No
Are nature and timing of reaction consistent with a drug hypersensitivity?

- Yes
  - Diagnostic test positive
  - OR
  - No accurate test available

- No
  - Accurate diagnostic test available and test is negative
    - Administer in usual manner
    - Consider a “graded challenge”

Non-cross-reacting AND Clinically equivalent drug available?

- Yes
  - Administer alternative non-cross-reacting drug

- No
  - Pre-treat if possible
  - Induce tolerance if possible

Diagnosing Drug Allergies

- History
- Physical examination
- Diagnostic tests
- “Challenge” Tests
Diagnosing Drug Allergies

- **History**
  - Physical examination
  - Diagnostic tests
  - “Challenge” Tests

- **PCN testing**
  - Physical examination
  - Diagnostic tests
  - “Challenge” Tests
10 Questions

1. Name of medicine?
   – May be uncertain of name; long ago; polypharmacy

2. How long ago did reaction occur?
   – Some allergies, (e.g. penicillin), may wane over time


10 Questions

3. When during the course did the reaction occur?
   – At onset, during, or after course completed

4. What were characteristics of reactions?
   – If cutaneous → type of rash
   – What other systems involved (liver, kidney, blood cells, etc.)


10 Questions

5. Why was the medication prescribed?
   – Symptoms of underlying disease may be confused for drug reaction

6. Taking any concurrent medications?
   – Opioids and NSAIDs, for example, are often prescribed with antibiotics

10 Questions

7. What treatment was given for rxn?
   – Response to antihistamines or steroids; pts may remember tx more accurately than rxn

8. Exposed to same or similar medication before or since the reaction?
   – Most allergic rxns require a period of sensitization
   – Pts. with “penicillin allergy” may subsequently tolerate Augmentin™ - not realizing it’s a penicillin

9. Same symptoms in absence of drug tx?
   – Reactions in absence of drug rules out drug allergy; may occur in chronic urticaria for example

10. Any underlying condition predisposing to drug reactions?
    – HIV+ more likely to have SMX/TMP reactions, CF have more anti-pseudomonal abx allergy

Classification of Drug Allergic Reactions

- Mechanism → helps guide treatment
  – Immune vs non-immune
  – Type of immune reaction
    (see tables in supplementary section)
- Time to onset
  – Immediate, late
- Involved organ system
  – Cutaneous vs non-cutaneous

Classification of Drug Allergic Reactions

- Cutaneous Drug Reactions
- Single & Multi-organ Drug Reactions

Non-Cutaneous Single Organ
- Hematologic – Cytopenias, hemolytic anemia
- Hepatic – Hepatitis, cholestatic jaundice
- Pulmonary – Pulmonary fibrosis, pneumonitis
- Renal – Interstitial nephritis, glomerulonephritis

"Cutaneous" Reactions
- Urticaria & Angioedema
- Exanthems
- Fixed drug eruption
- Erythema multiforme
- Pustular – AGEP
- Other bullous – Pemphigous, pemphigoid
- Photoallergic/toxic
- Pigmentation
- Many others

Multi-organ Reactions
- Anaphylaxis
- DRESS
- Serum sickness
- SLE
- Vasculitis
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
Cutaneous Drug Reactions

- Urticaria / Angioedema
- Exanthems
- Fixed drug eruptions
- Pruritus
- Anceform
- Acanthosis nigricans
- Alopecia
- Aphthous stomatitis
- Black hairy tongue
- Bullous eruptions
- Erythema nodosum
- Exfoliative dermatitis
- Gingival hyperplasia
- Lichenoid eruptions
- Lupus erythematosus
- Phototoxic
- Photoallergic
- Pigmentation
- Pityriasis rosea-like
- Psoriasis
- Purpura
- Vasculitis


Common Cutaneous Drug Reactions

- Common cutaneous adverse reactions
  - Exanthems
  - Urticaria / Angioedema (non-anaphylaxis)
  - Fixed drug eruptions
  - Erythema multiforme
  - Photosensitivity

- Serious cutaneous adverse reactions
  - Exfoliative dermatitis
  - Gingival hyperplasia
  - Lichenoid eruptions
  - Lupus erythematosus
  - Phototoxic
  - Photoallergic
  - Pigmentation
  - Pityriasis rosea-like
  - Psoriasis
  - Purpura
  - Vasculitis

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Serious Cutaneous Drug Reactions

- Serious cutaneous adverse reactions
  - DRESS
    - Drug rash with eosinophilia and systemic symptoms
  - SJS / TEN
    - Stevens-Johnson syndrome / Toxic epidermal necrolysis
    - Anaphylaxis (urticaria / angioedema)

Are nature and timing of reaction consistent with a drug hypersensitivity?

Yes

Diagnostic test positive

- No accurate test available

Accurate diagnostic test available and test is negative

- Administer in usual manner
- Consider a “graded challenge”

Pre-treat if possible

Induce tolerance if possible

Yes

Administer alternative non-cross-reacting drug

No

Diagnostic test positive

- OR

Diagnosis test available

- No accurate test available

Accurate diagnostic test available and test is negative

Non-cross-reacting AND Clinically equivalent drug available?

Yes

Administer alternative non-cross-reacting drug

No

Pre-treat if possible

Induce tolerance if possible

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Tests for Drug Allergies
The Bad News

• In general, there are very limited diagnostic tests available for drug allergies
• Most have poor sensitivity and specificity, or are unproven
  – Exception is for penicillin

Testing for Drug Allergies

• Skin prick testing (“scratch test”)
  – Mostly for IgE-mediated reactions
• Patch testing
  – Mostly for T-cell mediated reactions
• Blood testing
• Challenge

Skin Prick & Intradermal Tests

• Best method for detecting IgE-mediated drug allergies
• Most accurate of all is for penicillin
  – Has a very high PPV and NPV (97-99%) when all significant components used in testing:
    • PCN G, major determinant (PrePen®), minor determinants
**Skin Prick & Intradermal Tests**

- Can attempt skin test for most drugs suspected of causing IgE-mediated rxns
  - PPV & NPV for non-PCN vary significantly
  - Metabolites for non-PCN not available
  - Need to use “non-irritating” concentrations
- Delayed reaction (>24 hours) to intradermal skin test may help diagnosis of some T-cell mediated allergies

**Reading Skin Tests**

Diameter of skin wheal and flare is used to score degree of positivity of test
- Scale ‘0’ to ‘4’
- Actual measure (mm)

**Patch Testing**

- May be useful for some cutaneous drug reactions:
  - Some maculopapular exanthems
  - Acute generalized exanematous pustulosis (AGEP)
  - Fixed drug eruptions
  - SJS? DRESS?
Reading Patch Tests

- Read at 48 hrs, and possibly 72 & 96 hrs
- Negative
- ? – doubtful
- + - weak positive
- ++ - strong positive
- +++ - extreme positive
- IR - irritant

Blood Tests

For most ADRs, no blood tests are indicated

- Eosinophilia is suggestive, but has poor specificity & sensitivity
- Drug induced SLE or vasculitis
  - Systemic → antihistone antibodies
  - Cutaneous → anti-Ro/SSA & anti-La/SSB
- Elevated serum tryptase is evidence of mast cell activation
  - Best obtained 30-120 minutes after anaphylactic reaction
- Specific IgE tests (e.g. RAST), basophil activation or lymphocyte activation are not adequately validated and have unknown or poor specificity & sensitivity
Avoid the Need if Possible

- Minimize “empiric” antibiotic use
- Watchful waiting for probable viral infections
- Whenever possible, treat only culture proven bacterial infections
- Maximize treatment of any underlying conditions the predispose to infection
  – Allergic rhinitis, tonsillar/adenoidal hypertrophy, PETs, VUR, eczema, etc.
- Similar principle for non-antimicrobial drugs

Avoid the Drug

- Safest option (in terms of allergies) is to never again use the drug that caused the (suspected) allergic reaction
  – Not always clinically feasible
  – Not always in the best interest of patient
- Avoid drugs that are likely to cross-react with initial causative drug
Substitution

Chose a Non-Cross-reacting Antibiotic

- Beta lactams
  - Penicillins*
  - Cephalosporins (generations)*
  - Monobactam (aztreonam)*
  - Carbapenem (imipenem, meropenem)*
- Macrolides (erythromycin, azithromycin, clarithromycin)
- Sulfonamides (TMP-SMX)
- Quinolones (ciprofloxin, levofloxin)
- Tetracyclines (tetracycline, doxycycline, minocycline)
- Aminoglycosides (amikacin, gentamicin, neomycin, tobramycin)
- Glycopeptide (vancomycin)
- Lincosamides (clindamycin)
- Nitrofurans (nitrofurantoin)
- Polypeptide (bacitracin, colistin, polymyxin B)
- Other: chloramphenicol, linezolid, metronidazole, dapsone, rifampin

* May cross-react within beta lactam class

Penicillin & Cephalosporin Cross Reactivity

- Patients with proven PCN allergy
  - Current estimate 0.5 - 3+% (3rd <2nd <1st gen.)
- Patients with a history of penicillin allergy
  - ~15% will have true allergy
  - Of these, ~3% will react (3% x 15% = ~0.5%)
  - 0.5% of patients with history of PCN allergy will have true cephalosporin allergy
  - 99.5% won’t have an allergy

Other Beta Lactams

- Penicillin + carbapenem
  - Latest data shows very low cross-reactivity (~1%)
  - Previous studies as high as ~10%
Other Beta Lactams

- Penicillin and monobactam
  - Estimated low (~1%)
  - Ceftazidime and aztreonam specifically share a side chain → may have increased risk of cross-reactivity

Sulfa Drugs

- Antimicrobial sulfonamide
  - SMX/TMP (sulfonylarylamines)
- Non-antimicrobial sulfonamide
  - Diuretics
    - Loop: furosemide, bumetanide (not ethacrynic acid)
    - Other: hydrochlorothiazide, azetasolamide
  - Sulfonylurea anti-diabetic drugs
  - Others: Sulfasalazine, celecoxib, protease inhibitors, triptans, zonisamide
- Sulfone
  - Dapsone

Sulfa Cross-Reactivity

- Little evidence of cross-reactivity
  - Non-antimicrobial sulfonamides may be used in pts with antibiotic sulfa allergies
  - Need to be monitored
- Higher cross-reactivity within groups
  - E.g. one sulfonylurea with another
- Higher reaction rate in certain patients
  - HIV especially (glutathione deficiency, slow acetylators)
Sulfa Cross-Reactivity

- Not related to drugs that have a sulfur atom, but not a sulfonamide moiety
  - E.g. amoxicillin, captopril, omeprazole, ranitidine
- Not related to sulfite preservatives
- Not related to sulfate (SO₄²⁻)
  - E.g. albuterol sulfate, heparin sulfate...

Dibbern DA. Ann Allergy Asthma Immunol 2008;100:91.
Slatore CG. Immunol Allergy Clin NA 2004;24:477

Are nature and timing of reaction consistent with a drug hypersensitivity?

- Diagnostic test positive OR No accurate test available
  - Positive diagnostic test available and test is negative
    - Administer in usual manner
    - Consider a “graded challenge”
    - Pre-treat if possible
  - Non-cross-reacting AND Clinically equivalent drug available?
    - Yes
      - Administer alternative non-cross-reacting drug
    - No

What if Your Patient Really Needs The Medication?

- Graded Challenge
- Pre-Treat / Block reaction
- Induction of tolerance
  - “Desensitization”
Graded Challenge

• Consider for patients unlikely to be allergic
  – History is weak or inconsistent
  – Reaction is mild
  – Reaction occurred many years ago
• Testing is equivocal, impossible or impractical
• No reasonable alternative
• Graded challenge can be both “diagnostic” and “therapeutic”

Graded Challenge

• Be adequately prepared to treat potential reactions
• Start with 1 - 10% of total dose
  – Use oral formulation (rather than IV) if available
  – Observe for time interval dependent on mechanism of suspected reaction
    • 15-30 minutes for immediate, 24+ hours for delayed
• Administer remaining 90% of dose in 1-3 additional incrementally increasing doses
  – Example: 1% - 10% - 30% - 59%
  – Example: 10% - 25% - 65%
  – Example: 10% - 90%
• No reaction → use single full dose for subsequent doses

Pre-Treatment or Block Reactions

• Does not work for IgE-mediated (anaphylaxis) or serious T-cell-mediated (SJS, DRESS) reactions
• Works for some “anaphylactoid” (non-IgE-mediated reactions)
  – Radiocontrast material
  – Biologicals (IVIG, monoclonal ab’s)
  – Vancomycin (‘redman’), amphotericin
Typical Pre-Treatment Regimens

- H1-antihistamine
  - Diphenhydramine 1 mg/kg 30-60 minutes pre-medication
- Glucocorticoid
  - Prednisone 1 mg/kg 13, 7 & 1 hour pre-medication
- Optional
  - H2-antihistamine 1 hour pre-medications
  - Ephedrine 1 hour pre-medication (rarely used)
- Other
  - Ibuprofen, acetaminophen, meperidine
- Slow down infusion rate for IV meds

Induction of Tolerance

- For proven drug allergic reactions
  - By reliable testing
  - By compelling clinical history if no test available or if testing impractical
- When no effective alternative is available
- “Rapid” and “Slow” desensitization
  - Depends on mechanism of allergic reaction

“Rapid” Desensitization

- For IgE-mediated reactions
- Start very low first dose (IV or PO)
  - 1:10,000th to 1:1,000,000th of final dose
- Sequential doubling of doses
  - Typically every 15-20 minutes
  - Continue until cumulative dose equals full dose
  - Takes ~15-20 doublings (~4-6 hours)
- All subsequent doses given in single full dose
- Desensitized state last 3-4 drug half-lives
“Slow” Desensitization

- For non-IgE-mediated reactions
  - T-cell mediated, metabolic
- First dose is low (usually PO)
  - 1/100th to 1/1,000th of full dose (sometimes higher)
- Sequential increase of dose
  - Dose increase ranges from 1-2x/day to 1-2x/month
  - Continue until single full dose reached
  - Takes days to weeks
- Subsequent doses given in single full dose

Reactions Not Amenable to Induction of Tolerance

- Cytopenias, hemolytic anemia
- Cholestatic jaundice, hepatitis
- Pneumonitis, pulmonary fibrosis
- Interstitial nephritis, membranous glomerulonephritis
- Vasculitis, drug-induced lupus
- Stevens-Johnsons syndrome, toxic epidermal necrolysis, DRESS
### Immune Mediated Drug Allergic Reactions

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Clinical Manifestation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE-mediated</td>
<td>Anaphylaxis, urticaria, angioedema</td>
<td>β-lactam antibiotic, perioperative agents</td>
</tr>
<tr>
<td>Cytotoxic</td>
<td>Hemolytic anemia, thrombocytopenia</td>
<td>Penicillin, quinine, sulfonamides</td>
</tr>
<tr>
<td>Immune complex</td>
<td>Serum sickness</td>
<td>Penicillin, infliximab</td>
</tr>
<tr>
<td>Delayed type hypersensitivity</td>
<td>Contact dermatitis, exanthems</td>
<td>Neomycin, topical steroids, penicillin, sulfonamides</td>
</tr>
<tr>
<td>Hypersensitivity vasculitis</td>
<td>Cutaneous or visceral vasculitis</td>
<td>Hydralazine, penicillamine</td>
</tr>
<tr>
<td>DRESS (drug rash with eosinophilia and systemic symptoms)</td>
<td>Rash, fever, eosinophilia, hepatitis, LAD</td>
<td>Anticonvulsant, sulfonamide, minocycline, allopurinol</td>
</tr>
</tbody>
</table>


### Immune Mediated Drug Allergic Reactions

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Clinical Manifestation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary drug hypersensitivity</td>
<td>Pneumonitis, fibrosis</td>
<td>Nitrofurantoin, bleomycin, methotrexate</td>
</tr>
<tr>
<td>Systemic drug-induced lupus</td>
<td>Arthralgia, myalgia, fever</td>
<td>Hydralazine, procainamide, INH</td>
</tr>
<tr>
<td>Cutaneous drug-induced lupus</td>
<td>Erythematous scaly plaques, photosensitivity</td>
<td>Hydrochlorothiazide, Ca channel blockers, ACE inhibitors</td>
</tr>
<tr>
<td>Drug-induced granulomatous disease</td>
<td>Churg-Strauss syndrome, Wegener's granulomatosis</td>
<td>Propylthiouracil, leukotriene modifiers</td>
</tr>
</tbody>
</table>

Immune Mediated Drug Allergic Reactions

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Clinical Manifestation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune hepatitis</td>
<td>Hepatitis, cholestatic jaundice</td>
<td>Para-aminosalicylic acid, sulfonamides, phenothiazine</td>
</tr>
<tr>
<td>Blistering skin disorders</td>
<td>Erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)</td>
<td>Sulfonamides, cephalosporins, imidazole anticonvulsants, NSAIDs</td>
</tr>
<tr>
<td>Serum-sickness like reactions</td>
<td>Erythema multiforme, arthralgias</td>
<td>Cefaclor, cefprozil</td>
</tr>
<tr>
<td>Immune nephropathy</td>
<td>Interstitial nephritis, membranous glomerulonephritis</td>
<td>Penicillin, sulfonamides, gold, penicillamine, allopurinol</td>
</tr>
</tbody>
</table>

Exanthems

- Most common cutaneous drug reaction
- Macular, slightly papular rash
  - “Morbilliform” or “viral rash”
  - 2-10 mm erythematous slightly raised spots, may become confluent
  - Usually bilateral & symmetrical, mostly on trunk & proximal extremities, usually spares palms & soles
  - Often desquamates as rash resolves
  - Post-inflammatory hypo- or hyperpigmentation may occur
- Appears several (~2+ to 14) days into treatment
Exanthems

- Treatment
  - Discontinue causative drug
  - “Supportive” care: antihistamine, rarely steroids
  - Topical steroids for desquamation
- Risk of cross-reaction very low
- Diagnostic Tests (apart from history)
  - Patch testing and delayed rxn to intradermal skin testing reported to be helpful, rarely done
- Induction of tolerance
  - Slow desensitization may be possible, but not reported in literature

Urticaria/Angioedema (Anaphylaxis)

- IgE-mediated immediate hypersensitivity rxn
- May evolve to anaphylaxis:
  - Upper airway edema
    - Stridor, hoarse, drooling, throat lump / constriction
  - Lower airway
    - Wheezing, cough, tight chest
  - Gastrointestinal
    - Abdominal pain, nausea, vomit
  - Cardiovascular
    - Hypotension, syncope, seizure

Urticaria / Angioedema
IgE-Mediated Drug Allergy

- Treatment
  - Immediate discontinuation of causative drug
  - Minor symptoms: antihistamines
  - Major symptoms: epinephrine, steroids, fluids, pressors
- Risk of cross-reaction may be high within same class of agent, low across classes
- Diagnostic tests (apart from history)
  - Skin testing
- Induction of tolerance
  - Rapid desensitization is highly effective and has been reported for multiple drugs (multiple abx, chemotherapeutics, biologic proteins & many others)

Fixed Drug Eruption

- Solitary / few pruritic, well circumscribed annular/oval, erythematous macules (skin or mucous membranes)
  - Resolve leaving gray-brown hyperpigmentation
  - Rare severe cases - bullous lesions, fever, arthralgia
  - Typically occur at exactly same site with each admin.
- Sensitization (first occurrence) = weeks to years
- Flare within 0.5-8 hrs (mean 2 hrs) upon re-administration
  - May be preceded by sensation of burning
  - There may be a variable refractory period

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Fixed Drug Eruption

- Treatment
  - Discontinuation of causative agent
  - Rash will fade over time (months to years)
  - Topical steroids may help a little
- Risk of cross-reaction very low
- Diagnostic Tests (apart from history)
  - Patch testing
    - Best done at site of a previous FDE lesion, wait >2 weeks to test
    - False negatives occur, but positives are usually true
  - Oral challenge
    - Single, 10% dose
  - Skin biopsy can confirm diagnosis but not causative agent
- Induction of Tolerance
  - Slow desensitization has been reported

Erythema Multiforme

- Polymorphous maculopapular with classic “target” lesions
  - 3 zones: an erythematous central papule that may blister, an edematous middle ring and an erythematous outer ring
- Usually symmetrical
- Mainly acral distribution
- Mucosal involvement minor (less than SJS) and usually just 1-2 mucosal lesions
- Typically HSV related, less likely drug related
Erythema Multiforme

• Treatment
  – Treat HSV or discontinue causative agent
  – If drug induced, steroids early in course may help
  – No treatment necessary, rash will fade over time (days to weeks)
• Risk of cross-reaction unknown, likely low
• No diagnostic tests available
  – Skin biopsy can confirm diagnosis but not causative agent
• Induction of tolerance
  – Not described

Photosensitivity

Phototoxic & Photoallergic

• Phototoxic
  – Light causes chemicals within skin to generate free radical → host cytotoxic effect
  – Non-immunologic, dose dependent, ~immediate
  – Occurs on sun-exposed areas (face, presternum, dorsum of hand)
• Photoallergic
  – Immunologic reaction to light-induced conformation and haptenization of drug/metabolite
  – Period of sensitization, only small doses
Photosensitivity

- Treatment
  - Prevent (stay out of sun and use sunscreen)
  - Stop drug
  - Symptomatic (antihistamine, topical steroids, emollients). Oral steroids if very bad
- Risk of cross-reactivity unknown, but probably low across classes
- Diagnostic tests (apart from history)
  - Photopatch test possible
- Induction of tolerance is usually not helpful

Drug-Related Eosinophilia with Systemic Symptoms (DRESS)
AKA Drug Induced Hypersensitivity Syndrome (DIHS)

- Erythematous maculopapular exanthem and swelling
- Systemic symptoms
  - Fever, malaise, LAD, hepatitis (50%), interstitial nephritis (10%)
  - Less commonly colitis, interstitial pneumonitis, pancreatitis (IDDM), myocarditis, thyroiditis, encephalitis/meningitis, other serositis
  - Type of systemic involvement may be drug specific
- Marked eosinophilia in 70%
  - Also with leukocytosis (>11,000), atypical lymphocytosis (>5%)

Typically starts >3 wks into treatment- often at dose increases
- Symptoms may persist, recur or worsen for weeks-months after drug is withdrawn
  - Can be fatal (~10%), usually due to liver failure
- May be associated with reactivation of herpes viruses (HHV 6, EBV, CMV)
Drug-Related Eosinophilia with Systemic Symptoms (DRESS)
AKA Drug Induced Hypersensitivity Syndrome (DIHS)

- Treatment
  - Empiric supportive therapy
  - Glucocorticoids - often with long taper
- Causative drugs
  - Anticonvulsants (very high rate of cross-reactivity)
    - Carbamazepine, phenytoin, phenobarbital, zonisamide, lamotrigine
  - Allopurinol, Sulfonamides, Minocycline
- May be a genetic predisposition
  - Varies with drug and genetic background (eg. association with HLA B*1502 with CBM in certain Asian populations

Diagnostic tests (apart from history)
- Patch has been reported to be helpful, especially with aromatic anticonvulsants (higher PPV than NPV)
- Induction of Tolerance - not recommended
  - May be considered in extreme cases

Toxic Epidermal Necrolysis (TEN) & Stevens-Johnson Syndrome (SJS)

- Multifactorial, but drugs are a common cause
- Prodrome of fever and occ. stinging eyes and sore throat x 1-3 days before rash
- Erythematous - purpuric macules
  - Usually first on trunk, spread to face and proximal extremities
  - Buccal, oral, conjunctival and genital involvement common
- Progress to full-thickness necrosis w/ flaccid blisters
  - + Nikolsky sign
- SJS if epidermal detachment <10% body surface area
- TEN if epidermal detachment >30% body surface area
TEN & SJS -- Treatment

- Immediate discontinuation of causative drug
  - May be more effective in drugs with a short half-lives
- Supportive care (like a burn)
  - Fluid + electrolyte homeostasis, prevent and treat secondary infections, respiratory support, nutrition, pain control
- Attention to evaluation, treatment and prevention of ocular complications
- Specific treatment - insufficient evidence
  - Systemic corticosteroids
  - IVIG
  - Other treatments reported
    - Infliximab (anti-TNF-α monoclonal antibody)
    - Plasmapheresis

TEN & SJS

- Diagnostic tests (apart from history)
  - No specific diagnostic tests proven
  - Patch testing may be helpful
  - Biopsy can confirm diagnosis, but not cause
- Risk of cross-reactivity very low
- Induction of tolerance
  - No role for ‘test dose’, ‘graded challenges’ or ‘induction of tolerance’ (desensitization)
  - Rare reports in exceptional cases
Acute Generalized Exanthematous Pustulosis (AGEP)

- Drugs (esp. antimicrobials) are a major cause (90%)
  - Infections, psoriasis, spider bites, malignancy, pregnancy
- Acute edematous erythema, followed by dozens of small (1-3 mm) non-follicular sterile pustules
  - Onset typically 2-3 days after starting drug
  - Widespread or in big folds
  - Mild, non-erosive mucositis in ~20%
  - Usually self-resolves with ~2 weeks after stopping med, often leaving pinpoint desquamation at the pustule sites
- Usually with fever, leukocytosis, mild eosinophilia
  - Internal organs usually not involved

Treatment
- Discontinuation of causative drug
- Symptomatic treatment with antihistamines, systemic/topical steroids may help

Risk of cross-reactivity unknown, but probably low

Diagnostic tests (apart from history)
- Patch testing can be diagnostic
  - Can set off AGEP-like reaction
- In-vitro lymphoproliferative assays reported, but accuracy of clinically available tests unknown
- Skin biopsy helps confirm diagnosis (subcorneal pustules filled with neutrophils) but not cause

Induction of Tolerance - not reported
Serum Sickness

• **Description**
  – Antigen-antibody complexes (type III) deposit in microvasculature, activates complement leading to inflammation and tissue damage
  – Fever, pruritus, urticaria and arthralgias
  – Start 1-3 weeks after drug exposure

• **Treatment**
  – Stop causative drug
  – Symptomatic - pain, itch
  – Oral steroids if severe

Serum Sickness

• Risk of cross-reactivity appears very low, even within classes
• **Diagnostic tests (apart from history)**
  – None
  – Immune complex and complement studies rarely abnormal
• **Induction of tolerance** - not reported

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Drug Fever

• Febrile response coinciding temporally with the administration of a drug in the absence of underlying condition that can be responsible for the fever, and fever resolves after drug is discontinued
  – Degree of elevation of fever varies, most commonly 102°F-104°F (99°F-109°F)
  – May be only manifestation
  – May be early or part of more serious reaction, such as SJS, DRESS, TEN, etc.

Drug Fever

• May occur at anytime during course of treatment
  – Median is 7-10 days
  – May vary depending on drug class (shortest for antineoplastic & antimicrobial, longest for CNS and cardiac drugs)

• Various patterns of fever
  – Continuous - high fever all the time
  – Remittent - variable, but always febrile
  – Intermittent - periods of normal temps daily
  – Hectic - combo of remittent & intermittent (most common pattern)

• May be “inappropriately well” for degree of fever
  – May not even know they have fever

• Relative bradycardia (lack expected tachycardia) in ~11%

• Cutaneous manifestations in minority (18-29%)
  – Fever may be early sign of more serious reaction (SJS, TEN, DRESS)

Drug Fever

• Treatment
  – Discontinuation of causative drug
  – Resolution of fever in 24-48 hours
    • Longer for slowly metabolized drugs, or if other non-skin sx’s present

• Cross-reactivity rare

• Diagnostic tests (apart from history)
  – No specific test other than “drug challenge”
  – No specific laboratory tests, but many mild/variable reported (18-22% of cases) : ?WBC (occ. left shift), eosinophils, ESR, transaminases, LDH
    • None are consistent or diagnostic, but may support diagnosis

• Induction of Tolerance
  – Pre-treatment (H1-blocker, steroid) & desensitization reported